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ABSTRACT

Multi-specific binding proteins that bind the NKG2D receptor, CD16, and a tumor-associated antigen are described, as well as pharmaceutical compositions and therapeutic methods useful for the treatment of cancer.

PROTEINS BINDING NKG2D, CD16 AND A TUMOR-ASSOCIATED ANTIGEN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional application of Australian Patent Application No. 2018329937 and is related to International Patent Application No. PCT/US2018/050073, filed on 7 September 2018, which claims the benefit of andpriority to U.S. Provisional Patent Application No. 62/555,110, filed 7 September 2017, and U.S. Provisional Patent Application No. 62/566,824, filed on 2 October 2017, the entire disclosure of each of which is hereby incorporated by reference in its entirety for all purposes.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on September 6, 2018, is named DFY-038WO_SL.txt and is 321,395 bytes in size.

FIELD OF THE INVENTION

[0003] The invention relates to multi-specific binding proteins that bind to NKG2D, CD16, and a tumor-associated antigen.

BACKGROUND

[0004] Cancer continues to be a significant health problem despite the substantial research efforts and scientific advances reported in the literature for treating this disease. Some of the most frequently diagnosed cancers include prostate cancer, breast cancer, lung cancer, and colorectal cancer. Prostate cancer is the most common form of cancer in men. Breast cancer remains a leading cause of death in women. Blood and bone marrow cancers are also frequently diagnosed cancer types, including multiple myelomas, leukemia, and lymphomas. Current treatment options for these cancers are not effective for all patients and/or can have substantial adverse side effects. Other types of cancer also remain challenging to treat using existing therapeutic options.

[0005] Cancer immunotherapies are desirable because they are highly specific and can facilitate destruction of cancer cells using the patient's own immune system. Fusion proteins such as bi-specific T-cell engagers are cancer immunotherapies described in the literature that bind to tumor cells and T-cells to facilitate destruction of tumor cells. Antibodies that bind to certain tumor-associated antigens and to certain immune cells have been described in the literature. See, for example WO 2016/134371 and WO 2015/095412.

[0006] Natural killer (NK) cells are a component of the innate immune system and make up approximately 15% of circulating lymphocytes. NK cells infiltrate virtually all tissues and were originally characterized by their ability to kill tumor cells effectively without the need for prior sensitization. Activated NK cells kill target cells by means similar to cytotoxic T cells – *i.e.*, via cytolytic granules that contain perforin and granzymes as well as via death receptor pathways. Activated NK cells also secrete inflammatory cytokines such as IFN-gamma and chemokines that promote the recruitment of other leukocytes to the target tissue.

[0007] NK cells respond to signals through a variety of activating and inhibitory receptors on their surface. For example, when NK cells encounter healthy self-cells, their activity is inhibited through activation of the killer-cell immunoglobulin-like receptors (KIRs). Alternatively, when NK cells encounter foreign cells or cancer cells, they are activated via their activating receptors (*e.g.*, Natural killer group 2 member D (NKG2D), NCRs, DNAM1). NK cells are also activated by the constant region of some immunoglobulins through CD16 receptors on their surface. The overall sensitivity of NK cells to activation depends on the sum of stimulatory and inhibitory signals.

[0008] Epithelial cell adhesion molecule (EpCAM) is a transmembrane glycoprotein mediating Ca^{2+}-independent homotypic cell–cell adhesion in epithelia. EpCAM is also involved in cell signaling, migration, proliferation, and differentiation. Additionally, EpCAM has oncogenic potential via its capacity to upregulate c-myc, e-fabp, and cyclins A and E. Since EpCAM is expressed exclusively in epithelia and epithelial-derived neoplasms, EpCAM can be used as diagnostic marker for various cancers, such as head and neck cancer, ovarian cancer, bladder cancer, breast cancer, colorectal cancer, prostate cancer, gastric cancer, liver cancer, esophageal cancer, and lung cancer. It appears to play a role in tumorigenesis and metastasis of carcinomas, so it can also act as a potential prognostic marker and as a potential target for immunotherapeutic strategies.

[0009] CA125, also known as mucin 16, is a member of the mucin family glycoproteins. CA-125 has found application as a tumor marker or biomarker that may be elevated in the blood of some patients with specific types of cancers, including ovarian cancer, endometrial cancer, and pancreatic cancer. CA-125 has been shown to play a role in advancing tumorigenesis and tumor proliferation by several different mechanisms, including suppressing the response of natural killer cells, and thereby protecting cancer cells from the immune response; and by enabling cell growth and promoting cell motility.

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[0010] Sodium-dependent phosphate transport protein 2b (NaPi2b) is involved in actively transporting phosphate into cells via Na+ co-transport. For example, it is the main phosphate transport protein in the intestinal brush border membrane, and has a role in the synthesis of surfactant in lungs' alveoli. NaPi2b is also an antigen expressed in a variety of cancer, such as lung cancer, ovarian cancer, and thyroid cancer.

[0011] Nectin4 is a member of the Nectin family, which is a family of cellular adhesion molecules involved in Ca^{2+}-independent cellular adhesion. Nectins are ubiquitously expressed and have adhesive roles in a wide range of tissues such as the adherens junction of epithelia or the chemical synapse of the neuronal tissue. It is also a tumor associated antigen, and expressed in cancers such as bladder cancer, breast cancer, ovarian cancer, pancreatic cancer, colorectal cancer, and lung cancer.

[0012] Gangliosides have been implicated in many physiological processes, including growth, differentiation, migration, and apoptosis through modulating both cell signaling processes and cell-to-cell and cell-to-matrix interactions. GM1 is a ganglioside, and Fucosyl-GM1 is a ganglioside with a unique structure in which the terminal galactose is α-1,2-fucosylated at the non-reducing end. It is expressed in very few normal tissues but occurs in a variety of cancers such as in small cell lung cancer, neuroblastoma, liver cancer. Consequently, fucosyl-GM1 has been considered to be a candidate as a tumor marker and target antigen in antibody immunotherapy small cell lung cancer, neuroblastoma, liver cancer.

[0013] ADAM (a disintegrin and metalloproteinase) proteins have a predominant role in the protein ectodomain shedding of membrane-bound molecules. They have emerged as critical regulators of cell-cell signaling during development and homeostasis, and are believed to contribute to pathologies, such as cancer, where their regulation is altered. ADAM8, a member the ADAM family, is overexpressed in pancreatic cancer, breast cancer, lung cancer, and renal cancer. ADAM9 has been shown to cleave and release a number of molecules with important roles in tumorigenesis and angiogenesis, such as EGF, FGFR2iiib, Tie-2, Flk-1, EphB4, CD40, VCAM-1, and VE-cadherin. ADAM9 is overexpressed in renal cancer, breast cancer, lung cancer, liver cancer, pancreatic cancer, melanoma, cervical cancer, prostate cancer, osteosarcoma, and brain cancer.

[0014] SLC44A4, also known as CTL4, is a member of the family of solute carrier proteins known as choline transporter-like proteins (CTL1-5). SLC44A4 has not been shown

to be involved in choline transport, but it has been linked with acetylcholine synthesis and transport as well as uptake of thiamine pyrophosphate, the phosphorylated form of vitamin B1. SLC44A4 is normally expressed on the apical surface of secretory epithelial cells, but it is markedly upregulated in a variety of epithelial tumors, most notably pancreatic cancer, prostate cancer, and gastric cancer.

[0015] CA19-9 is the common term for carbohydrate antigen sialyl Lewis a. It is overexpressed in cancer of the digestive organs such as pancreatic cancer, colorectal cancer, cholangiocarcinoma, and liver cancer. Therefore, it is the most frequently applied serum tumor marker for diagnosis of these above mentioned cancers.

SUMMARY

[0016] The invention provides multi-specific binding proteins that bind to a tumor-associated antigen (selected from any one of the antigens provided in Table 11) and to the NKG2D receptor and CD16 receptor on natural killer cells. Such proteins can engage more than one kind of NK activating receptor, and may block the binding of natural ligands to NKG2D. In certain embodiments, the proteins can agonize NK cells in humans, and in other species such as rodents and cynomolgus monkeys. Various aspects and embodiments of the invention are described in further detail below.

[0017] Accordingly, one aspect of the invention provides a protein that incorporates a first antigen-binding site that binds NKG2D; a second antigen-binding site that binds an antigen selected from EpCAM, Cancer Antigen 125 (CA125), sodium/phosphate cotransporter 2B (NaPi2b), Nectin cell adhesion molecule 4 (Nectin4), Fucosyl-GM1 (monosialotetrahexosylganglioside), disintegrin and metalloproteinase domain-containing protein 8 (ADAM8), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), solute carrier family 44 member 4 (SLC44A4), and sialylated Lewis a antigen (CA19-9); and an antibody Fc domain, a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16. The antigen-binding sites may each incorporate an antibody heavy chain variable domain and an antibody light chain variable domain (*e.g.* arranged as in an antibody, or fused together to from an scFv), or one or more of the antigen-binding sites may be a single domain antibody, such as a V_HH antibody like a camelid antibody or a V_{NAR} antibody like those found in cartilaginous fish.

[0018] The invention provides multi-specific binding proteins that bind the NKG2D receptor, CD16, and an antigen selected from EpCAM, Cancer Antigen 125 (CA125),

sodium/phosphate cotransporter 2B (NaPi2b), Nectin cell adhesion molecule 4 (Nectin4), Fucosyl-GM1 (monosialotetrahexosylganglioside), disintegrin and metalloproteinase domain-containing protein 8 (ADAM8), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), solute carrier family 44 member 4 (SLC44A4), and sialylated Lewis a antigen (CA19-9).

[0019] Some proteins of the present disclosure include an Fab fragment linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or the third antigen-binding site that binds CD16.

[0020] Some proteins of the present disclosure include an Fab fragment, wherein the heavy chain portion of the Fab fragment comprises a heavy chain variable domain and a CH1 domain, and wherein the heavy chain variable domain is linked to the CH1 domain.

[0021] Some proteins of the present disclosure include an Fab fragment linked to the antibody Fc domain.

[0022] In one aspect, the invention provides a protein comprising (a) a first antigen-binding site comprising an Fab fragment that binds NKG2D; (b) a second antigen-binding site comprising a single-chain variable fragment (scFv) that binds EpCAM; and (c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16. The present invention provides a protein in which the first antigen-binding site that binds NKG2D is an Fab fragment, and the second antigen-binding site that binds a tumor-associated antigen EpCAM is an scFv.

[0023] Certain proteins described in the present disclosure include an scFv-targeting EpCAM, comprising a heavy chain variable domain and a light chain variable domain, linked to an antibody Fc domain or a portion thereof sufficient to bind CD16, or the third antigen-binding site that binds CD16, via a hinge comprising Ala-Ser or Gly-Ala-Ser. Some proteins of the present disclosure includes an scFv-targeting EpCAM linked to an antibody Fc domain. Some proteins of the present disclosure includes a heavy chain variable domain of an scFv-targeting EpCAM, which forms a disulfide bridge with the light chain variable domain of the scFv.

[0024] Some proteins of the present disclosure include an scFv-targeting EpCAM, in which a disulfide bridge is formed between C44 from the heavy chain variable domain and C100 from the light chain variable domain.

[0025] Some proteins of the present disclosure include an scFv-targeting EpCAM linked to an antibody Fc domain, in which the light chain variable domain of the scFv is positioned

at the N-terminus of the heavy chain variable domain of the scFv, and is linked to the heavy chain variable domain of the scFv via a flexible linker $(GlyGlyGlyGlySer)_4$ $(G4S)_4$) (SEQ ID NO:206), and the Fab fragment that binds NKG2D is linked to the antibody Fc domain.

[0026] Some proteins of the present disclosure include an scFv-targeting EpCAM in which the heavy chain variable domain is positioned at the N-terminus or the C-terminus of the light chain variable domain of the scFv.

[0027] Some proteins of the present disclosure include an scFv-targeting EpCAM in which the light chain variable domain is positioned at the N-terminus of the heavy chain variable domain of the scFv.

[0028] In one aspect of the invention provides a protein comprising (a) a first antigen-binding site comprising a single-chain variable fragment (scFv) that binds NKG2D; (b) a second antigen-binding site that binds EpCAM; and (c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16. In certain embodiments, a protein of the present disclosure further comprises an additional antigen-binding site that binds EpCAM. In certain embodiments, the second antigen-binding site of a protein described in the present disclosure is an Fab fragment that binds EpCAM. In certain embodiments, the second and the additional antigen-binding site of a protein described in the present disclosure are Fab fragments that bind EpCAM.

[0029] In certain embodiments, the second and the additional antigen-binding site of a protein described in the present disclosure are scFvs that bind EpCAM. In certain embodiments, the heavy chain variable domain of the scFv that binds NKG2D is positioned at the N-terminus or the C-terminus of the light chain variable domain of the scFv. In certain embodiments, the light chain variable domain is positioned at the N-terminus of the heavy chain variable domain of the scFv that binds NKG2D.

[0030] In certain embodiments, the scFv that binds to NKG2D is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16. In certain embodiments, the scFv that binds to NKG2D is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16 *via* a hinge comprising Ala-Ser (*e.g.*, in a TriNKET that comprises an additional antigen-binding site that binds EpCAM, CA125, NaPi2b, Nectin4, Fucosyl-GM1, ADAM8, ADAM9, SLC44A4, or CA19-9) or Gly-Ala-Ser (*e.g.*, in a TriNKET that does not comprise an additional antigen-binding site that binds EpCAM, CA125, NaPi2b, Nectin4, Fucosyl-GM1, ADAM8, ADAM9, SLC44A4, or CA19-9). In certain embodiments, the scFv that binds to NKG2D is linked to the C-terminus of the antibody Fc domain or a portion thereof

sufficient to bind CD16, or a third antigen-binding site that binds CD16 *via* a flexible linker comprising G4S. In certain embodiments, the C-terminus of the antibody Fc domain is linked to the N-terminus of the light chain variable domain of the scFv that binds NKG2D.

[0031] In certain embodiments, within the scFv that binds NKG2D, a disulfide bridge is formed between the heavy chain variable domain of the scFv and the light chain variable domain of the scFv. In certain embodiments, the disulfide bridge is formed between C44 from the heavy chain variable domain and C100 from the light chain variable domain.

[0032] Some proteins of the present disclosure include a sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

[0033] Some proteins of the present disclosure include an scFv linked to an antibody Fc domain, wherein the scFv linked to the antibody Fc domain is represented by a sequence selected from SEQ ID NO:208 and SEQ ID NO:209.

[0034] Some proteins of the present disclosure include a sequence of SEQ ID NO:205 and SEQ ID NO:213.

[0035] Some proteins of the present disclosure include a sequence at least 90% identical to an amino acid sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

[0036] Some proteins of the present disclosure include a sequence at least 95% identical to an amino acid sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

[0037] Some proteins of the present disclosure include a sequence at least 99% identical to an amino acid sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

[0038] Some proteins of the present disclosure include an amino acid sequence of SEQ ID NO:203.

[0039] Some proteins of the present disclosure include an amino acid sequence of SEQ ID NO:203 and SEQ ID NO:204.

[0040] Some proteins of the present disclosure include an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:203. Some proteins of the present disclosure include an amino acid sequence at least 95% identical to an amino acid sequence of SEQ ID NO:203. Some proteins of the present disclosure include an amino acid sequence at least 99% identical to an amino acid sequence of SEQ ID NO:203.

[0041] The first antigen-binding site, which binds to NKG2D, in some embodiments, can incorporate a heavy chain variable domain related to SEQ ID NO:1, such as by having an amino acid sequence at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:1, and/or incorporating amino acid sequences identical to the CDR1 (SEQ ID NO:105), CDR2 (SEQ ID NO:106), and CDR3 (SEQ ID

NO:107) sequences of SEQ ID NO:1. The heavy chain variable domain related to SEQ ID NO:1 can be coupled with a variety of light chain variable domains to form an NKG2D binding site. For example, the first antigen-binding site that incorporates a heavy chain variable domain related to SEQ ID NO:1 can further incorporate a light chain variable domain selected from any one of the sequences related to SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40. For example, the first antigen-binding site incorporates a heavy chain variable domain with amino acid sequences at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:1 and a light chain variable domain with amino acid sequences at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to any one of the sequences selected from SEQ ID NOs:2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, and 40.

[0042] Alternatively, the first antigen-binding site can incorporate a heavy chain variable domain related to SEQ ID NO:41 and a light chain variable domain related to SEQ ID NO:42. For example, the heavy chain variable domain of the first antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:41, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:43), CDR2 (SEQ ID NO:44), and CDR3 (SEQ ID NO:45) sequences of SEQ ID NO:41. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:42, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:46), CDR2 (SEQ ID NO:47), and CDR3 (SEQ ID NO:48) sequences of SEQ ID NO:42.

[0043] In other embodiments, the first antigen-binding site can incorporate a heavy chain variable domain related to SEQ ID NO:49 and a light chain variable domain related to SEQ ID NO:50. For example, the heavy chain variable domain of the first antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:49, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:51), CDR2 (SEQ ID NO:52), and CDR3 (SEQ ID NO:53) sequences of SEQ ID NO:49. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:50, and/or incorporate amino acid sequences identical to the CDR1

(SEQ ID NO:54), CDR2 (SEQ ID NO:55), and CDR3 (SEQ ID NO:56) sequences of SEQ ID NO:50.

[0044] Alternatively, the first antigen-binding site can incorporate a heavy chain variable domain related to SEQ ID NO:57 and a light chain variable domain related to SEQ ID NO:58, such as by having amino acid sequences at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:57 and at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:58, respectively.

[0045] In another embodiment, the first antigen-binding site can incorporate a heavy chain variable domain related to SEQ ID NO:59 and a light chain variable domain related to SEQ ID NO:60, For example, the heavy chain variable domain of the first antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:59, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:109), CDR2 (SEQ ID NO:110), and CDR3 (SEQ ID NO:111) sequences of SEQ ID NO:59. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:60, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:112), CDR2 (SEQ ID NO:113), and CDR3 (SEQ ID NO:114) sequences of SEQ ID NO:60.

[0046] The first antigen-binding site, which binds to NKG2D, in some embodiments, can incorporate a heavy chain variable domain related to SEQ ID NO:61 and a light chain variable domain related to SEQ ID NO:62. For example, the heavy chain variable domain of the first antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:61, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:63), CDR2 (SEQ ID NO:64), and CDR3 (SEQ ID NO:65) sequences of SEQ ID NO:61. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:62, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:66), CDR2 (SEQ ID NO:67), and CDR3 (SEQ ID NO:68) sequences of SEQ ID NO:62.

[0047] In some embodiments, the first antigen-binding site can incorporate a heavy chain variable domain related to SEQ ID NO:69 and a light chain variable domain related to SEQ

ID NO:70. For example, the heavy chain variable domain of the first antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:69, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:71), CDR2 (SEQ ID NO:72), and CDR3 (SEQ ID NO:73) sequences of SEQ ID NO:69. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:70, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:74), CDR2 (SEQ ID NO:75), and CDR3 (SEQ ID NO:76) sequences of SEQ ID NO:70.

[0048] In some embodiments, the first antigen-binding site can incorporate a heavy chain variable domain related to SEQ ID NO:77 and a light chain variable domain related to SEQ ID NO:78. For example, the heavy chain variable domain of the first antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:77, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:79), CDR2 (SEQ ID NO:80), and CDR3 (SEQ ID NO:81) sequences of SEQ ID NO:77. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:78, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:82), CDR2 (SEQ ID NO:83), and CDR3 (SEQ ID NO:84) sequences of SEQ ID NO:78.

[0049] In some embodiments, the first antigen-binding site can incorporate a heavy chain variable domain related to SEQ ID NO:85 and a light chain variable domain related to SEQ ID NO:86. For example, the heavy chain variable domain of the first antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:85, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:87), CDR2 (SEQ ID NO:88), and CDR3 (SEQ ID NO:89) sequences of SEQ ID NO:85. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:86, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:90), CDR2 (SEQ ID NO:91), and CDR3 (SEQ ID NO:92) sequences of SEQ ID NO:86.

[0050] In some embodiments, the first antigen-binding site can incorporate a heavy chain variable domain related to SEQ ID NO:93 and a light chain variable domain related to SEQ

ID NO:94. For example, the heavy chain variable domain of the first antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:93, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:95), CDR2 (SEQ ID NO:96), and CDR3 (SEQ ID NO:97) sequences of SEQ ID NO:93. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:94, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:98), CDR2 (SEQ ID NO:99), and CDR3 (SEQ ID NO:100) sequences of SEQ ID NO:94.

[0051] In some embodiments, the first antigen-binding site can incorporate a heavy chain variable domain related to SEQ ID NO:101 and a light chain variable domain related to SEQ ID NO:102, such as by having amino acid sequences at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:101 and at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:102, respectively.

[0052] In some embodiments, the first antigen-binding site can incorporate a heavy chain variable domain related to SEQ ID NO:103 and a light chain variable domain related to SEQ ID NO:104, such as by having amino acid sequences at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:103 and at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:104, respectively.

[0053] In some embodiments, the second antigen-binding site can bind to EpCAM and can incorporate a heavy chain variable domain related to SEQ ID NO:115 and a light chain variable domain related to SEQ ID NO:119. For example, the heavy chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:115, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:116), CDR2 (SEQ ID NO:117), and CDR3 (SEQ ID NO:118) sequences of SEQ ID NO:115. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:119, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:120), CDR2 (SEQ ID NO:121), and CDR3 (SEQ ID NO:122) sequences of SEQ ID NO:119.

[0054] In some embodiments, the second antigen-binding site can bind to EpCAM and can incorporate a heavy chain variable domain related to SEQ ID NO:123 and a light chain variable domain related to SEQ ID NO:127. For example, the heavy chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:123, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:124), CDR2 (SEQ ID NO:125), and CDR3 (SEQ ID NO:126) sequences of SEQ ID NO:123. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:127, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:128), CDR2 (SEQ ID NO:129), and CDR3 (SEQ ID NO:130) sequences of SEQ ID NO:127.

[0055] In some embodiments, the second antigen-binding site can bind to EpCAM and can incorporate a heavy chain variable domain related to SEQ ID NO:131 and a light chain variable domain related to SEQ ID NO:135. For example, the heavy chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:131, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:132), CDR2 (SEQ ID NO:133), and CDR3 (SEQ ID NO:134) sequences of SEQ ID NO:131. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:135, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:136), CDR2 (SEQ ID NO:137), and CDR3 (SEQ ID NO:138) sequences of SEQ ID NO:135.

[0056] In some embodiments, the second antigen-binding site can bind to EpCAM and can incorporate a heavy chain variable domain related to SEQ ID NO:139 and a light chain variable domain related to SEQ ID NO:143. For example, the heavy chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:139, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:140), CDR2 (SEQ ID NO:141), and CDR3 (SEQ ID NO:142) sequences of SEQ ID NO:139. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:143, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:144), CDR2 (SEQ ID NO:145), and CDR3 (SEQ ID NO:146) sequences of SEQ ID NO:143.

[0057] In some embodiments, the second antigen-binding site can bind to CA125 and can incorporate a heavy chain variable domain related to SEQ ID NO:155 and a light chain variable domain related to SEQ ID NO:159. For example, the heavy chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:155, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:156), CDR2 (SEQ ID NO:157), and CDR3 (SEQ ID NO:158) sequences of SEQ ID NO:155. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:159, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:160), CDR2 (SEQ ID NO:161), and CDR3 (SEQ ID NO:162) sequences of SEQ ID NO:159.

[0058] In some embodiments, the second antigen-binding site can bind to CA125 and can incorporate a heavy chain variable domain related to SEQ ID NO:163 and a light chain variable domain related to SEQ ID NO:167. For example, the heavy chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:163, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:164), CDR2 (SEQ ID NO:165), and CDR3 (SEQ ID NO:166) sequences of SEQ ID NO:163. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:167, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:168), CDR2 (SEQ ID NO:169), and CDR3 (SEQ ID NO:170) sequences of SEQ ID NO:167.

[0059] In some embodiments, the second antigen-binding site can bind to NaPi2b and can incorporate a heavy chain variable domain related to SEQ ID NO:171 and a light chain variable domain related to SEQ ID NO:175. For example, the heavy chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:171, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:172), CDR2 (SEQ ID NO:173), and CDR3 (SEQ ID NO:174) sequences of SEQ ID NO:171. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:175, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:176), CDR2 (SEQ ID NO:177), and CDR3 (SEQ ID NO:178) sequences of SEQ ID NO:175.

[0060] In some embodiments, the second antigen-binding site can bind to Nectin4 and can incorporate a heavy chain variable domain related to SEQ ID NO:179 and a light chain variable domain related to SEQ ID NO:183. For example, the heavy chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:179, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:180), CDR2 (SEQ ID NO:181), and CDR3 (SEQ ID NO:182) sequences of SEQ ID NO:179. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:183, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:184), CDR2 (SEQ ID NO:185), and CDR3 (SEQ ID NO:186) sequences of SEQ ID NO:183.

[0061] In some embodiments, the second antigen-binding site can bind to fucosyl-GM1 and can incorporate a heavy chain variable domain related to SEQ ID NO:187 and a light chain variable domain related to SEQ ID NO:191. For example, the heavy chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:187, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:188), CDR2 (SEQ ID NO:189), and CDR3 (SEQ ID NO:190) sequences of SEQ ID NO:187. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:191, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:192), CDR2 (SEQ ID NO:193), and CDR3 (SEQ ID NO:194) sequences of SEQ ID NO:191.

[0062] In some embodiments, the second antigen-binding site can bind to SLC44A4 and can incorporate a heavy chain variable domain related to SEQ ID NO:195 and a light chain variable domain related to SEQ ID NO:199. For example, the heavy chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:195, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:196), CDR2 (SEQ ID NO:197), and CDR3 (SEQ ID NO:198) sequences of SEQ ID NO:195. Similarly, the light chain variable domain of the second antigen-binding site can be at least 90% (*e.g.*, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%) identical to SEQ ID NO:199, and/or incorporate amino acid sequences identical to the CDR1 (SEQ ID NO:200), CDR2 (SEQ ID NO:201), and CDR3 (SEQ ID NO:202) sequences of SEQ ID NO:199.

[0063] In some embodiments, the second antigen binding site incorporates a light chain variable domain having an amino acid sequence identical to the amino acid sequence of the light chain variable domain present in the first antigen binding site.

[0064] In some embodiments, the protein incorporates a portion of an antibody Fc domain sufficient to bind CD16, wherein the antibody Fc domain comprises hinge and CH2 domains, and/or amino acid sequences at least 90% identical to amino acid sequence 234-332 of a human IgG antibody.

[0065] Some proteins of the present disclosure bind to NKG2D with a K_D of 10 nM or weaker affinity.

[0066] Formulations containing one of these proteins; cells containing one or more nucleic acids expressing these proteins, and methods of enhancing tumor cell death using these proteins are also provided.

[0067] Another aspect of the invention provides a method of treating cancer in a patient. The method comprises administering to a patient in need thereof a therapeutically effective amount of the multi-specific binding protein described herein. Exemplary cancers for treatment using the multi-specific binding proteins include, for example, head and neck cancer, ovarian cancer, bladder cancer, breast cancer, colorectal cancer, prostate cancer, gastric cancer, liver cancer, esophageal cancer, and lung cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0068] **FIG. 1** is a representation of a heterodimeric, multi-specific antibody (a trispecific binding protein (TriNKET)). Each arm can represent either the NKG2D-binding domain, or the tumor associated antigen-binding domain. In some embodiments, the NKG2D- and the tumor associated antigen- binding domains can share a common light chain.

[0069] **FIG. 2** is a representation of a heterodimeric, multi-specific antibody. Either the NKG2D-binding domain or the tumor associated antigen-binding domain can take the scFv format (right arm).

[0070] **FIG. 3** are line graphs demonstrating the binding affinity of NKG2D-binding domains (listed as clones) to human recombinant NKG2D in an ELISA assay.

[0071] **FIG. 4** are line graphs demonstrating the binding affinity of NKG2D-binding domains (listed as clones) to cynomolgus recombinant NKG2D in an ELISA assay.

[0072] **FIG. 5** are line graphs demonstrating the binding affinity of NKG2D-binding domains (listed as clones) to mouse recombinant NKG2D in an ELISA assay.

[0073] **FIG. 6** are bar graphs demonstrating the binding of NKG2D-binding domains (listed as clones) to EL4 cells expressing human NKG2D by flow cytometry showing mean fluorescence intensity (MFI) fold over background (FOB).

[0074] **FIG. 7** are bar graphs demonstrating the binding of NKG2D-binding domains (listed as clones) to EL4 cells expressing mouse NKG2D by flow cytometry showing mean fluorescence intensity (MFI) fold over background (FOB).

[0075] **FIG. 8** are line graphs demonstrating specific binding affinity of NKG2D-binding domains (listed as clones) to recombinant human NKG2D-Fc by competing with natural ligand ULBP-6.

[0076] **FIG. 9** are line graphs demonstrating specific binding affinity of NKG2D-binding domains (listed as clones) to recombinant human NKG2D-Fc by competing with natural ligand MICA.

[0077] **FIG. 10** are line graphs demonstrating specific binding affinity of NKG2D-binding domains (listed as clones) to recombinant mouse NKG2D-Fc by competing with natural ligand Rae-1 delta.

[0078] **FIG. 11** are bar graphs showing activation of human NKG2D by NKG2D-binding domains (listed as clones) by quantifying the percentage of TNF-α positive cells, which express human NKG2D-CD3 zeta fusion proteins.

[0079] **FIG. 12** are bar graphs showing activation of mouse NKG2D by NKG2D-binding domains (listed as clones) by quantifying the percentage of TNF-α positive cells, which express mouse NKG2D-CD3 zeta fusion proteins.

[0080] **FIG. 13** are bar graphs showing activation of human NK cells by NKG2D-binding domains (listed as clones).

[0081] **FIG. 14** are bar graphs showing activation of human NK cells by NKG2D-binding domains (listed as clones).

[0082] **FIG. 15** are bar graphs showing activation of mouse NK cells by NKG2D-binding domains (listed as clones).

[0083] **FIG. 16** are bar graphs showing activation of mouse NK cells by NKG2D-binding domains (listed as clones).

[0084] **FIG. 17** are bar graphs showing the cytotoxic effect of NKG2D-binding domains (listed as clones) on tumor cells.

[0085] **FIG. 18** are bar graphs showing the melting temperature of NKG2D-binding domains (listed as clones) measured by differential scanning fluorimetry.

[0086] **FIGs. 19A-19C** are bar graphs of synergistic activation of NK cells using CD16 and NKG2D-binding. FIG. 19A demonstrates levels of CD107a; FIG. 19B demonstrates levels of IFN-γ; FIG. 19C demonstrates levels of CD107a and IFN-γ. Graphs indicate the mean (n = 2) ± SD. Data are representative of five independent experiments using five different healthy donors.

[0087] **FIG. 20** is a representation of a trispecific binding protein (TriNKET) in the Triomab form, which is a trifunctional, bispecific antibody that maintains an IgG-like shape. This chimera consists of two half antibodies, each with one light and one heavy chain, that originate from two parental antibodies. Triomab form may be a heterodimeric construct containing 1/2 of rat antibody and 1/2 of mouse antibody.

[0088] **FIG. 21** is a representation of a TriNKET in the KiH Common Light Chain form, which involves the knobs-into-holes (KIHs) technology. KiH is a heterodimer containing 2 Fab fragments binding to target 1 and 2, and an Fc stabilized by heterodimerization mutations. TriNKET in the KiH format may be a heterodimeric construct with 2 Fab fragments binding to target 1 and target 2, containing two different heavy chains and a common light chain that pairs with both heavy chains.

[0089] **FIG. 22** is a representation of a TriNKET in the dual-variable domain immunoglobulin (DVD-Ig™) form, which combines the target-binding domains of two monoclonal antibodies via flexible naturally occurring linkers, and yields a tetravalent IgG-like molecule. DVD-Ig™ is a homodimeric construct where variable domain targeting antigen 2 is fused to the N-terminus of a variable domain of Fab fragment targeting antigen 1. DVD-Ig™ form contains normal Fc.

[0090] **FIG. 23** is a representation of a TriNKET in the Orthogonal Fab interface (Ortho-Fab) form, which is a heterodimeric construct that contains 2 Fab fragments binding to target 1 and target 2 fused to Fc. Light chain (LC)-heavy chain (HC) pairing is ensured by orthogonal interface. Heterodimerization is ensured by mutations in the Fc.

[0091] **FIG. 24** is a representation of a TriNKET in the 2-in-1 Ig format.

[0092] **FIG. 25** is a representation of a TriNKET in the ES form, which is a heterodimeric construct containing two different Fab fragments binding to target 1 and target 2 fused to the Fc. Heterodimerization is ensured by electrostatic steering mutations in the Fc.

[0093] **FIG. 26** is a representation of a TriNKET in the Fab fragment Arm Exchange form: antibodies that exchange Fab arms by swapping a heavy chain and attached light chain (half-molecule) with a heavy-light chain pair from another molecule, resulting in bispecific antibodies. Fab Arm Exchange form (cFae) is a heterodimer containing 2 Fab fragments binding to target 1 and 2, and an Fc stabilized by heterodimerization mutations.

[0094] **FIG. 27** is a representation of a TriNKET in the SEED Body form, which is a heterodimer containing 2 Fab fragments binding to target 1 and 2, and an Fc stabilized by heterodimerization mutations.

[0095] **FIG. 28** is a representation of a TriNKET in the LuZ-Y form, in which a leucine zipper is used to induce heterodimerization of two different HCs. The LuZ-Y form is a heterodimer containing two different scFabs binding to target 1 and 2, fused to Fc. Heterodimerization is ensured through leucine zipper motifs fused to C-terminus of Fc.

[0096] **FIG. 29** is a representation of a TriNKET in the Cov-X-Body form.

[0097] **FIGs. 30A and 30B** are representations of TriNKETs in the κλ-Body forms, which are heterodimeric constructs with two different Fab fragments fused to Fc stabilized by heterodimerization mutations: one Fab fragment targeting antigen 1 contains kappa LC, and the second Fab fragment targeting antigen 2 contains lambda LC. FIG. 30A is an exemplary representation of one form of a κλ-Body; FIG. 30B is an exemplary representation of another κλ-Body.

[0098] **FIG. 31** is an Oasc-Fab heterodimeric construct that includes Fab fragment binding to target 1 and scFab binding to target 2, both of which are fused to the Fc domain. Heterodimerization is ensured by mutations in the Fc domain.

[0099] **FIG. 32** is a DuetMab, which is a heterodimeric construct containing two different Fab fragments binding to antigens 1 and 2, and an Fc that is stabilized by heterodimerization mutations. Fab fragments 1 and 2 contain differential S-S bridges that ensure correct light chain and heavy chain pairing.

[0100] **FIG. 33** is a CrossmAb, which is a heterodimeric construct with two different Fab fragments binding to targets 1 and 2, and an Fc stabilized by heterodimerization mutations.

CL and CH1 domains, and VH and VL domains are switched, *e.g.*, CH1 is fused in-line with VL, while CL is fused in-line with VH.

[0101] **FIG. 34** is a Fit-Ig, which is a homodimeric construct where Fab fragment binding to antigen 2 is fused to the N-terminus of HC of Fab fragment that binds to antigen 1. The construct contains wild-type Fc.

[0102] **FIG. 35** illustrates a trispecific antibody (TriNKET) that contains a tumor-associated antigen-binding scFv, a NKG2D-targeting Fab, and a heterodimerized antibody constant region/domain ("CD domain") that binds CD16 (scFv-Fab format). The antibody format is referred herein as F3'-TriNKET.

[0103] **FIG. 36** illustrates an exemplary trispecific antibodies (TriNKET), which includes an scFv first antigen-binding site that binds NKG2D, a second antigen-binding site that binds a tumor-associated antigen-binding (*e.g.*, EpCAM), an additional tumor-associated antigen-binding site that binds a tumor-associated antigen-binding (*e.g.*, EpCAM), and a heterodimerized antibody constant region that binds CD16. These antibody formats are referred herein as F4-TriNKET.

[0104] **FIG. 37** are line graphs demonstrating that TriNKETs and mAb bind to EpCAM expressed on H747 human colorectal cancer cells.

[0105] **FIG. 38** are line graphs demonstrating that TriNKETs and mAb bind to EpCAM expressed on HCC827 human lung cancer cells.

[0106] **FIG. 39** are line graphs demonstrating that TriNKETs and mAb bind to EPCAM expressed on HCT116 human colorectal cancer cells.

[0107] **FIG. 40A** and **FIG. 40B** are line graphs showing TriNKET-mediated killing of H747 cells with rested human NK cells from two different donors. The effector-to-target ratio was 10:1.

[0108] **FIG. 41A** and **FIG. 41B** are line graphs showing TriNKET-mediated killing of HCC827 cells with rested human NK cells from two different donors. The effector-to-target ratio was 10:1.

[0109] **FIG. 42A** and **FIG. 42B** are line graphs showing TriNKET-mediated killing of MCF7 cells with rested human NK cells from two different donors. The effector-to-target ratio was 10:1.

[0110] **FIG 43A** and **FIG. 43B** are line graphs showing TriNKET-mediated killing of HCT116 cells with rested human NK cells from two different donors. The effector-to-target ratio was 10:1.

DETAILED DESCRIPTION

[0111] The invention provides multi-specific binding proteins that bind EPCAM on a cancer cell and the NKG2D receptor and CD16 receptor on natural killer cells to activate the natural killer cells, pharmaceutical compositions comprising such multi-specific binding proteins, and therapeutic methods using such multi-specific proteins and pharmaceutical compositions, including for the treatment of cancer. Various aspects of the invention are set forth below in sections; however, aspects of the invention described in one particular section are not to be limited to any particular section.

[0112] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0113] The terms “a” and “an” as used herein mean “one or more” and include the plural unless the context is inappropriate.

[0114] As used herein, the term "antigen-binding site" refers to the part of the immunoglobulin molecule that participates in antigen binding. In human antibodies, the antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as "framework regions," or "FR". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In a human antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs." In certain animals, such as camels and cartilaginous fish, the antigen-binding site is formed by a single antibody chain providing a “single domain antibody.” Antigen-binding sites can exist in an intact antibody, in an antigen-binding fragment of an antibody that retains the antigen-binding surface, or in a recombinant polypeptide such as an scFv, using a peptide linker to

connect the heavy chain variable domain to the light chain variable domain in a single polypeptide.

[0115] The term "tumor associated antigen" as used herein means any antigen including but not limited to a protein, glycoprotein, ganglioside, carbohydrate, lipid that is associated with cancer. Such antigen can be expressed on malignant cells or in the tumor microenvironment such as on tumor-associated blood vessels, extracellular matrix, mesenchymal stroma, or immune infiltrates.

[0116] As used herein, the terms "subject" and "patient" refer to an organism to be treated by the methods and compositions described herein. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and more preferably include humans.

[0117] As used herein, the term "effective amount" refers to the amount of a compound (*e.g.*, a compound of the present invention) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. As used herein, the term "treating" includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof.

[0118] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0119] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, s*ee e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0120] As used herein, the term "pharmaceutically acceptable salt" refers to any pharmaceutically acceptable salt (*e.g.*, acid or base) of a compound of the present invention which, upon administration to a subject, is capable of providing a compound of this invention or an active metabolite or residue thereof. As is known to those of skill in the art, "salts" of the compounds of the present invention may be derived from inorganic or organic acids and

bases. Exemplary acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0121] Exemplary bases include, but are not limited to, alkali metal (*e.g.*, sodium) hydroxides, alkaline earth metal (*e.g.*, magnesium) hydroxides, ammonia, and compounds of formula NW_4^+, wherein W is C_{1-4} alkyl, and the like.

[0122] Exemplary salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention compounded with a suitable cation such as Na^+, NH_4^+, and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like.

[0123] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0124] Throughout the description, where compositions are described as having, including, or comprising specific components, or where processes and methods are described as having, including, or comprising specific steps, it is contemplated that, additionally, there are compositions of the present invention that consist essentially of, or consist of, the recited components, and that there are processes and methods according to the present invention that consist essentially of, or consist of, the recited processing steps.

[0125] As a general matter, compositions specifying a percentage are by weight unless otherwise specified. Further, if a variable is not accompanied by a definition, then the previous definition of the variable controls.

I. PROTEINS

[0126] The invention provides multi-specific binding proteins that bind to the NKG2D receptor and CD16 receptor on natural killer cells, and the tumor-associated antigen selected from any one of the antigens provided in Table 11. The multi-specific binding proteins are useful in the pharmaceutical compositions and therapeutic methods described herein. Binding of the multi-specific binding proteins to the NKG2D receptor and CD16 receptor on a natural killer cell enhances the activity of the natural killer cell toward destruction of tumor cells expressing the tumor-associated antigen selected from any one of the antigens provided in Table 11. Binding of the multi-specific binding proteins to tumor-associated antigen-expressing cells brings the cancer cells into proximity with the natural killer cell, which facilitates direct and indirect destruction of the cancer cells by the natural killer cell. Further description of some exemplary multi-specific binding proteins is provided below.

[0127] The first component of the multi-specific binding proteins binds to NKG2D receptor-expressing cells, which can include but are not limited to NK cells, γδ T cells and $CD8^+$ αβ T cells. Upon NKG2D binding, the multi-specific binding proteins may block natural ligands, such as ULBP6 (UL16 binding protein 6) and MICA (Major Histocompatibility Complex Class I Chain-Related A), from binding to NKG2D and activating NKG2D receptors.

[0128] The second component of the multi-specific binding proteins binds a tumor-associated antigen selected from any one of the antigens provided in Table 11. The tumor-associated antigen-expressing cells, which may be found in leukemias such as, for example, acute myeloid leukemia and T-cell leukemia.

[0129] The third component for the multi-specific binding proteins binds to cells expressing CD16, an Fc receptor on the surface of leukocytes including natural killer cells, macrophages, neutrophils, eosinophils, mast cells, and follicular dendritic cells.

[0130] The multi-specific binding proteins described herein can take various formats. For example, one format is a heterodimeric, multi-specific antibody including a first immunoglobulin heavy chain, a first immunoglobulin light chain, a second immunoglobulin heavy chain and a second immunoglobulin light chain (FIG. 1). The first immunoglobulin

heavy chain includes a first Fc (hinge-CH2-CH3) domain, a first heavy chain variable domain and optionally a first CH1 heavy chain domain. The first immunoglobulin light chain includes a first light chain variable domain and a first light chain constant domain. The first immunoglobulin light chain, together with the first immunoglobulin heavy chain, forms an antigen-binding site that binds NKG2D. The second immunoglobulin heavy chain comprises a second Fc (hinge-CH2-CH3) domain, a second heavy chain variable domain and optionally a second CH1 heavy chain domain. The second immunoglobulin light chain includes a second light chain variable domain and a second light chain constant domain. The second immunoglobulin light chain, together with the second immunoglobulin heavy chain, forms an antigen-binding site that binds a tumor-associated antigen selected from any one of the antigens provided in Table 11. The first Fc domain and second Fc domain together are able to bind to CD16 (FIG. 1). In some embodiments, the first immunoglobulin light chain is identical to the second immunoglobulin light chain.

[0131] Another exemplary format involves a heterodimeric, multi-specific antibody including a first immunoglobulin heavy chain, a second immunoglobulin heavy chain and an immunoglobulin light chain (FIG. 2). The first immunoglobulin heavy chain includes a first Fc (hinge-CH2-CH3) domain fused via either a linker or an antibody hinge to a single-chain variable fragment (scFv) composed of a heavy chain variable domain and light chain variable domain which pair and bind NKG2D, or bind a tumor-associated antigen selected from any one of the antigens provided in Table 11. The second immunoglobulin heavy chain includes a second Fc (hinge-CH2-CH3) domain, a second heavy chain variable domain and optionally a CH1 heavy chain domain. The immunoglobulin light chain includes a light chain variable domain and a light chain constant domain. The second immunoglobulin heavy chain pairs with the immunoglobulin light chain and binds to NKG2D or binds a tumor-associated antigen selected from any one of the antigens provided in Table 11. The first Fc domain and the second Fc domain together are able to bind to CD16 (FIG. 2).

[0132] One or more additional binding motifs may be fused to the C-terminus of the constant region CH3 domain, optionally via a linker sequence. In certain embodiments, the antigen-binding motif is a single-chain or disulfide-stabilized variable region (scFv) forming a tetravalent or trivalent molecule.

[0133] In some embodiments, the multi-specific binding protein is in the Triomab form, which is a trifunctional, bispecific antibody that maintains an IgG-like shape. This chimera

consists of two half antibodies, each with one light and one heavy chain, that originate from two parental antibodies.

[0134] In some embodiments, the multi-specific binding protein is the KiH Common Light Chain (LC) form, which involves the knobs-into-holes (KIHs) technology. The KIH involves engineering C_H3 domains to create either a "knob" or a "hole" in each heavy chain to promote heterodimerization. The concept behind the "Knobs-into-Holes (KiH)" Fc technology was to introduce a "knob" in one CH3 domain (CH3A) by substitution of a small residue with a bulky one (*e.g.*, $T366W_{CH3A}$ in EU numbering). To accommodate the "knob," a complementary "hole" surface was created on the other CH3 domain (CH3B) by replacing the closest neighboring residues to the knob with smaller ones (*e.g.*, $T366S/L368A/Y407V_{CH3B}$). The "hole" mutation was optimized by structured-guided phage library screening (Atwell S, Ridgway JB, Wells JA, Carter P., Stable heterodimers from remodeling the domain interface of a homodimer using a phage display library, *J. Mol. Biol.* (1997) 270(1):26–35). X-ray crystal structures of KiH Fc variants (Elliott JM, Ultsch M, Lee J, Tong R, Takeda K, Spiess C, *et al.*, Antiparallel conformation of knob and hole aglycosylated half-antibody homodimers is mediated by a CH2-CH3 hydrophobic interaction. *J. Mol. Biol.* (2014) 426(9):1947–57; Mimoto F, Kadono S, Katada H, Igawa T, Kamikawa T, Hattori K. Crystal structure of a novel asymmetrically engineered Fc variant with improved affinity for FcγRs. *Mol. Immunol.* (2014) 58(1):132–8) demonstrated that heterodimerization is thermodynamically favored by hydrophobic interactions driven by steric complementarity at the inter-CH3 domain core interface, whereas the knob–knob and the hole–hole interfaces do not favor homodimerization owing to steric hindrance and disruption of the favorable interactions, respectively.

[0135] In some embodiments, the multi-specific binding protein is in the dual-variable domain immunoglobulin (DVD-Ig™) form, which combines the target binding domains of two monoclonal antibodies via flexible naturally occurring linkers, and yields a tetravalent IgG-like molecule.

[0136] In some embodiments, the multi-specific binding protein is in the Orthogonal Fab interface (Ortho-Fab) form. In the ortho-Fab IgG approach (Lewis SM, Wu X, Pustilnik A, Sereno A, Huang F, Rick HL, *et al.*, Generation of bispecific IgG antibodies by structure-based design of an orthogonal Fab interface. *Nat. Biotechnol.* (2014) 32(2):191–8), structure-based regional design introduces complementary mutations at the LC and $HC_{VH\text{-}CH1}$ interface in only one Fab fragment, without any changes being made to the other Fab fragment.

[0137] In some embodiments, the multi-specific binding protein is in the 2-in-1 Ig format. In some embodiments, the multi-specific binding protein is in the ES form, which is a heterodimeric construct containing two different Fab fragments binding to targets 1 and target 2 fused to the Fc. Heterodimerization is ensured by electrostatic steering mutations in the Fc.

[0138] In some embodiments, the multi-specific binding protein is in the κλ-Body form, which is a heterodimeric construct with two different Fab fragments fused to Fc stabilized by heterodimerization mutations: Fab fragment1 targeting antigen 1 contains kappa LC, while second Fab fragment targeting antigen 2 contains lambda LC. FIG. 30A is an exemplary representation of one form of a κλ-Body; FIG. 30B is an exemplary representation of another κλ-Body.

[0139] In some embodiments, the multi-specific binding protein is in Fab Arm Exchange form (antibodies that exchange Fab arms by swapping a heavy chain and attached light chain (half-molecule) with a heavy-light chain pair from another molecule, which results in bispecific antibodies).

[0140] In some embodiments, the multi-specific binding protein is in the SEED Body form. The strand-exchange engineered domain (SEED) platform was designed to generate asymmetric and bispecific antibody-like molecules, a capability that expands therapeutic applications of natural antibodies. This protein engineered platform is based on exchanging structurally related sequences of immunoglobulin within the conserved CH3 domains. The SEED design allows efficient generation of AG/GA heterodimers, while disfavoring homodimerization of AG and GA SEED CH3 domains. (Muda M. *et al.*, *Protein Eng. Des. Sel.* (2011, 24(5):447-54)).

[0141] In some embodiments, the multi-specific binding protein is in the LuZ-Y form, in which a leucine zipper is used to induce heterodimerization of two different HCs. (Wranik, BJ. *et al.*, *J. Biol. Chem.* (2012), 287:43331-9).

[0142] In some embodiments, the multi-specific binding protein is in the Cov-X-Body form. In bispecific CovX-Bodies, two different peptides are joined together using a branched azetidinone linker and fused to the scaffold antibody under mild conditions in a site-specific manner. Whereas the pharmacophores are responsible for functional activities, the antibody scaffold imparts long half-life and Ig-like distribution. The pharmacophores can be chemically optimized or replaced with other pharmacophores to generate optimized or unique bispecific antibodies. (Doppalapudi VR *et al.*, *PNAS* (2010), 107(52);22611-22616).

[0143] In some embodiments, the multi-specific binding protein is in an Oasc-Fab heterodimeric form that includes Fab fragment binding to target 1, and scFab binding to target 2 fused to Fc. Heterodimerization is ensured by mutations in the Fc.

[0144] In some embodiments, the multi-specific binding protein is in a DuetMab form, which is a heterodimeric construct containing two different Fab fragments binding to antigens 1 and 2, and Fc stabilized by heterodimerization mutations. Fab fragments 1 and 2 contain differential S-S bridges that ensure correct LC and HC pairing.

[0145] In some embodiments, the multi-specific binding protein is in a CrossmAb form, which is a heterodimeric construct with two different Fab fragments binding to targets 1 and 2, fused to Fc stabilized by heterodimerization. CL and CH1 domains and VH and VL domains are switched, *e.g.*, CH1 is fused in-line with VL, while CL is fused in-line with VH.

[0146] In some embodiments, the multi-specific binding protein is in a Fit-Ig form, which is a homodimeric construct where Fab fragment binding to antigen 2 is fused to the N terminus of HC of Fab fragment that binds to antigen 1. The construct contains wild-type Fc.

[0147] Table 1 lists peptide sequences of heavy chain variable domains and light chain variable domains that, in combination, can bind to NKG2D. The NKG2D binding domains can vary in their binding affinity to NKG2D, nevertheless, they all activate human NKG2D and NK cells.

Table 1		
Clone	Heavy chain variable region amino acid sequence	Light chain variable region amino acid sequence
ADI-27705	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:1) CDR1 (SEQ ID NO:105) – GSFSGYYWS CDR2 (SEQ ID NO:106) – EIDHSGSTNYNPSLKS	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYNSYPITFGGGTKVEIK (SEQ ID NO:2)

	CDR3 (SEQ ID NO:107) – ARARGPWSFDP	
ADI-27724	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:3)	EIVLTQSPGTLSLSPGERATLS CRASQSVSSSYLAWYQQKPG QAPRLLIYGASSRATGIPDRFS GSGSGTDFTLTISRLEPEDFAV YYCQQYGSSPITFGGGTKVEI K (SEQ ID NO:4)
ADI-27740 (A40)	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:5)	DIQMTQSPSTLSASVGDRVTIT CRASQSIGSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYHSFYTFGGGTKVEIK (SEQ ID NO:6)
ADI-27741	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:7)	DIQMTQSPSTLSASVGDRVTIT CRASQSIGSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQSNSYYTFGGGTKVEIK (SEQ ID NO:8)
ADI-27743	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:9)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYNSYPTFGGGTKVEIK (SEQ ID NO:10)
ADI-28153	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWGFDPWGQGTLVTVSS	ELQMTQSPSSLSASVGDRVTIT CRTSQSISSYLNWYQQKPGQP PKLLIYWASTRESGVPDRFSGS GSGTDFTLTISSLQPEDSATYY CQQSYDIPYTFGQGTKLEIK

	(SEQ ID NO:11)	(SEQ ID NO:12)
ADI-28226 (C26)	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:13)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYGSFPITFGGGTKVEIK (SEQ ID NO:14)
ADI-28154	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:15)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTDFTLTISSLQPDDFATY YCQQSKEVPWTFGQGTKVEIK (SEQ ID NO:16)
ADI-29399	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:17)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYNSFPTFGGGTKVEIK (SEQ ID NO:18)
ADI-29401	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:19)	DIQMTQSPSTLSASVGDRVTIT CRASQSIGSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYDIYPTFGGGTKVEIK (SEQ ID NO:20)
ADI-29403	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:21)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYDSYPTFGGGTKVEIK (SEQ ID NO:22)
ADI-29405	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK

	GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:23)	APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYGSFPTFGGGTKVEIK (SEQ ID NO:24)
ADI- 29407	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:25)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYQSFPTFGGGTKVEIK (SEQ ID NO:26)
ADI- 29419	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:27)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYSSFSTFGGGTKVEIK (SEQ ID NO:28)
ADI- 29421	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:29)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYESYSTFGGGTKVEIK (SEQ ID NO:30)
ADI- 29424	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:31)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYDSFITFGGGTKVEIK (SEQ ID NO:32)
ADI- 29425	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYQSYPTFGGGTKVEIK

	(SEQ ID NO:33)	(SEQ ID NO:34)
ADI-29426	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:35)	DIQMTQSPSTLSASVGDRVTIT CRASQSIGSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYHSFPTFGGGTKVEIK (SEQ ID NO:36)
ADI-29429	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:37)	DIQMTQSPSTLSASVGDRVTIT CRASQSIGSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYELYSYTFGGGTKVEIK (SEQ ID NO:38)
ADI-29447 (F47)	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:39)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCQQYDTFITFGGGTKVEIK (SEQ ID NO:40)
ADI-27727	QVQLVQSGAEVKKPGSSVKVSCKA SGGTFSSYAISWVRQAPGQGLEWM GGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCAR GDSSIRHAYYYYGMDVWGQGTTV TVSS (SEQ ID NO:41) CDR1 (SEQ ID NO:43) – GTFSSYAIS CDR2 (SEQ ID NO:44) – GIIPIFGTANYAQKFQG CDR3 (SEQ ID NO:45) – ARGDSSIRHAYYYYGMDV	DIVMTQSPDSLAVSLGERATIN CKSSQSVLYSSNNKNYLAWY QQKPGQPPKLLIYWASTRESG VPDRFSGSGSGTDFTLTISSLQ AEDVAVYYCQQYYSTPITFGG GTKVEIK (SEQ ID NO:42) CDR1 (SEQ ID NO:46) – KSSQSVLYSSNNKNYLA CDR2 (SEQ ID NO:47) – WASTRES CDR3 (SEQ ID NO:48) – QQYYSTPIT

ADI-29443 (F43)	QLQLQESGPGLVKPSETLSLTCTVS GGSISSSSYYWGWIRQPPGKGLEWI GSIYYSGSTYYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARG SDRFHPYFDYWGQGTLVTVSS (SEQ ID NO:49) CDR1 (SEQ ID NO:51) – GSISSSSYYWG CDR2 (SEQ ID NO:52) – SIYYSGSTYYNPSLKS CDR3 (SEQ ID NO:53) – ARGSDRFHPYFDY	EIVLTQSPATLSLSPGERATLS CRASQSVSRYLAWYQQKPGQ APRLLIYDASNRATGIPARFSG SGSGTDFTLTISSLEPEDFAVY YCQQFDTWPPTFGGGTKVEIK (SEQ ID NO:50) CDR1 (SEQ ID NO:54) – RASQSVSRYLA CDR2 (SEQ ID NO:55) – DASNRAT CDR3 (SEQ ID NO:56) – QQFDTWPPT
ADI-29404 (F04)	QVQLQQWGAGLLKPSETLSLTCAV YGGSFSGYYWSWIRQPPGKGLEWI GEIDHSGSTNYNPSLKSRVTISVDTS KNQFSLKLSSVTAADTAVYYCARA RGPWSFDPWGQGTLVTVSS (SEQ ID NO:57)	DIQMTQSPSTLSASVGDRVTIT CRASQSISSWLAWYQQKPGK APKLLIYKASSLESGVPSRFSG SGSGTEFTLTISSLQPDDFATY YCEQYDSYPTFGGGTKVEIK (SEQ ID NO:58)
ADI-28200	QVQLVQSGAEVKKPGSSVKVSCKA SGGTFSSYAISWVRQAPGQGLEWM GGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCAR RGRKASGSFYYYYGMDVWGQGTT VTVSS (SEQ ID NO:59) CDR1 (SEQ ID NO:109) – GTFSSYAIS CDR2 (SEQ ID NO:110) – GIIPIFGTANYAQKFQG CDR3 (SEQ ID NO:111) – ARRGRKASGSFYYYYGMDV	DIVMTQSPDSLAVSLGERATIN CESSQSLLNSGNQKNYLTWY QQKPGQPPKPLIYWASTRESG VPDRFSGSGSGTDFTLTISSLQ AEDVAVYYCQNDYSYPYTFG QGTKLEIK (SEQ ID NO:60) CDR1 (SEQ ID NO:112) – ESSQSLLNSGNQKNYLT CDR2 (SEQ ID NO:113) – WASTRES CDR3 (SEQ ID NO:114) – QNDYSYPYT
ADI-	QVQLVQSGAEVKKPGASVKVSCK	EIVMTQSPATLSVSPGERATLS

29379 (E79)	ASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYY CARGAPNYGDTTHDYYYMDVWG KGTTVTVSS (SEQ ID NO:61) CDR1 (SEQ ID NO:63) - YTFTSYYMH CDR2 (SEQ ID NO:64) - IINPSGGSTSYAQKFQG CDR3 (SEQ ID NO:65) - ARGAPNYGDTTHDYYYMDV	CRASQSVSSNLAWYQQKPGQ APRLLIYGASTRATGIPARFSG SGSGTEFTLTISSLQSEDFAVY YCQQYDDWPFTFGGGTKVEI K (SEQ ID NO:62) CDR1 (SEQ ID NO:66) - RASQSVSSNLA CDR2 (SEQ ID NO:67) - GASTRAT CDR3 (SEQ ID NO:68) - QQYDDWPFT
ADI-29463 (F63)	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTGYYMHWVRQAPGQGLE WMGWINPNSGGTNYAQKFQGRVT MTRDTSISTAYMELSRLRSDDTAV YYCARDTGEYYDTDDHGMDVWG QGTTVTVSS (SEQ ID NO:69) CDR1 (SEQ ID NO:71) - YTFTGYYMH CDR2 (SEQ ID NO:72) - WINPNSGGTNYAQKFQG CDR3 (SEQ ID NO:73) - ARDTGEYYDTDDHGMDV	EIVLTQSPGTLSLSPGERATLS CRASQSVSSNLAWYQQKPGQ APRLLIYGASTRATGIPARFSG SGSGTEFTLTISSLQSEDFAVY YCQQDDYWPPTFGGGTKVEI K (SEQ ID NO:70) CDR1 (SEQ ID NO:74) - RASQSVSSNLA CDR2 (SEQ ID NO:75) - GASTRAT CDR3 (SEQ ID NO:76) - QQDDYWPPT
ADI-27744 (A44)	EVQLLESGGGLVQPGGSLRLSCAAS GFTFSSYAMSWVRQAPGKGLEWV SAISGSGGSTYYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYC AKDGGYYDSGAGDYWGQGTLVTV SS (SEQ ID NO:77) CDR1 (SEQ ID NO:79) - FTFSSYAMS	DIQMTQSPSSVSASVGDRVTIT CRASQGIDSWLAWYQQKPGK APKLLIYAASSLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATY YCQQGVSYPRTFGGGTKVEIK (SEQ ID NO:78) CDR1 (SEQ ID NO:82) - RASQGIDSWLA

	CDR2 (SEQ ID NO:80) - AISGSGGSTYYADSVKG CDR3 (SEQ ID NO:81) - AKDGGYYDSGAGDY	CDR2 (SEQ ID NO:83) - AASSLQS CDR3 (SEQ ID NO:84) - QQGVSYPRT
ADI-27749 (A49)	EVQLVESGGGLVKPGGSLRLSCAA SGFTFSSYSMNWVRQAPGKGLEW VSSISSSSSYIYYADSVKGRFTISRD NAKNSLYLQMNSLRAEDTAVYYC ARGAPMGAAAGWFDPWGQGTLVT VSS (SEQ ID NO:85) CDR1 (SEQ ID NO:87) - FTFSSYSMN CDR2 (SEQ ID NO:88) - SISSSSSYIYYADSVKG CDR3 (SEQ ID NO:89) - ARGAPMGAAAGWFDP	DIQMTQSPSSVSASVGDRVTIT CRASQGISSWLAWYQQKPGK APKLLIYAASSLQSGVPSRFSG SGSGTDFTLTISSLQPEDFATY YCQQGVSFPRTFGGGTKVEIK (SEQ ID NO:86) CDR1 (SEQ ID NO:90) - RASQGISSWLA CDR2 (SEQ ID NO:91) - AASSLQS CDR3 (SEQ ID NO:92) - QQGVSFPRT
ADI-29378 (E78)	QVQLVQSGAEVKKPGASVKVSCK ASGYTFTSYYMHWVRQAPGQGLE WMGIINPSGGSTSYAQKFQGRVTM TRDTSTSTVYMELSSLRSEDTAVYY CAREGAGFAYGMDYYYMDVWGK GTTVTVSS (SEQ ID NO:93) CDR1 (SEQ ID NO:95) - YTFTSYYMH CDR2 (SEQ ID NO:96) - IINPSGGSTSYAQKFQG CDR3 (SEQ ID NO:97) - AREGAGFAYGMDYYYMDV	EIVLTQSPATLSLSPGERATLS CRASQSVSSYLAWYQQKPGQ APRLLIYDASNRATGIPARFSG SGSGTDFTLTISSLEPEDFAVY YCQQSDNWPFTFGGGTKVEIK (SEQ ID NO:94) CDR1 (SEQ ID NO:98) - RASQSVSSYLA CDR2 (SEQ ID NO:99) - DASNRAT CDR3 (SEQ ID NO:100) - QQSDNWPFT

[0148] Alternatively, a heavy chain variable domain represented by SEQ ID NO:101 can be paired with a light chain variable domain represented by SEQ ID NO:102 to form an antigen-binding site that can bind to NKG2D, as illustrated in US 9,273,136.

SEQ ID NO:101

QVQLVESGGGLVKPGGSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFI
RYDGSNKYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDRGL
GDGTYFDYWGQGTTVTVSS

SEQ ID NO:102

QSALTQPASVSGSPGQSITISCSGSSSNIGNNAVNWYQQLPGKAPKLLIYYDDL
LPSGVSDRFSGSKSGTSAFLAISGLQSEDEADYYCAAWDDSLNGPVFGGGTK
LTVL

[0149] Alternatively, a heavy chain variable domain represented by SEQ ID NO:103 can be paired with a light chain variable domain represented by SEQ ID NO:104 to form an antigen-binding site that can bind to NKG2D, as illustrated in US 7,879,985.

SEQ ID NO:103

QVHLQESGPGLVKPSETLSLTCTVSDDSISSYYWSWIRQPPGKGLEWIGHISYS
GSANYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCANWDDAFNIWG
QGTMVTVSS

SEQ ID NO:104

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASS
RATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK

[0150] Table 2 lists peptide sequences of heavy chain variable domains and light chain variable domains that, in combination, can bind to EpCAM.

Table 2		
Clones	Heavy chain variable domain amino acid sequence	Light chain variable domain amino acid sequence
Oportuzumab	EVQLVQSGPGLVQPGGSVRISCA ASGYTFTNYGMNWVKQAPGKGL EWMGWINTYTGESTYADSFKGRF TFSLDTSASAAYLQINSLRAEDTA VYYCARFAIKGDYWGQGTLLTVS	DIQMTQSPSSLSASVGDRVTITCRS TKSLLHSNGITYLYWYQQKPGKAP KLLIYQMSNLASGVPSRFSSSGSGT DFTLTISSLQPEDFATYYCAQNLEI PRTFGQGTKVELKR

	SE (SEQ ID NO:115) CDR1 (SEQ ID NO:116) - GYTFTNY CDR2 (SEQ ID NO:117) - NTYTGE CDR3 (SEQ ID NO:118) - FAIKGDY	(SEQ ID NO:119) CDR1(SEQ ID NO:120) - KSLLHSNGITYLY CDR2 (SEQ ID NO:121) - QMSNLAS CDR3 (SEQ ID NO:122) - AQNLEIPRT
Adecatumumab	EVQLLESGGGVVQPGRSLRLSCA ASGFTFSSYGMHWVRQAPGKGL EWVAVISYDGSNKYYADSVKGR FTISRDNSKNTLYLQMNSLRAEDT AVYYCAKDMGWGSGWRPYYYY GMDVWGQGTTVTVSSA (SEQ ID NO:123) CDR1 (SEQ ID NO:124) - GFTFSSY CDR2 (SEQ ID NO:125) - SYDGSN CDR3 (SEQ ID NO:126) - DMGWGSGWRPYYYYGMDV	ELQMTQSPSSLSASVGDRVTITCRT SQSISSYLNWYQQKPGQPPKLLIY WASTRESGVPDRFSGSGSGTDFTL TISSLQPEDSATYYCQQSYDIPYTF GQGTKLEIKR (SEQ ID NO:127) CDR1 (SEQ ID NO:128) - QSISSYLN CDR2 (SEQ ID NO:129) - WASTRES CDR3 (SEQ ID NO:130) - QQSYDIPYT
Citatuzumab	EVQLVQSGPGLVQPGGSVRISCA ASGYTFTNYGMNWVKQAPGKGL EWMGWINTYTGESTYADSFKGRF TFSLDTSASAAYLQINSLRAEDTA VYYCARFAIKGDYWGQGTLLTVS SA (SEQ ID NO:131) CDR1 (SEQ ID NO:132) - GYTFTNY CDR2 (SEQ ID NO:133) - NTYTGE CDR3 (SEQ ID NO:134) - FAIKGDY	DIQMTQSPSSLSASVGDRVTITCRS TKSLLHSNGITYLYWYQQKPGKAP KLLIYQMSNLASGVPSRFSSSGSGT DFTLTISSLQPEDFATYYCAQNLEI PRTFGQGTKVELKR (SEQ ID NO:135) CDR1 (SEQ ID NO:136) - KSLLHSNGITYLY CDR2 (SEQ ID NO:137) - QMSNLAS CDR3 (SEQ ID NO:138) - AQNLEIPRT
Solitomab (MT110)	EVQLLEQSGAELVRPGTSVKISCK ASGYAFTNYWLGWVKQRPGHGL EWIGDIFPGSGNIHYNEKFKGKAT LTADKSSSTAYMQLSSLTFEDSAV YFCARLRNWDEPMDYWGQGTTV	ELVMTQSPSSLTVTAGEKVTMSCK SSQSLLNSGNQKNYLTWYQQKPG QPPKLLIYWASTRESGVPDRFTGS GSGTDFTLTISSVQAEDLAVYYCQ NDYSYPLTFGAGTKLEIKG

	TVSS (SEQ ID NO:139) CDR1 (SEQ ID NO:140) - GYAFTNY CDR2 (SEQ ID NO:141) - FPGSGN CDR3 (SEQ ID NO:142) - LRNWDEPMDY	(SEQ ID NO:143) CDR1 (SEQ ID NO:144) - QSLLNSGNQKNYLT CDR2 (SEQ ID NO:145) - WASTRES CDR3 (SEQ ID NO:146) - QNDYSYPLT

[0151] Alternatively, novel antigen-binding sites that can bind to EpCAM can be identified by screening for binding to the amino acid sequence defined by SEQ ID NO:147.

SEQ ID NO:147

MAPPQVLAFGLLLAAATATFAAAQEECVCENYKLAVNCFVNNNRQCQCTSVGAQN
TVICSKLAAKCLVMKAEMNGSKLGRRAKPEGALQNNDGLYDPDCDESGLFKAKQC
NGTSMCWCVNTAGVRRTDKDTEITCSERVRTYWIIIELKHKAREKPYDSKSLRTALQ
KEITTRYQLDPKFITSILYENNVITIDLVQNSSQKTQNDVDIADVAYYFEKDVKGESLF
HSKKMDLTVNGEQLDLDPGQTLIYYVDEKAPEFSMQGLKAGVIAVIVVVVIAVVAGI
VVLVISRKKRMAKYEKAEIKEMGEMHRELNA

[0152] Antigen-binding sites that can bind to tumor associated antigen CA125 can be identified by screening for binding to the amino acid sequence defined by SEQ ID NO:148.

SEQ ID NO:148

MLKPSGLPGSSSPTRSLMTGSRSTKATPEMDSGLTGATLSPKTSTGAIVVTEHTLPFTS
PDKTLASPTSSVVGRTTQSLGVMSSALPESTSRGMTHSEQRTSPSLSPQVNGTPSRNY
PATSMVSGLSSPRTRTSSTEGNFTKEASTYTLTVETTSGPVTEKYTVPTETSTTEGDST
ETPWDTRYIPVKITSPMKTFADSTASKENAPVSMTPAETTVTDSHTPGRTNPSFGTLY
SSFLDLSPKGTPNSRGETSLELILSTTGYPFSSPEPGSAGHSRISTSAPLSSSASVLDNKI
SETSIFSGQSLTSPLSPGVPEARASTMPNSAIPFSMTLSNAETSAERVRSTISSLGTPSIS
TKQTAETILTFHAFAETMDIPSTHIAKTLASEWLGSPGTLGGTSTSALTTTSPSTTLVSE
ETNTHHSTSGKETEGTLNTSMTPLETSAPGEESEMTATLVPTLGFTTLDSKIRSPSQVS
SSHPTRELRTTGSTSGRQSSSTAAHGSSDILRATTSSTSKASSWTSESTAQQFSEPQHT
QWVETSPSMKTERPPASTSVAAPITTSVPSVVSGFTTLKTSSTKGIWLEETSADTLIGE
STAGPTTHQFAVPTGISMTGGSSTRGSQGTTHLLTRATASSETSADLTLATNGVPVSV
SPAVSKTAAGSSPPGGTKPSYTMVSSVIPETSSLQSSAFREGTSLGLTPLNTRHPFSSPE
PDSAGHTKISTSIPLLSSASVLEDKVSATSTFSHHKATSSITTGTPEISTKTKPSSAVLSS
MTLSNAATSPERVRNATSPLTHPSPSGEETAGSVLTLSTSAETTDSPNIHPTGTLTSESS
ESPSTLSLPSVSGVKTTFSSSTPSTHLFTSGEETEETSNPSVSQPETSVSRVRTTLASTSV
PTPVFPTMDTWPTRSAQFSSSHLVSELRATSSTSVTNSTGSALPKISHLTGTATMSQT
NRDTFNDSAAPQSTTWPETSPRFKTGLPSATTTVSTSATSLSATVMVSKFTSPATSSM

EATSIREPSTTILTTETTNGPGSMAVASTNIPIGKGYITEGRLDTSHLPIGTTASSETSMD
FTMAKESVSMSVSPSQSMDAAGSSTPGRTSQFVDTFSDDVYHLTSREITIPRDGTSSA
LTPQMTATHPPSPDPGSARSTWLGILSSSPSSPTPKVTMSSTFSTQRVTTSMIMDTVET
SRWNMPNLPSTTSLTPSNIPTSGAIGKSTLVPLDTPSPATSLEASEGGLPTLSTYPESTN
TPSIHLGAHASSESPSTIKLTMASVVKPGSYTPLTFPSIETHIHVSTARMAYSSGSSPEM
TAPGETNTGSTWDPTTYITTTDPKDTSSAQVSTPHSVRTLRTTENHPKTESATPAAYS
GSPKISSSPNLTSPATKAWTITDTTEHSTQLHYTKLAEKSSGFETQSAPGPVSVVIPTSP
TIGSSTLELTSDVPGEPLVLAPSEQTTITLPMATWLSTSLTEEMASTDLDISSPSSPMST
FAIFPPMSTPSHELSKSEADTSAIRNTDSTTLDQHLGIRSLGRTGDLTTVPITPLTTTWT
SVIEHSTQAQDTLSATMSPTHVTQSLKDQTSIPASASPSHLTEVYPELGTQGRSSSEAT
TFWKPSTDTLSREIETGPTNIQSTPPMDNTTTGSSSSGVTLGIAHLPIGTSSPAETSTNM
ALERRSSTATVSMAGTMGLLVTSAPGRSISQSLGRVSSVLSESTTEGVTDSSKGSSPR
LNTQGNTALSSSLEPSYAEGSQMSTSIPLTSSPTTPDVEFIGGSTFWTKEVTTVMTSDI
SKSSARTESSSATLMSTALGSTENTGKEKLRTASMDLPSPTPSMEVTPWISLTLSNAP
NTTDSLDLSHGVHTSSAGTLATDRSLNTGVTRASRLENGSDTSSKSLSMGNSTHTSM
TYTEKSEVSSSIHPRPETSAPGAETTLTSTPGNRAISLTLPFSSIPVEEVISTGITSGPDIN
SAPMTHSPITPPTIVWTSTGTIEQSTQPLHAVSSEKVSVQTQSTPYVNSVAVSASPTHE
NSVSSGSSTSSPYSSASLESLDSTISRRNAITSWLWDLTTSLPTTTWPSTSLSEALSSGH
SGVSNPSSTTTEFPLFSAASTSAAKQRNPETETHGPQNTAASTLNTDASSVTGLSETPV
GASISSEVPLPMAITSRSDVSGLTSESTANPSLGTASSAGTKLTRTISLPTSESLVSFRM
NKDPWTVSIPLGSHPTTNTETSIPVNSAGPPGLSTVASDVIDTPSDGAESIPTVSFSPSP
DTEVTTISHFPEKTTHSFRTISSLTHELTSRVTPIPGDWMSSAMSTKPTGASPSITLGER
RTITSAAPTTSPIVLTASFTETSTVSLDNETTVKTSDILDARKTNELPSDSSSSSDLINTSI
ASSTMDVTKTASISPTSISGMTASSSPSLFSSDRPQVPTSTTETNTATSPSVSSNTYSLD
GGSNVGGTPSTLPPFTITHPVETSSALLAWSRPVRTFSTMVSTDTASGENPTSSNSVVT
SVPAPGTWTSVGSTTDLPAMGFLKTSPAGEAHSLLASTIEPATAFTPHLSAAVVTGSS
ATSEASLLTTSESKAIHSSPQTPTTPTSGANWETSATPESLLVVTETSDTTLTSKILVTD
TILFSTVSTPPSKFPSTGTLSGASFPTLLPDTPAIPLTATEPTSSLATSFDSTPLVTIASDS
LGTVPETTLTMSETSNGDALVLKTVSNPDRSIPGITIQGVTESPLHPSSTSPSKIVAPRN
TTYEGSITVALSTLPAGTTGSLVFSQSSENSETTALVDSSAGLERASVMPLTTGSQGM
ASSGGIRSGSTHSTGTKTFSSLPLTMNPGEVTAMSEITTNRLTATQSTAPKGIPVKPTS
AESGLLTPVSASSSPSKAFASLTTAPPTWGIPQSTLTFEFSEVPSLDTKSASLPTPGQSL
NTIPDSDASTASSSLSKSPEKNPRARMMTSTKAISASSFQSTGFTETPEGSASPSMAGH
EPRVPTSGTGDPRYASESMSYPDPSKASSAMTSTSLASKLTTLFSTGQAARSGSSSSPI
SLSTEKETSFLSPTASTSRKTSLFLGPSMARQPNILVHLQTSALTLSPTSTLNMSQEEPP
ELTSSQTIAEEEGTTAETQTLTFTPSETPTSLLPVSSPTEPTARRKSSPETWASSISVPAK
TSLVETTDGTLVTTIKMSSQAAQGNSTWPAPAEETGSSPAGTSPGSPEMSTTLKIMSS
KEPSISPEIRSTVRNSPWKTPETTVPMETTVEPVTLQSTALGSGSTSISHLPTGTTSPTK
SPTENMLATERVSLSPSPPEAWTNLYSGTPGGTRQSLATMSSVSLESPTARSITGTGQ
QSSPELVSKTTGMEFSMWHGSTGGTTGDTHVSLSTSSNILEDPVTSPNSVSSLTDKSK
HKTETWVSTTAIPSTVLNNKIMAAEQQTSRSVDEAYSSTSSWSDQTSGSDITLGASPD
VTNTLYITSTAQTTSLVSLPSGDQGITSLTNPSGGKTSSASSVTSPSIGLETLRANVSAV
KSDIAPTAGHLSQTSSPAEVSILDVTTAPTPGISTTITTMGTNSISTTTPNPEVGMSTMD
STPATERRTTSTEHPSTWSSTAASDSWTVTDMTSNLKVARSPGTISTMHTTSFLASST
ELDSMSTPHGRITVIGTSLVTPSSDASAVKTETSTSERTLSPSDTTASTPISTFSRVQRM
SISVPDILSTSWTPSSTEAEDVPVSMVSTDHASTKTDPNTPLSTFLFDSLSTLDWDTGR
SLSSATATTSAPQGATTPQELTLETMISPATSQLPFSIGHITSAVTPAAMARSSGVTFSR
PDPTSKKAEQTSTQLPTTTSAHPGQVPRSAATTLDVIPHTAKTPDATFQRQGQTALTT
EARATSDSWNEKEKSTPSAPWITEMMNSVSEDTIKEVTSSSSVLRTLNTLDINLESGT
TSSPSWKSSPYERIAPSESTTDKEAIHPSTNTVETTGWVTSSEHASHSTIPAHSASSKLT

SPVVTTSTREQAIVSMSTTTWPESTRARTEPNSFLTIELRDVSPYMDTSSTTQTSIISSP
GSTAITKGPRTEITSSKRISSSFLAQSMRSSDSPSEAITRLSNFPAMTESGGMILAMQTS
PPGATSLSAPTLDTSATASWTGTPLATTQRFTYSEKTTLFSKGPEDTSQPSPPSVEETS
SSSSLVPIHATTSPSNILLTSQGHSPSSTPPVTSVFLSETSGLGKTTDMSRISLEPGTSLPP
NLSSTAGEALSTYEASRDTKAIHHSADTAVTNMEATSSEYSPIPGHTKPSKATSPLVT
SHIMGDITSSTSVFGSSETTEIETVSSVNQGLQERSTSQVASSATETSTVITHVSSGDAT
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TQGPYLLDTSTMPYLTETPLAVTPDFMQSEKTTLISKGPKDVSWTSPPSVAETSYPSS
LTPFLVTTIPPATSTLQGQHTSSPVSATSVLTSGLVKTTDMLNTSMEPVTNSPQNLNN
PSNEILATLAATTDIETIHPSINKAVTNMGTASSAHVLHSTLPVSSEPSTATSPMVPASS
MGDALASISIPGSETTDIEGEPTSSLTAGRKENSTLQEMNSTTESNIILSNVSVGAITEA
TKMEVPSFDATFIPTPAQSTKFPDIFSVASSRLSNSPPMTISTHMTTTQTGSSGATSKIP
LALDTSTLETSAGTPSVVTEGFAHSKITTAMNNDVKDVSQTNPPFQDEASSPSSQAPV
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DISVTSAATTDIETTHPSINTVVTNVGTTGSAFESHSTVSAYPEPSKVTSPNVTTSTME
DTTISRSIPKSSKTTRTETETTSSLTPKLRETSISQEITSSTETSTVPYKELTGATTEVSRT
DVTSSSSTSFPGPDQSTVSLDISTETNTRLSTSPIMTESAEITITTQTGPHGATSQDTFTM
DPSNTTPQAGIHSAMTHGFSQLDVTTLMSRIPQDVSWTSPPSVDKTSSPSSFLSSPAM
TTPSLISSTLPEDKLSSPMTSLLTSGLVKITDILRTRLEPVTSSLPNFSSTSDKILATSKDS
KDTKEIFPSINTEETNVKANNSGHESHSPALADSETPKATTQMVITTTVGDPAPSTSM
PVHGSSETTNIKREPTYFLTPRLRETSTSQESSFPTDTSFLLSKVPTGTITEVSSTGVNSS
SKISTPDHDKSTVPPDTFTGEIPRVFTSSIKTKSAEMTITTQASPPESASHSTLPLDTSTT
LSQGGTHSTVTQGFPYSEVTTLMGMGPGNVSWMTTPPVEETSSVSSLMSSPAMTSPS
PVSSTSPQSIPSSPLPVTALPTSVLVTTTDVLGTTSPESVTSSPPNLSSITHERPATYKDT
AHTEAAMHHSTNTAVTNVGTSGSGHKSQSSVLADSETSKATPLMSTTSTLGDTSVST
STPNISQTNQIQTEPTASLSPRLRESSTSEKTSSTTETNTAFSYVPTGAITQASRTEISSS
RTSISDLDRPTIAPDISTGMITRLFTSPIMTKSAEMTVTTQTTTPGATSQGILPWDTSTT
LFQGGTHSTVSQGFPHSEITTLRSRTPGDVSWMTTPPVEETSSGFSLMSPSMTSPSPVS
STSPESIPSSPLPVTALLTSVLVTTTNVLGTTSPEPVTSSPPNLSSPTQERLTTYKDTAH
TEAMHASMHTNTAVANVGTSISGHESQSSVPADSHTSKATSPMGITFAMGDTSVSTS
TPAFFETRIQTESTSSLIPGLRDTRTSEEINTVTETSTVLSEVPTTTTTEVSRTEVITSSRT
TISGPDHSKMSPYISTETITRLSTFPFVTGSTEMAITNQTGPIGTISQATLTLDTSSTASW
EGTHSPVTQRFPHSEETTTMSRSTKGVSWQSPPSVEETSSPSSPVPLPAITSHSSLYSAV
SGSSPTSALPVTSLLTSGRRKTIDMLDTHSELVTSSLPSASSFSGEILTSEASTNTETIHF
SENTAETNMGTTNSMHKLHSSVSIHSQPSGHTPPKVTGSMMEDAIVSTSTPGSPETKN
VDRDSTSPLTPELKEDSTALVMNSTTESNTVFSSVSLDAATEVSRAEVTYYDPTFMP
ASAQSTKSPDISPEASSSHSNSPPLTISTHKTIATQTGPSGVTSLGQLTLDTSTIATSAGT
PSARTQDFVDSETTSVMNNDLNDVLKTSPFSAEEANSLSSQAPLLVTTSPSPVTSTLQ
EHSTSSLVSVTSVPTPTLAKITDMDTNLEPVTRSPQNLRNTLATSEATTDTHTMHPSIN
TAVANVGTTSSPNEFYFTVSPDSDPYKATSAVVITSTSGDSIVSTSMPRSSAMKKIESE
TTFSLIFRLRETSTSQKIGSSSDTSTVFDKAFTAATTEVSRTELTSSSRTSIQGTEKPTMS
PDTSTRSVTMLSTFAGLTKSEERTIATQTGPHRATSQGTLTWDTSITTSQAGTHSAMT
HGFSQLDLSTLTSRVPEYISGTSPPSVEKTSSSSSLLSLPAITSPSPVPTTLPESRPSSPVH
LTSLPTSGLVKTTDMLASVASLPPNLGSTSHKIPTTSEDIKDTEKMYPSTNIAVTNVGT
TTSEKESYSSVPAYSEPPKVTSPMVTSFNIRDTIVSTSMPGSSEITRIEMESTFSLAHGL
KGTSTSQDPIVSTEKSAVLHKLTTGATETSRTEVASSRRTSIPGPDHSTESPDISTEVIPS
LPISLGITESSNMTIITRTGPPLGSTSQGTFTLDTPTTSSRAGTHSMATQEFPHSEMTTV
MNKDPEILSWTIPPSIEKTSFSSSLMPSPAMTSPPVSSTLPKTIHTTPSPMTSLLTPSLV
MTTDTLGTSPEPTTSSPPNLSSTSHEILTTDEDTTAIEAMHPSTSTAATNVETTSSGHGS
QSSVLADSEKTKATAPMDTTSTMGHTTVSTSMSVSSETTKIKRESTYSLTPGLRETSIS

QNASFSTDTSIVLSEVPTGTTAEVSRTEVTSSGRTSIPGPSQSTVLPEISTRTMTRLFASP
TMTESAEMTIPTQTGPSGSTSQDTLTLDTSTTKSQAKTHSTLTQRFPHSEMTTLMSRG
PGDMSWQSSPSLENPSSLPSLLSLPATTSPPPISSTLPVTISSSPLPVTSLLTSSPVTTTD
MLHTSPELVTSSPPKLSHTSDERLTTGKDTTNTEAVHPSTNTAASNVEIPSSGHESPSS
ALADSETSKATSPMFITSTQEDTTVAISTPHFLETSRIQKESISSLSPKLRETGSSVETSS
AIETSAVLSEVSIGATTEISRTEVTSSSRTSISGSAESTMLPEISTTRKIIKFPTSPILAE
SSEMTIKTQTSPPGSTSESTFTLDTSTTPSLVITHSTMTQRLPHSEITTLVSRGAGDVPR
PSSLPVEETSPPSSQLSLSAMISPSPVSSTLPASSHSSSASVTSLLTPGQVKTTEVLDAS
AEPETSSPPSLSSTSVEILATSEVTTDTEKIHPFSNTAVTKVGTSSSGHESPSSVLPDSE
TTKATSAMGTISIMGDTSVSTLTPALSNTRKIQSEPASSLTTRLRETSTSEETSLATEAN
TVLSKVSTGATTEVSRTEAISFSRTSMSGPEQSTMSQDISIGTIPRISASSVLTESAKMT
ITTQTGPSESTLESTLNLNTATTPSWVETHSIVIQGFPHPEMTTSMGRGPGGVSWPSPP
FVKETSPPSSPLSLPAVTSPHPVSTTFLAHIPPSPLPVTSLLTSGPATTTDILGTSTEPGT
SSSSSLSTTSHERLTTYKDTAHTEAVHPSTNTGGTNVATTSSGYKSQSSVLADSSPMC
TTSTMGDTSVLTSTPAFLETRRIQTELASSLTPGLRESSGSEGTSSGTKMSTVLSKVPT
GATTEISKEDVTSIPGPAQSTISPDISTRTVSWFSTSPVMTESAEITMNTHTSPLGATTQ
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SSPATTSPSPVSSTLPESISSSPLPVTSLLTSGLAKTTDMLHKSSEPVTNSPANLSSTSVE
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TSVSTSTPGFFETSRIQTEPTSSLTLGLRKTSSSEGTSLATEMSTVLSGVPTGATAEVSR
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TTSPSPVSSTLVEDFPSASLPVTSLLNPGLVITTDRMGISREPGTSSTSNLSSTSHERLTT
LEDTVDTEDMQPSTHTAVTNVRTSISGHESQSSVLSDSETPKATSPMGTTYTMGETS
VSISTSDFFETSRIQIEPTSSLTSGLRETSSSERISSATEGSTVLSEVPSGATTEVSRTEVIS
SRGTSMSGPDQFTISPDISTEAITRLSTSPIMTESAESAITIETGSPGATSEGTLTLDTSTT
TFWSGTHSTASPGFSHSEMTTLMSRTPGDVPWPSLPSVEEASSVSSSLSSPAMTSTSFF
STLPESISSSPHPVTALLTLGPVKTTDMLRTSSEPETSSPPNLSSTSAEILATSEVTKDRE
KIHPSSNTPVVNVGTVIYKHLSPSSVLADLVTTKPTSPMATTSTLGNTSVSTSTPAFPE
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SHSSPLRVTSLFTPVMMKTTDMLDTSLEPVTTSPPSMNITSDESLATSKATMETEAIQ
LSENTAVTQMGTISARQEFYSSYPGLPEPSKVTSPVVTSSTIKDIVSTTIPASSEITRIEM
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SQDISTEVITRLSTSPIKTESTEMTITTQTGSPGATSRGTLTLDTSTTFMSGTHSTASQG
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VTSLLTSGLVKTTELLGTSSEPETSSPPNLSSTSAEILAITEVTTDTEKLEMTNVVTSGY
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TSISEETSSATEKSTVLSSVPTGATTEVSRTEAISSSRTSIPGPAQSTMSSDTSMETITRIS
TPLTRKESTDMAITPKTGPSGATSQGTFTLDSSSTASWPGTHSATTQRFPQSVVTTPM
SRGPEDVSWPSPLSVEKNSPPSSLVSSSSVTSPSPLYSTPSGSSHSSPVPVTSLFTSIMM
KATDMLDASLEPETTSAPNMNITSDESLAASKATTETEAIHVFENTAASHVETTSATE
ELYSSSPGFSEPTKVISPVVTSSSIRDNMVSTTMPGSSGITRIEIESMSSLTPGLRETRTS
QDITSSTETSTVLYKMPSGATPEVSRTEVMPSSRTSIPGPAQSTMSLDISDEVVTRLST
SPIMTESAEITITTQTGYSLATSQVTLPLGTSMTFLSGTHSTMSQGLSHSEMTNLMSRG
PESLSWTSPRFVETTRSSSSLTSLPLTTSLSPVSSTLLDSSPSSPLPVTSLILPGLVKTTEV
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ADSETTITIPSMGITSAVDDTTVFTSNPAFSETRRIPTEPTFSLTPGFRETSTSEETTSITE
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MTITTQKSSPGATAQSTLTLATTTAPLARTHSTVPPRFLHSEMTTLMSRSPENPSWKS
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PNLSGTSVEILAASEVTTDTEKIHPSSSMAVTNVGTTSSGHELYSSVSIHSEPSKATYP
VGTPSSMAETSISTSMPANFETTGFEAEPFSHLTSGFRKTNMSLDTSSVTPTNTPSSPG
STHLLQSSKTDFTSSAKTSSPDWPPASQYTEIPVDIITPFNASPSITESTGITSFPESRFTM
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DATLSTIAESLPSSTPVPFSSSTFTTTDSSTIPALHEITSSSATPYRVDTSLGTESSTTEGR
LVMVSTLDTSSQPGRTSSSPILDTRMTESVELGTVTSAYQVPSLSTRLTRTDGIMEHIT
KIPNEAAHRGTIRPVKGPQTSTSPASPKGLHTGGTKRMETTTTALKTTTTALKTTSRA
TLTTSVYTPTLGTLTPLNASMQMASTIPTEMMITTPYVFPDVPETTSSLATSLGAETST
ALPRTTPSVFNRESETTASLVSRSGAERSPVIQTLDVSSSEPDTTASWVIHPAETIPTVS
KTTPNFFHSELDTVSSTATSHGADVSSAIPTNISPSELDALTPLVTISGTDTSTTFPTLTK
SPHETETRTTWLTHPAETSSTIPRTIPNFSHHESDATPSIATSPGAETSSAIPIMTVSPGA
EDLVTSQVTSSGTDRNMTIPTLTLSPGEPKTIASLVTHPEAQTSSAIPTSTISPAVSRLV
TSMVTSLAAKTSTTNRALTNSPGEPATTVSLVTHPAQTSPTVPWTTSIFFHSKSDTTPS
MTTSHGAESSSAVPTPTVSTEVPGVVTPLVTSSRAVISTTIPILTLSPGEPETTPSMATS
HGEEASSAIPTPTVSPGVPGVVTSLVTSSRAVTSTTIPILTFSLGEPETTPSMATSHGTE
AGSAVPTVLPEVPGMVTSLVASSRAVTSTTLPTLTLSPGEPETTPSMATSHGAEASST
VPTVSPEVPGVVTSLVTSSSGVNSTSIPTLILSPGELETTPSMATSHGAEASSAVPTPTV
SPGVSGVVTPLVTSSRAVTSTTIPILTLSSSEPETTPSMATSHGVEASSAVLTVSPEVPG
MVTSLVTSSRAVTSTTIPTLTISSDEPETTTSLVTHSEAKMISAIPTLAVSPTVQGLVTS
LVTSSGSETSAFSNLTVASSQPETIDSWVAHPGTEASSVVPTLTVSTGEPFTNISLVTH
PAESSSTLPRTTSRFSHSELDTMPSTVTSPEAESSSAISTTISPGIPGVLTSLVTSSGRDIS
ATFPTVPESPHESEATASWVTHPAVTSTTVPRTTPNYSHSEPDTTPSIATSPGAEATSD
FPTITVSPDVPDMVTSQVTSSGTDTSITIPTLTLSSGEPETTTSFITYSETHTSSAIPTLPV
SPGASKMLTSLVISSGTDSTTTFPTLTETPYEPETTAIQLIHPAETNTMVPRTTPKFSHS
KSDTTLPVAITSPGPEASSAVSTTTISPDMSDLVTSLVPSSGTDTSTTFPTLSETPYEPET
TATWLTHPAETSTTVSGTIPNFSHRGSDTAPSMVTSPGVDTRSGVPTTTIPPSIPGVVT
SQVTSSATDTSTAIPTLTPSPGEPETTASSATHPGTQTGFTVPIRTVPSSEPDTMASWV
THPPQTSTPVSRTTSSFSHSSPDATPVMATSPRTEASSAVLTTISPGAPEMVTSQITSSG
AATSTTVPTLTHSPGMPETTALLSTHPRTETSKTFPASTVFPQVSETTASLTIRPGAETS
TALPTQTTSSLFTLLVTGTSRVDLSPTASPGVSAKTAPLSTHPGTETSTMIPTSTLSLGL
LETTGLLATSSSAETSTSTLTLTVSPAVSGLSSASITTDKPQTVTSWNTETSPSVTSVGP
PEFSRTVTGTTMTLIPSEMPTPPKTSHGEGVSPTTILRTTMVEATNLATTGSSPTVAKT
TTTFNTLAGSLFTPLTTPGMSTLASESVTSRTSYNHRSWISTTSSYNRRYWTPATSTPV
TSTFSPGISTSSIPSSTAATVPFMVPFTLNFTITNLQYEEDMRHPGSRKFNATERELQGL
LKPLFRNSSLEYLYSGCRLASLRPEKDSSATAVDAICTHRPDPEDLGLDRERLYWELS
NLTNGIQELGPYTLDRNSLYVNGFTHRSSMPTTSTPGTSTVDVGTSGTPSSSPSPTTAG
PLLMPFTLNFTITNLQYEEDMRRTGSRKFNTMESVLQGLLKPLFKNTSVGPLYSGCR
LTLLRPEKDGAATGVDAICTHRLDPKSPGLNREQLYWELSKLTNDIEELGPYTLDRN
SLYVNGFTHQSSVSTTSTPGTSTVDLRTSGTPSSLSSPTIMAAGPLLVPFTLNFTITNLQ
YGEDMGHPGSRKFNTTERVLQGLLGPIFKNTSVGPLYSGCRLTSLRSEKDGAATGVD
AICIHHLDPKSPGLNRERLYWELSQLTNGIKELGPYTLDRNSLYVNGFTHRTSVPTSS
TPGTSTVDLGTSGTPFSLPSPATAGPLLVLFTLNFTITNLKYEEDMHRPGSRKFNTTER
VLQTLLGPMFKNTSVGLLYSGCRLTLLRSEKDGAATGVDAICTHRLDPKSPGVDREQ
LYWELSQLTNGIKELGPYTLDRNSLYVNGFTHWIPVPTSSTPGTSTVDLGSGTPSSLPS
PTTAGPLLVPFTLNFTITNLKYEEDMHCPGSRKFNTTERVLQSLLGPMFKNTSVGPLY
SGCRLTLLRSEKDGAATGVDAICTHRLDPKSPGVDREQLYWELSQLTNGIKELGPYT
LDRNSLYVNGFTHQTSAPNTSTPGTSTVDLGTSGTPSSLPSPTSAGPLLVPFTLNFTIT
NLQYEEDMHHPGSRKFNTTERVLQGLLGPMFKNTSVGLLYSGCRLTLLRPEKNGAA

TGMDAICSHRLDPKSPGLNREQLYWELSQLTHGIKELGPYTLDRNSLYVNGFTHRSS
VAPTSTPGTSTVDLGTSGTPSSLPSPTTAVPLLVPFTLNFTITNLQYGEDMRHPGSRKF
NTTERVLQGLLGPLFKNSSVGPLYSGCRLISLRSEKDGAATGVDAICTHHLNPQSPGL
DREQLYWQLSQMTNGIKELGPYTLDRNSLYVNGFTHRSSGLTTSTPWTSTVDLGTSG
TPSPVPSPTTTGPLLVPFTLNFTITNLQYEENMGHPGSRKFNITESVLQGLLKPLFKSTS
VGPLYSGCRLTLLRPEKDGVATRVDAICTHRPDPKIPGLDRQQLYWELSQLTHSITEL
GPYTLDRDSLYVNGFTQRSSVPTTSTPGTFTVQPETSETPSSLPGPTATGPVLLPFTLN
FTITNLQYEEDMRRPGSRKFNTTERVLQGLLMPLFKNTSVSSLYSGCRLTLLRPEKDG
AATRVDAVCTHRPDPKSPGLDRERLYWKLSQLTHGITELGPYTLDRHSLYVNGFTH
QSSMTTTRTPDTSTMHLATSRTPASLSGPMTASPLLVLFTINFTITNLRYEENMHHPG
SRKFNTTERVLQGLLRPVFKNTSVGPLYSGCRLTLLRPKKDGAATKVDAICTYRPDP
KSPGLDREQLYWELSQLTHSITELGPYTLDRDSLYVNGFTQRSSVPTTSIPGTPTVDLG
TSGTPVSKPGPSAASPLLVLFTLNFTITNLRYEENMQHPGSRKFNTTERVLQGLLRSLF
KSTSVGPLYSGCRLTLLRPEKDGTATGVDAICTHHPDPKSPRLDREQLYWELSQLTH
NITELGPYALDNDSLFVNGFTHRSSVSTTSTPGTPTVYLGASKTPASIFGPSAASHLLIL
FTLNFTITNLRYEENMWPGSRKFNTTERVLQGLLRPLFKNTSVGPLYSGCRLTLLRPE
KDGEATGVDAICTHRPDPTGPGLDREQLYLELSQLTHSITELGPYTLDRDSLYVNGFT
HRSSVPTTSTGVVSEEPFTLNFTINNLRYMADMGQPGSLKFNITDNVMQHLLSPLFQR
SSLGARYTGCRVIALRSVKNGAETRVDLLCTYLQPLSGPGLPIKQVFHELSQQTHGIT
RLGPYSLDKDSLYLNGYNEPGPDEPPTTPKPATTFLPPLSEATTAMGYHLKTLTLNFT
ISNLQYSPDMGKGSATFNSTEGVLQHLLRPLFQKSSMGPFYLGCQLISLRPEKDGAAT
GVDTTCTYHPDPVGPGLDIQQLYWELSQLTHGVTQLGFYVLDRDSLFINGYAPQNLS
IRGEYQINFHIVNWNLSNPDPTSSEYITLLRDIQDKVTTLYKGSQLHDTFRFCLVTNLT
MDSVLVTVKALFSSNLDPSLVEQVFLDKTLNASFHWLGSTYQLVDIHVTEMESSVY
QPTSSSSTQHFYLNFTITNLPYSQDKAQPGTTNYQRNKRNIEDALNQLFRNSSIKSYFS
DCQVSTFRSVPNRHHTGVDSLCNFSPLARRVDRVAIYEEFLRMTRNGTQLQNFTLDR
SSVLVDGYSPNRNEPLTGNSDLPFWAVILIGLAGLLGVITCLICGVLVTTRRRKKEGE
YNVQQQCPGYYQSHLDLEDLQ

[0153] Antigen-binding sites that can bind to tumor associated antigen NaPi2b can be identified by screening for binding to the amino acid sequence defined by SEQ ID NO:149.

SEQ ID NO:149

MAPWPELGDAQPNPDKYLEGAAGQQPTAPDKSKETNKTDNTEAPVTKIELLPSYST
ATLIDEPTEVDDPWNLPTLQDSGIKWSERDTKGKILCFFQGIGRLILLLGFLYFFVCSL
DILSSAFQLVGGKMAGQFFSNSSIMSNPLLGLVIGVLVTVLVQSSSTSTSIVVSMVSSS
LLTVRAAIPIIMGANIGTSITNTIVALMQVGDRSEFRRAFAGATVHDFFNWLSVLVLL
PVEVATHYLEIITQLIVESFHFKNGEDAPDLLKVITKPFTKLIVQLDKKVISQIAMNDE
KAKNKSLVKIWCKTFTNKTQINVTVPSTANCTSPSLCWTDGIQNWTMKNVTYKENI
AKCQHIFVNFHLPDLAVGTILLILSLLVLCGCLIMIVKILGSVLKGQVATVIKKTINTDF
PFPFAWLTGYLAILVGAGMTFIVQSSSVFTSALTPLIGIGVITIERAYPLTLGSNIGTTTT
AILAALASPGNALRSSLQIALCHFFFNISGILLWYPIPFTRLPIRMAKGLGNISAKYRWF
AVFYLIIFFFLIPLTVFGLSLAGWRVLVGVGVPVVFIIILVLCLRLLQSRCPRVLPKKLQ
NWNFLPLWMRSLKPWDAVVSKFTGCFQMRCCCCCRVCCRACCLLCDCPKCCRCSK
CCEDLEEAQEGQDVPVKAPETFDNITISREAQGEVPASDSKTECTAL

[0154] Antigen-binding sites that can bind to tumor associated antigen Nectin4 can be identified by screening for binding to the amino acid sequence defined by SEQ ID NO:150.

SEQ ID NO:150

MPLSLGAEMWGPEAWLLLLLLLASFTGRCPAGELETSDVVTVVLGQDAKLPCFYRG
DSGEQVGQVAWARVDAGEGAQELALLHSKYGLHVSPAYEGRVEQPPPPRNPLDGS
VLLRNAVQADEGEYECRVSTFPAGSFQARLRLRVLVPPLPSLNPGPALEEGQGLTLA
ASCTAEGSPAPSVTWDTEVKGTTSSRSFKHSRSAAVTSEFHLVPSRSMNGQPLTCVV
SHPGLLQDQRITHILHVSFLAEASVRGLEDQNLWHIGREGAMLKCLSEGQPPPSYNW
TRLDGPLPSGVRVDGDTLGFPPLTTEHSGIYVCHVSNEFSSRDSQVTVDVLDPQEDSG
KQVDLVSASVVVVGVIAALLFCLLVVVVVLMSRYHRRKAQQMTQKYEEELTLTRE
NSIRRLHSHHTDPRSQPEESVGLRAEGHPDSLKDNSSCSVMSEEPEGRSYSTLTTVREI
ETQTELLSPGSGRAEEEEDQDEGIKQAMNHFVQENGTLRAKPTGNGIYINGRGHLV

[0155] Antigen-binding sites that can bind to tumor associated antigen Fucosyl-GM1 can be identified by screening for binding to monosialotetrahexosylganglioside.

[0156] Antigen-binding sites that can bind to tumor associated antigen ADAM8 can be identified by screening for binding to the amino acid sequence defined by SEQ ID NO:151.

SEQ ID NO:151

LGATGHNFTLHLRKNRDLLGSGYTETYTAANGSEVTEQPRGQDHCFYQGHVEGYPD
SAASLSTCAGLRGFFQVGSDLHLIEPLDEGGEGGRHAVYQAEHLLQTAGTCGVSDDS
LGSLLGPRTAAVFRPRPGDSLPSRETRYVELYVVVDNAEFQMLGSEAAVRHRVLEV
VNHVDKLYQKLNFRVVLVGLEIWNSQDRFHVSPDPSVTLENLLTWQARQRTRRHLH
DNVQLITGVDFTGTTVGFARVSAMCSHSSGAVNQDHSKNPVGVACTMAHEMGHNL
GMDHDENVQGCRCQERFEAGRCIMAGSIGSSFPRMFSDCSQAYLESFLERPQSVCLA
NAPDLSHLVGGPVCGNLFVERGEQCDCGPPEDCRNRCCNSTTCQLAEGAQCAHGTC
CQECKVKPAGELCRPKKDMCDLEEFCDGRHPECPEDAFQENGTPCSGGYCYNGACP
TLAQQCQAFWGPGGQAAEESCFSYDILPGCKASRYRADMCGVLQCKGGQQPLGRAI
CIVDVCHALTTEDGTAYEPVPEGTRCGPEKVCWKGRCQDLHVYRSSNCSAQCHNH
GVCNHKQECHCHAGWAPPHCAKLLTEVHAASGSLPVFVVVVLVLLAVVLVTLAGII
VYRKARSRILSRNVAPKTTMGRSNPLFHQAASRVPAKGGAPAPSRGPQELVPTTHPG
QPARHPASSVALKRPPPAPPVTVSSPPFPVPVYTRQAPKQVIKPTFAPPVPPVKPGAG
AANPGPAEGAVGPKVALKPPIQRKQGAGAPTAP

[0157] Antigen-binding sites that can bind to tumor associated antigen ADAM9 can be identified by screening for binding to the amino acid sequence defined by SEQ ID NO:152.

SEQ ID NO:152

MGSGARFPSGTLRVRWLLLLGLVGPVLGAARPGFQQTSHLSSYEIITPWRLTRERRE
APRPYSKQVSYVIQAEGKEHIIHLERNKDLLPEDFVVYTYNKEGTLITDHPNIQNHCH
YRGYVEGVHNSSIALSDCFGLRGLLHLENASYGIEPLQNSSHFEHIIYRMDDVYKEPL
KCGVSNKDIEKETAKDEEEEPPSMTQLLRRRRAVLPQTRYVELFIVVDKERYDMMG
RNQTAVREEMILLANYLDSMYIMLNIRIVLVGLEIWTNGNLINIVGGAGDVLGNFVQ
WREKFLITRRRHDSAQLVLKKGFGGTAGMAFVGTVCSRSHAGGINVFGQITVETFAS
IVAHELGHNLGMNHDDGRDCSCGAKSCIMNSGASGSRNFSSCSAEDFEKLTLNKGG
NCLLNIPKPDEAYSAPSCGNKLVDAGEECDCGTPKECELDPCCEGSTCKLKSFAECA
YGDCCKDCRFLPGGTLCRGKTSECDVPEYCNGSSQFCQPDVFIQNGYPCQNNKAYC
YNGMCQYYDAQCQVIFGSKAKAAPKDCFIEVNSKGDRFGNCGFSGNEYKKCATGN
ALCGKLQCENVQEIPVFGIVPAIIQTPSRGTKCWGVDFQLGSDVPDPGMVNEGTKCG

AGKICRNFQCVDASVLNYDCDVQKKCHGHGVCNSNKNCHCENGWAPPNCETKGY
GGSVDSGPTYNEMNTALRDGLLVFFFLIVPLIVCAIFIFIKRDQLWRSYFRKKRSQTYE
SDGKNQANPSRQPGSVPRHVSPVTPPREVPIYANRFAVPTYAAKQPQQFPSRPPPPQP
KVSSQGNLIPARPAPAPPLYSSLT

[0158] Antigen-binding sites that can bind to tumor associated antigen SLC44A4 can be identified by screening for binding to the amino acid sequence defined by SEQ ID NO:153.

SEQ ID NO:153

MGGKQRDEDDEAYGKPVKYDPSFRGPIKNRSCTDVICCVLFLLFILGYIVVGIVAWL
YGDPRQVLYPRNSTGAYCGMGENKDKPYLLYFNIFSCILSSNIISVAENGLQCPTPQV
CVSSCPEDPWTVGKNEFSQTVGEVFYTKNRNFCLPGVPWNMTVITSLQQELCPSFLL
PSAPALGRCFPWTNVTPPALPGITNDTTIQQGISGLIDSLNARDISVKIFEDFAQSWYW
ILVALGVALVLSLLFILLLRLVAGPLVLVLILGVLGVLAYGIYYCWEEYRVLRDKGAS
ISQLGFTTNLSAYQSVQETWLAALIVLAVLEAILLLMLIFLRQRIRIAIALLKEASKAV
GQMMSTMFYPLVTFVLLLICIAYWAMTALYLATSGQPQYVLWASNISSPGCEKVPIN
TSCNPTAHLVNSSCPGLMCVFQGYSSKGLIQRSVFNLQIYGVLGLFWTLNWVLALG
QCVLAGAFASFYWAFHKPQDIPTFPLISAFIRTLRYHTGSLAFGALILTLVQIARVILEY
IDHKLRGVQNPVARCIMCCFKCCLWCLEKFIKFLNRNAYIMIAIYGKNFCVSAKNAF
MLLMRNIVRVVVLDKVTDLLLFFGKLLVVGGVGVLSFFFFSGRIPGLGKDFKSPHLN
YYWLPIMTSILGAYVIASGFFSVFGMCVDTLFLCFLEDLERNNGSLDRPYYMSKSLL
KILGKKNEAPPDNKKRKK

[0159] Antigen-binding sites that can bind to tumor associated antigen CA19-9 can be identified by screening for binding to the amino acid sequence defined by SEQ ID NO:154.

SEQ ID NO:154

MACSRPPSQCEPTSLPPGPPAGRRHLPLSRRRREMSSNKEQRSAVFVILFALITILILYS
SNSANEVFHYGSLRGRSRRPVNLKKWSITDGYVPILGNKTLPSRCHQCVIVSSSSHLL
GTKLGPEIERAECTIRMNDAPTTGYSADVGNKTTYRVVAHSSVFRVLRRPQEFVNRT
PETVFIFWGPPSKMQKPQGSLVRVIQRAGLVFPNMEAYAVSPGRMRQFDDLFRGET
GKDREKSHSWLSTGWFTMVIAVELCDHVHVYGMVPPNYCSQRPRLQRMPYHYYEP
KGPDECVTYIQNEHSRKGNHHRFITEKRVFSSWAQLYGITFSHPSWT

[0160] Alternatively, Table 3 lists peptide sequences of heavy chain variable domains and light chain variable domains that, in combination, can bind to CA125 (abagovomab, sofituzumab), NaPi2b (lifastuzumab), Nectin4 (enfortumab), Fucosyl-GM1 (described in US Patent Application Publication No.: 20130142789, specific sequences are incorporated by reference herein), or SLC44A4 (described in International Application Publication No.: WO2010111018, specific sequences are incorporated by reference herein).

Table 3		
Clones	Heavy chain variable domain amino acid sequence	Light chain variable domain amino acid sequence
abagovomab	QVKLQESGAELARPGASVKLSC KASGYTFTNYWMQWVKQRPGQ GLDWIGAIYPGDGNTRYTHKFK GKATLTADKSSSTAYMQLSSLAS EDSGVYYCARGEGNYAWFAYW GQGTTVTVSSA (SEQ ID NO:155) CDR1 (SEQ ID NO:156) - GYTFTNY CDR2 (SEQ ID NO:157) - YPGDGN CDR3 (SEQ ID NO:158) – GEGNYAWFAY	DIELTQSPASLSASVGETVTITCQA SENIYSYLAWHQQKQGKSPQLLV YNAKTLAGGVSSRFSGSGSGTHFS LKIKSLQPEDFGIYYCQHHYGILPT FGGGTKLEIKR (SEQ ID NO:159) CDR1(SEQ ID NO:160) - ENIYSYLA CDR2 (SEQ ID NO:161) - NAKTLAG CDR3 (SEQ ID NO:162) - QHHYGILPT
sofituzumab	EVQLVESGGGLVQPGGSLRLSCA ASGYSITNDYAWNWVRQAPGK GLEWVGYISYSGYTTYNPSLKSR FTISRDTSKNTLYLQMNSLRAED TAVYYCARWTSGLDYWGQGTL VTVSSA (SEQ ID NO:163) CDR1 (SEQ ID NO:164) - GYSITNDY CDR2 (SEQ ID NO:165) - SYSGY CDR3 (SEQ ID NO:166) - WTSGLDY	DIQMTQSPSSLSASVGDRVTITCKA SDLIHNWLAWYQQKPGKAPKLLI YGATSLETGVPSRFSGSGSGTDFTL TISSLQPEDFATYYCQQYWTTPFTF GQGTKVEIKR (SEQ ID NO:167) CDR1 (SEQ ID NO:168) - DLIHNWLA CDR2 (SEQ ID NO:169) - GATSLET CDR3 (SEQ ID NO:170) - QQYWTTPFT
lifastuzumab	EVQLVESGGGLVQPGGSLRLSCA ASGFSFSDFAMSWVRQAPGKGL EWVATIGRVAFHTYYPDSMKGR FTISRDNSKNTLYLQMNSLRAED	DIQMTQSPSSLSASVGDRVTITCRS SETLVHSSGNTYLEWYQQKPGKA PKLLIYRVSNRFSGVPSRFSGSGSG TDFTLTISSLQPEDFATYYCFQGSF

	TAVYYCARHRGFDVGHFDFWG QGTLVTVSSA (SEQ ID NO:171) CDR1 (SEQ ID NO:172) - GFSFSDF CDR2 (SEQ ID NO:173) - GRVAFH CDR3 (SEQ ID NO:174) - HRGFDVGHFDF	NPLTFGQGTKVEIKR(SEQ ID NO:175) CDR1 (SEQ ID NO:176) - ETLVHSSGNTYLE CDR2 (SEQ ID NO:177) - RVSNRFS CDR3 (SEQ ID NO:178) - FQGSFNPLT
enfortumab	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSSYNMNWVRQAPGKGL EWVSYISSSSSTIYYADSVKGRFT ISRDNAKNSLSLQMNSLRDEDTA VYYCARAYYYGMDVWGQGTTV TVSSA (SEQ ID NO:179) CDR1 (SEQ ID NO:180) - GFTFSSY CDR2 (SEQ ID NO:181) - SSSSST CDR3 (SEQ ID NO:182) - AYYYGMDV	DIQMTQSPSSVSASVGDRVTITCRA SQGISGWLAWYQQKPGKAPKFLIY AASTLQSGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQANSFPPTFG GGTKVEIKR (SEQ ID NO:183) CDR1(SEQ ID NO:184) - QGISGWLA CDR2 (SEQ ID NO:185) - AASTLQS CDR3 (SEQ ID NO:186) - QQANSFPPT
Anti- Fucosyl- GM1	EVQLVESGGGSVQPGESLRLSCV ASGFTFSRYKMNWVRQAPGKGL EWVSYISRSGRDIYYADSVKGRF TISRDNAKNSLYLQMNSLRDEDT AVYYCAGTVTTYYYDFGMDVW GQGTTVTVSS (SEQ ID NO:187) CDR1 (SEQ ID NO:188) - GFTFSRY CDR2 (SEQ ID NO:189) - SRSGRD CDR3 (SEQ ID NO:190) - TVTTYYYDFGMDV	DIQMTQSPSSLSASVGDRVTITCRA SQGISSWLAWYQQKPEKAPKSLIY AASSLQSGVPSRFSGSGSGTDFTLT ISSLQPEDFATYYCQQYNSYPPTFG GGTKVEIK (SEQ ID NO:191) CDR1 (SEQ ID NO:192) - QGISSWLA CDR2 (SEQ ID NO:193) - AASSLQS CDR3 (SEQ ID NO:194) - QQYNSYPPT

Anti-SLC44A4	QVQLVESGGGVVQPGRSLRLSC AASGFTFSSYGMHWVRQAPGKG LEWVAVMSYDGSKKFYTDSVK GRFTISRDNSKNTLYLQMNSLRA EDTAVYYCARDGGDYVRYHYY GMDVWGQGTTVTVSSA (SEQ ID NO:195) CDR1 (SEQ ID NO:196) - GFTFSSY CDR2 (SEQ ID NO:197) - SYDGSK CDR3 (SEQ ID NO:198) - DGGDYVRYHYYGMDV	DIQMTQSPSTLSASIGDRVTITCRA SQGISYYLAWYQQKPGKIPKLLIY DTSSLQSGVPSRFSGSRSGTDLSLTI SSLQPEDVATYYCQRYDSAPLTFG GGTKVEIKR (SEQ ID NO:199) CDR1 (SEQ ID NO:200) - QGISYYLA CDR2 (SEQ ID NO:201) - DTSSLQS CDR3 (SEQ ID NO:202) - QRYDSAPLT

[0161] Listed below are examples of the scFv linked to an antibody constant region that also includes mutations that enable heterodimerization of two polypeptide chains. The scFv containing a heavy chain variable domain (V_H) and a light chain variable domain (V_L) from an anti-NKG2D antibody is used in preparing a multispecific protein of the present disclosure. Each sequence represents V_L-$(G4S)_4$-V_H-hinge (AS or GAS)-Fc containing heterodimerization mutations (underlined). V_L and V_H contain $100V_L$ - $44V_H$ S-S bridge (underlined), and can be from any tumor targeting or NKG2D binding antibody. The Ala-Ser (AS, bolded & underlined) is included at the elbow hinge region sequence to balance between flexibility and optimal geometry. In certain embodiments, an additional Gly can be added to the N-terminus of the AS sequence, generating a hinge having the sequence of Gly-Ala-Ser (GAS, bolded & underlined). In certain embodiments, an additional sequence Thr-Lys-Gly can be added to the AS sequence at the hinge. $(G4S)_4$ linker is underlined in the sequences listed in the paragraph below.

[0162] A TriNKET of the present disclosure is NKG2D-binding-F4-TriNKET-EpCAM comprising a first polypeptide comprising the sequence of SEQ ID NO:203 (F4- EpCAMFc-AJchainB-NKG2D-binding scFv), and a second polypeptide comprising the sequence of SEQ ID NO:204 (Anti-EpCAM HC-hinge-Fc). The NKG2D-binding-F4-TriNKET-EpCAM also comprises two EpCAM-targeting light chains each comprising an anti-EpCAM V_L- Constant domain comprising the sequence of SEQ ID NO:214. For example, in the structure of FIG. 36, when the Fab fragments target EpCAM, the NKG2D-binding-F4-TriNKET-EpCAM

includes SEQ ID NO:203 and SEQ ID NO:214 forming one arm of the TriNKET, and SEQ ID NO:204 and SEQ ID NO:214 forming the second arm of the TriNKET.

[0163] Each of the arms comprises an EpCAM-binding Fab fragment, which comprises a heavy chain portion comprising a heavy chain variable domain and a CH1 domain, in which the heavy chain variable domain is connected to the CH1 domain; and a light chain portion comprising a light chain variable domain and a light chain constant domain (SEQ ID NO:214). In the first arm (*e.g.*, in F4- EpCAMFc-AJchainB-NKG2D-binding scFv) the CH1 domain is connected to the Fc domain, which is connected to an scFv-targeting NKG2D, forming a polypeptide comprising the sequence of SEQ ID NO:203. In the second arm, the CH1 domain is connected to the Fc domain, forming a polypeptide comprising the sequence of SEQ ID NO:204.

[0164] For example, F4-EpCAMFc-AJchainB-NKG2D-binding scFv (SEQ ID NO:203) comprises a EpCAM-targeting heavy chain variable domain (V_H) (SEQ ID NO:139) and a CH1 domain connected to an Fc domain (hinge-CH2-CH3), which at the C-terminus of the Fc is linked to a single-chain variable fragment (scFv) that binds NKG2D. The Fc domain in SEQ ID NO:203 comprises a S354C substitution, which forms a disulfide bond with a Y349C substitution in another Fc domain (SEQ ID NO:204, described below). The Fc domain in SEQ ID NO:203 includes Q347R, D399V, and F405T substitutions. The scFv that binds NKG2D is represented by the amino acid sequence of SEQ ID NO:205, and includes a light chain variable domain (V_L) linked to an heavy chain variable domain (V_H) *via* a $(G4S)_4$ linker, GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:206). The V_L and V_H comprised within SEQ ID NO:205 are connected as V_L-$(G4S)_4$-V_H; V_L and V_H contain $100V_L$ - $44V_H$ S-S bridge (resulting from G100C and G44C substitutions, respectively) (cysteine residues are bold-italics-underlined). As represented in SEQ ID NO:203, the C-terminus of the Fc domain is linked to the N-terminus of the scFv (SEQ ID NO:205) *via* a short SGSGGGGS linker (SEQ ID NO:207).

NKG2D-binding scFv

DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSG
VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGVSFPRTFG***C***GTKVEIK*GGGGSGGG*
*GSGGGGSGGGGS*EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGK***C***
LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGAP
MGAAAGWFDPWGQGTLVTVSS (SEQ ID NO:205)

F4-EpCAMFc-AJchainB-NKG2D-binding scFv

EVQLLEQSGAELVRPGTSVKISCKASGYAFTNYWLGWVKQRPGHGLEWIGDIFPGSG
NIHYNEKFKGKATLTADKSSSTAYMQLSSLTFEDSAVYFCARLRNWDEPMDYWGQ
GTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREP**R**VYTLPP**C**RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVL**V**SDGSF**T**LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
*SGSGGGGS*DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIY
AASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGVSFPRTFG**C**GTKVEIK*G*
*GGGSGGGGSGGGGSGGGGS*EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWV
RQAPGK**C**LEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVY
YCARGAPMGAAAGWFDPWGQGTLVTVSS (SEQ ID NO:203)

[0165] Anti-EpCAM HC-hinge-Fc (SEQ ID NO:204) includes a EpCAM-targeting heavy chain variable domain and a CH1 domain connected to an Fc domain (hinge-CH2-CH3). The Fc domain in SEQ ID NO:204 includes a Y349C substitution, which forms a disulfide bond with an S354C substitution in the CH3 domain of the Fc linked to the NKG2D-binding scFv (SEQ ID NO:203). In SEQ ID NO:204, the Fc domain also includes K360E and K409W substitutions.

Anti-EpCAM V_H-CH1-Fc

EVQLLEQSGAELVRPGTSVKISCKASGYAFTNYWLGWVKQRPGHGLEWIGDIFPGSG
NIHYNEKFKGKATLTADKSSSTAYMQLSSLTFEDSAVYFCARLRNWDEPMDYWGQ
GTTVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSG
VHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT
HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVD
GVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI
SKAKGQPREPQV**C**TLPPSRDELT**E**NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKT
TPPVLDSDGSFFLYS**W**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
(SEQ ID NO:204)

[0166] Anti-EpCAM V_L- Constant domain (SEQ ID NO:214) includes a EpCAM-targeting light chain portion comprising a light chain variable domain and a light chain constant domain.

Anti-EpCAM V_L- Constant domain

ELVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYW
ASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPLTFGAGTKLEIKG
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVT
EQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID
NO:214)

[0167] In an exemplary embodiment, the Fc domain linked to the NKG2D-binding scFv fragment comprises the mutations of K360E and K409W, and the Fc domain linked to the EPCAM Fab fragment comprises matching mutations Q347R, D399V, and F405T for forming a heterodimer.

[0168] In an exemplary embodiment, the Fc domain linked to the NKG2D-binding scFv includes a Y349C substitution in the CH3 domain, which forms a disulfide bond with a S354C substitution on the Fc domain that is not linked to an NKG2D-binding scFv.

[0169] Another TriNKET of the present disclosure is NKG2D-binding-F3'-TriNKET-EPCAM, sequences of which are described below (CDRs (Kabat numbering) are underlined).

[0170] Some TriNKETs of the present disclosure are in the form A49-F3'-TriNKET-EPCAM, sequences of which are provided below (CDRs (Kabat numbering) are underlined).

[0171] An A49-F3'-TriNKET-EPCAM includes a single-chain variable fragment (scFv) that binds EPCAM (SEQ ID NOs:208 and 209 are exemplary sequences of such EPCAM-binding scFv polypeptides), linked to an Fc domain via a hinge comprising Gly-Ala-Ser (for example, in SEQ ID NO:210 and SEQ ID NO:211); and an NKG2D-binding Fab fragment ("A49") including a heavy chain portion comprising an heavy chain variable domain (SEQ ID NO:85) and a CH1 domain, and a light chain portion comprising a light chain variable domain (SEQ ID NO:86) and a light chain constant domain, wherein the heavy chain variable domain is connected to the CH1 domain, and the CH1 domain is connected to the Fc domain. The Fc domain linked to the EpCAM-targeting Fab comprises Q347R, D399V, and F405T substitutions for forming a heterodimer with an Fab comprising K360E and K409W substitutions (*see, e.g.*, SEQ ID NO:212 described below).

[0172] An EPCAM-binding scFv of the present disclosure can include a heavy chain variable domain connected to a light chain variable domain with a $(G4S)_4$ linker (represented as $V_L(G4S)_4V_H$ or LH where V_L is N-terminal to V_H, and represented as $V_H(G4S)_4V_L$ or HL where V_H is N-terminal to V_L). SEQ ID NOs:208 and 209 are exemplary sequences of such EPCAM-binding scFv polypeptides. The V_L and V_H comprised within the scFv (SEQ ID NOs:208 or 209) contain $100V_L$ - $44V_H$ S-S bridge (resulting from G100C and G44C substitutions, respectively) (cysteine residues are in bold-italics-underlined in the sequences below). $(G4S)_4$ is the bolded-underlined sequence GGGGSGGGGSGGGGSGGGGS (SEQ ID NO:206) in SEQ ID NO:208 and SEQ ID NO:209.

EPCAM (MT110LH) scFv

ELVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYW
ASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPLTFG**C**GTKLEIK
GGGGSGGGGSGGGGSGGGGSEVQLLEQSGAELVRPGTSVKISCKASGYAFTNYW
LGWVKQRPGH**C**LEWIGDIFPGSGNIHYNEKFKGKATLTADKSSSTAYMQLSSLTFED
SAVYFCARLRNWDEPMDYWGQGTTVTVSS (SEQ ID NO:208)

EPCAM (MT100HL) scFv

EVQLLEQSGAELVRPGTSVKISCKASGYAFTNYWLGWVKQRPGH**C**LEWIGDIFPGSG
NIHYNEKFKGKATLTADKSSSTAYMQLSSLTFEDSAVYFCARLRNWDEPMDYWGQ
GTTVTVSS**GGGGSGGGGSGGGGSGGGGS**ELVMTQSPSSLTVTAGEKVTMSCKSSQ
SLLNSGNQKNYLTWYQQKPGQPPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSV
QAEDLAVYYCQNDYSYPLTFG**C**GTKLEIK (SEQ ID NO:209)

[0173] SEQ ID NO:210 and SEQ ID NO:211 represent two sequences of an EPCAM-binding scFv, which can be linked to an Fc domain via a hinge comprising Gly-Ala-Ser (bold-underlined). The Fc domain linked to the scFv includes Q347R, D399V, and F405T substitutions.

EPCAM (MT110LH) scFv-Fc

ELVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYW
ASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPLTFG**C**GTKLEIK
GGGGSGGGGSGGGGSGGGGSEVQLLEQSGAELVRPGTSVKISCKASGYAFTNYW
LGWVKQRPGH**C**LEWIGDIFPGSGNIHYNEKFKGKATLTADKSSSTAYMQLSSLTFED
SAVYFCARLRNWDEPMDYWGQGTTVTVSS**GAS**DKTHTCPPCPAPELLGGPSVFLFP
PKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDE
LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:210)

EPCAM (MT110HL) scFv-Fc

EVQLLEQSGAELVRPGTSVKISCKASGYAFTNYWLGWVKQRPGH**C**LEWIGDIFPGSG
NIHYNEKFKGKATLTADKSSSTAYMQLSSLTFEDSAVYFCARLRNWDEPMDYWGQ
GTTVTVSS**GGGGSGGGGSGGGGSGGGGS**ELVMTQSPSSLTVTAGEKVTMSCKSSQ
SLLNSGNQKNYLTWYQQKPGQPPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSV
QAEDLAVYYCQNDYSYPLTFG**C**GTKLEIKG**AS**DKTHTCPPCPAPELLGGPSVFLFPPK
PKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP**R**VYTLPP**C**RDELT
KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL**V**SDGSF**T**LYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:211)

[0174] SEQ ID NO:212 represents the heavy chain portion of a Fab fragment, which comprises an heavy chain variable domain (SEQ ID NO:85) of an NKG2D-binding site and a

CH1 domain, connected to an Fc domain. The Fc domain in SEQ ID NO:212 includes a Y349C substitution in the CH3 domain, which forms a disulfide bond with a S354C substitution on the Fc linked to the EpCAM-binding scFv (*e.g.*, SEQ ID NO:210 and SEQ ID NO:211). In SEQ ID NO:212, the Fc domain also includes K360E and K409W substitutions.

A49 - V_H

EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYI YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGAPMGAAAGWFDPW GQGTLVTVSS (SEQ ID NO:85)

A49 V_H-CH1-Fc

EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYI YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARGAPMGAAAGWFDPW GQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALT SGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCD KTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQV**C**TLPPSRDELT**E**NQVSLTCLVKGFYPSDIAVEWESNGQPENNY KTTPPVLDSDGSFFLYS**W**LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO:212)

[0175] SEQ ID NO:213 represents the light chain portion of a Fab fragment comprising a light chain variable domain (SEQ ID NO:86) of an NKG2D-binding site and a light chain constant domain.

A49 – V_L

DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGVSFPRTFGGGTKVEIK (SEQ ID NO:86)

A49 LC V_L - Constant domain

DIQMTQSPSSVSASVGDRVTITCRASQGISSWLAWYQQKPGKAPKLLIYAASSLQSG VPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQGVSFPRTFGGGTKVEIK RTVAAPSPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQD SKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO:213)

[0176] In an exemplary embodiment, the Fc domain linked to the NKG2D-binding Fab fragment includes the mutations of Q347R, D399V, and F405T, and the Fc domain linked to the EPCAM scFv comprises matching mutations K360E and K409W for forming a heterodimer. In an exemplary embodiment, the Fc domain linked to the NKG2D-binding Fab

fragment includes a S354C substitution in the CH3 domain, which forms a disulfide bond with a Y349C substitution on the Fc linked to the EPCAM-binding scFv.

[0177] Within the Fc domain, CD16 binding is mediated by the hinge region and the CH2 domain. For example, within human IgG1, the interaction with CD16 is primarily focused on amino acid residues Asp 265 – Glu 269, Asn 297 – Thr 299, Ala 327 – Ile 332, Leu 234 – Ser 239, and carbohydrate residue N-acetyl-D-glucosamine in the CH2 domain (see, Sondermann *et al.*, Nature, 406 (6793):267-273). Based on the known domains, mutations can be selected to enhance or reduce the binding affinity to CD16, such as by using phage-displayed libraries or yeast surface-displayed cDNA libraries, or can be designed based on the known three-dimensional structure of the interaction.

[0178] The assembly of heterodimeric antibody heavy chains can be accomplished by expressing two different antibody heavy chain sequences in the same cell, which may lead to the assembly of homodimers of each antibody heavy chain as well as assembly of heterodimers. Promoting the preferential assembly of heterodimers can be accomplished by incorporating different mutations in the CH3 domain of each antibody heavy chain constant region as shown in US13/494870, US16/028850, US11/533709, US12/875015, US13/289934, US14/773418, US12/811207, US13/866756, US14/647480, and US14/830336. For example, mutations can be made in the CH3 domain based on human IgG1 and incorporating distinct pairs of amino acid substitutions within a first polypeptide and a second polypeptide that allow these two chains to selectively heterodimerize with each other. The positions of amino acid substitutions illustrated below are all numbered according to the EU index as in Kabat.

[0179] In one scenario, an amino acid substitution in the first polypeptide replaces the original amino acid with a larger amino acid, selected from arginine (R), phenylalanine (F), tyrosine (Y) or tryptophan (W), and at least one amino acid substitution in the second polypeptide replaces the original amino acid(s) with a smaller amino acid(s), chosen from alanine (A), serine (S), threonine (T), or valine (V), such that the larger amino acid substitution (a protuberance) fits into the surface of the smaller amino acid substitutions (a cavity). For example, one polypeptide can incorporate a T366W substitution, and the other can incorporate three substitutions including T366S, L368A, and Y407V.

[0180] An antibody heavy chain variable domain of the invention can optionally be coupled to an amino acid sequence at least 90% identical to an antibody constant region, such

as an IgG constant region including hinge, CH2 and CH3 domains with or without CH1 domain. In some embodiments, the amino acid sequence of the constant region is at least 90% identical to a human antibody constant region, such as an human IgG1 constant region, an IgG2 constant region, IgG3 constant region, or IgG4 constant region. In some other embodiments, the amino acid sequence of the constant region is at least 90% identical to an antibody constant region from another mammal, such as rabbit, dog, cat, mouse, or horse. One or more mutations can be incorporated into the constant region as compared to human IgG1 constant region, for example at Q347, Y349, L351, S354, E356, E357, K360, Q362, S364, T366, L368, K370, N390, K392, T394, D399, S400, D401, F405, Y407, K409, T411 and/or K439. Exemplary substitutions include, for example, Q347E, Q347R, Y349S, Y349K, Y349T, Y349D, Y349E, Y349C, T350V, L351K, L351D, L351Y, S354C, E356K, E357Q, E357L, E357W, K360E, K360W, Q362E, S364K, S364E, S364H, S364D, T366V, T366I, T366L, T366M, T366K, T366W, T366S, L368E, L368A, L368D, K370S, N390D, N390E, K392L, K392M, K392V, K392F, K392D, K392E, T394F, T394W, D399R, D399K, D399V, S400K, S400R, D401K, F405A, F405T, Y407A, Y407I , Y407V, K409F, K409W, K409D, T411D, T411E, K439D, and K439E.

[0181] In certain embodiments, mutations that can be incorporated into the CH1 of a human IgG1 constant region may be at amino acid V125, F126, P127, T135, T139, A140, F170, P171, and/or V173. In certain embodiments, mutations that can be incorporated into the Cκ of a human IgG1 constant region may be at amino acid E123, F116, S176, V163, S174, and/or T164.

[0182] Alternatively, amino acid substitutions could be selected from the following sets of substitutions shown in Table 4.

Table 4		
	First Polypeptide	Second Polypeptide
Set 1	S364E/F405A	Y349K/T394F
Set 2	S364H/D401K	Y349T/T411E
Set 3	S364H/T394F	Y349T/F405A
Set 4	S364E/T394F	Y349K/F405A
Set 5	S364E/T411E	Y349K/D401K
Set 6	S364D/T394F	Y349K/F405A

Set 7	S364H/F405A	Y349T/T394F
Set 8	S364K/E357Q	L368D/K370S
Set 9	L368D/K370S	S364K
Set 10	L368E/K370S	S364K
Set 11	K360E/Q362E	D401K
Set 12	L368D/K370S	S364K/E357L
Set 13	K370S	S364K/E357Q
Set 14	F405L	K409R
Set 15	K409R	F405L

[0183] Alternatively, amino acid substitutions could be selected from the following sets of substitutions shown in Table 5.

Table 5		
	First Polypeptide	Second Polypeptide
Set 1	K409W	D399V/F405T
Set 2	Y349S	E357W
Set 3	K360E	Q347R
Set 4	K360E/K409W	Q347R/D399V/F405T
Set 5	Q347E/K360E/K409W	Q347R/D399V/F405T
Set 6	Y349S/K409W	E357W/D399V/F405T

[0184] Alternatively, amino acid substitutions could be selected from the following set of substitutions shown in Table 6.

Table 6		
	First Polypeptide	Second Polypeptide
Set 1	T366K/L351K	L351D/L368E
Set 2	T366K/L351K	L351D/Y349E
Set 3	T366K/L351K	L351D/Y349D
Set 4	T366K/L351K	L351D/Y349E/L368E
Set 5	T366K/L351K	L351D/Y349D/L368E
Set 6	E356K/D399K	K392D/K409D

[0185] Alternatively, at least one amino acid substitution in each polypeptide chain could be selected from Table 7.

Table 7	
First Polypeptide	Second Polypeptide
L351Y, D399R, D399K, S400K, S400R, Y407A, Y407I, Y407V	T366V, T366I, T366L, T366M, N390D, N390E, K392L, K392M, K392V, K392F K392D, K392E, K409F, K409W, T411D and T411E

[0186] Alternatively, at least one amino acid substitutions could be selected from the following set of substitutions in Table 8, where the position(s) indicated in the First Polypeptide column is replaced by any known negatively-charged amino acid, and the position(s) indicated in the Second Polypeptide Column is replaced by any known positively-charged amino acid.

Table 8	
First Polypeptide	Second Polypeptide
K392, K370, K409, or K439	D399, E356, or E357

[0187] Alternatively, at least one amino acid substitutions could be selected from the following set of in Table 9, where the position(s) indicated in the First Polypeptide column is replaced by any known positively-charged amino acid, and the position(s) indicated in the Second Polypeptide Column is replaced by any known negatively-charged amino acid.

Table 9	
First Polypeptide	Second Polypeptide
D399, E356, or E357	K409, K439, K370, or K392

[0188] Alternatively, amino acid substitutions could be selected from the following set in Table 10.

Table 10	
First Polypeptide	Second Polypeptide

T350V, L351Y, F405A, and Y407V	T350V, T366L, K392L, and T394W

[0189] Alternatively, or in addition, the structural stability of a hetero-multimeric protein may be increased by introducing S354C on either of the first or second polypeptide chain, and Y349C on the opposing polypeptide chain, which forms an artificial disulfide bridge within the interface of the two polypeptides.

[0190] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at position T366, and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of T366, L368 and Y407.

[0191] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of T366, L368 and Y407, and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at position T366.

[0192] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of E357, K360, Q362, S364, L368, K370, T394, D401, F405, and T411 and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of Y349, E357, S364, L368, K370, T394, D401, F405 and T411.

[0193] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of Y349, E357, S364, L368, K370, T394, D401, F405 and T411 and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of E357, K360, Q362, S364, L368, K370, T394, D401, F405, and T411.

[0194] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at

one or more positions selected from the group consisting of L351, D399, S400 and Y407 and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of T366, N390, K392, K409 and T411.

[0195] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of T366, N390, K392, K409 and T411 and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of L351, D399, S400 and Y407.

[0196] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of Q347, Y349, K360, and K409, and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of Q347, E357, D399 and F405.

[0197] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of Q347, E357, D399 and F405, and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of Y349, K360, Q347 and K409.

[0198] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of K370, K392, K409 and K439, and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of D356, E357 and D399.

[0199] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of D356, E357 and D399, and wherein the amino acid sequence of the other polypeptide chain of the antibody constant

region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of K370, K392, K409 and K439.

[0200] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of L351, E356, T366 and D399, and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of Y349, L351, L368, K392 and K409.

[0201] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of Y349, L351, L368, K392 and K409, and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region at one or more positions selected from the group consisting of L351, E356, T366 and D399.

[0202] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by an S354C substitution and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by a Y349C substitution.

[0203] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by a Y349C substitution and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by an S354C substitution.

[0204] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by K360E and K409W substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by O347R, D399V and F405T substitutions.

[0205] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by O347R, D399V and F405T substitutions and wherein the amino acid sequence of the other

polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by K360E and K409W substitutions.

[0206] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by a T366W substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T366S, T368A, and Y407V substitutions.

[0207] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T366S, T368A, and Y407V substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by a T366W substitution.

[0208] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T350V, L351Y, F405A, and Y407V substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T350V, T366L, K392L, and T394W substitutions.

[0209] In some embodiments, the amino acid sequence of one polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T350V, T366L, K392L, and T394W substitutions and wherein the amino acid sequence of the other polypeptide chain of the antibody constant region differs from the amino acid sequence of an IgG1 constant region by T350V, L351Y, F405A, and Y407V substitutions.

[0210] The multi-specific proteins described above can be made using recombinant DNA technology well known to a skilled person in the art. For example, a first nucleic acid sequence encoding the first immunoglobulin heavy chain can be cloned into a first expression vector; a second nucleic acid sequence encoding the second immunoglobulin heavy chain can be cloned into a second expression vector; a third nucleic acid sequence encoding the immunoglobulin light chain can be cloned into a third expression vector; and the first, second, and third expression vectors can be stably transfected together into host cells to produce the multimeric proteins.

[0211] To achieve the highest yield of the multi-specific protein, different ratios of the first, second, and third expression vector can be explored to determine the optimal ratio for

transfection into the host cells. After transfection, single clones can be isolated for cell bank generation using methods known in the art, such as limited dilution, ELISA, FACS, microscopy, or Clonepix.

[0212] Clones can be cultured under conditions suitable for bio-reactor scale-up and maintained expression of the multi-specific protein. The multispecific proteins can be isolated and purified using methods known in the art including centrifugation, depth filtration, cell lysis, homogenization, freeze-thawing, affinity purification, gel filtration, ion exchange chromatography, hydrophobic interaction exchange chromatography, and mixed-mode chromatography.

II. CHARACTERISTICS OF THE MULTI-SPECIFIC PROTEINS

[0213] The multi-specific proteins described herein include an NKG2D-binding site, a CD16-binding site, and a tumor-associated antigen selected from any one of the antigens provided in Table 11. In some embodiments, the multi-specific proteins bind simultaneously to cells expressing NKG2D and/or CD16, such as NK cells, and to tumor cells expressing a tumor-associated antigen selected from any one of the antigens provided in Table 11. Binding of the multi-specific proteins to NK cells can enhance the activity of the NK cells toward destruction of the tumor cells.

[0214] Table 11

Type of Antigen	**Biological Name**
Transmembrane glycoprotein mediating Ca^{2+}-independent homotypic cell–cell adhesion in epithelia	Epithelial cell adhesion molecule (EpCAM)
Mucin family glycoproteins	Cancer Antigen 125 (CA125)
Phosphate transport protein involved in transporting phosphate into cells via Na+ co-transport	sodium/phosphate cotransporter 2B (NaPi2b)
Cellular adhesion molecules involved in Ca^{2+}-independent cellular adhesion	Nectin cell adhesion molecule 4 (Nectin4)
Gangliosides	Fucosyl-GM1 (monosialotetrahexosylganglioside)
ADAM (a disintegrin and metalloproteinase) protein	disintegrin and metalloproteinase domain-containing protein 8 (ADAM8)

ADAM (a disintegrin and metalloproteinase) protein	disintegrin and metalloproteinase domain-containing protein 9 (ADAM9)
Solute carrier proteins known as choline transporter-like proteins (CTL1-5)	solute carrier family 44 member 4 (SLC44A4)
Carbohydrate antigen sialyl Lewis a	sialylated Lewis a antigen (CA19-9)

[0215] In some embodiments, the multi-specific proteins bind to a tumor-associated antigen selected from any one of the antigens provided in Table 11 with a similar affinity to the corresponding monoclonal antibody (*i.e.,* a monoclonal antibody containing the same a tumor-associated antigen-binding site as the one incorporated in the multi-specific proteins (selected from any one of the antigens provided in Table 11)). In some embodiments, the multi-specific proteins are more effective in killing the tumor cells expressing a tumor-associated antigen selected from any one of the antigens provided in Table 11 than the corresponding monoclonal antibodies.

[0216] In certain embodiments, the multi-specific proteins described herein, which include an NKG2D-binding site and a binding site for a tumor-associated antigen selected from any one of the antigens provided in Table 11, activate primary human NK cells when co-culturing with cells expressing the tumor-associated antigen. NK cell activation is marked by the increase in CD107a degranulation and IFN-γ cytokine production. Furthermore, compared to a corresponding monoclonal antibody for a tumor-associated antigen selected from any one of the antigens provided in Table 11, the multi-specific proteins may show superior activation of human NK cells in the presence of cells expressing the tumor-associated antigen.

[0217] In certain embodiments, the multi-specific proteins described herein, which include an NKG2D-binding site and a binding site for a tumor-associated antigen selected from any one of the antigens provided in Table 11, enhance the activity of rested and IL-2-activated human NK cells co-culturing with cells expressing the tumor-associated antigen.

[0218] In certain embodiments, compared to a corresponding monoclonal antibody that binds to a tumor-associated antigen selected from any one of the antigens provided in Table 11, the multi-specific proteins offer an advantage in targeting tumor cells that express the tumor-associated antigen. The multi-specific binding proteins described herein may be more effective in reducing tumor growth and killing cancer cells.

[0219] In certain embodiments, EpCAM-targeting F4-TriNKET (*e.g.*, NKG2D-binding-F4-TriNKET-EpCAM) killed target cells more effectively than the parental mAb targeting EpCAM. In certain embodiments, the F4-TriNKET also killed target cells more potently than F3'-TriNKET (*e.g.*, NKG2D-binding-F3'-TriNKET-EpCAM), which may be a reflection of the stronger binding of F4-TriNKET to target cells.

III. THERAPEUTIC APPLICATIONS

[0220] The invention provides methods for treating cancer using a multi-specific binding protein described herein and/or a pharmaceutical composition described herein. The methods may be used to treat a variety of cancers which express EPCAM by administering to a patient in need thereof a therapeutically effective amount of a multi-specific binding protein described herein.

[0221] The therapeutic method can be characterized according to the cancer to be treated. For example, in certain embodiments, the cancer is acute myeloid leukemia, multiple myeloma, diffuse large B cell lymphoma, thymoma, adenoid cystic carcinoma, gastrointestinal cancer, renal cancer, breast cancer, glioblastoma, lung cancer, ovarian cancer, brain cancer, prostate cancer, pancreatic cancer, or melanoma.

[0222] In certain other embodiments, the cancer is a solid tumor. In certain other embodiments, the cancer is colon cancer, bladder cancer, cervical cancer, endometrial cancer, esophageal cancer, leukemia, liver cancer, rectal cancer, stomach cancer, testicular cancer, or uterine cancer. In yet other embodiments, the cancer is a vascularized tumor, squamous cell carcinoma, adenocarcinoma, small cell carcinoma, melanoma, glioma, neuroblastoma, sarcoma (*e.g.*, an angiosarcoma or chondrosarcoma), larynx cancer, parotid cancer, bilary tract cancer, thyroid cancer, acral lentiginous melanoma, actinic keratoses, acute lymphocytic leukemia, acute myeloid leukemia, adenoid cycstic carcinoma, adenomas, adenosarcoma, adenosquamous carcinoma, anal canal cancer, anal cancer, anorectum cancer, astrocytic tumor, bartholin gland carcinoma, basal cell carcinoma, biliary cancer, bone cancer, bone marrow cancer, bronchial cancer, bronchial gland carcinoma, carcinoid, cholangiocarcinoma, chondosarcoma, choriod plexus papilloma/carcinoma, chronic lymphocytic leukemia, chronic myeloid leukemia, clear cell carcinoma, connective tissue cancer, cystadenoma, digestive system cancer, duodenum cancer, endocrine system cancer, endodermal sinus tumor, endometrial hyperplasia, endometrial stromal sarcoma, endometrioid adenocarcinoma, endothelial cell cancer, ependymal cancer, epithelial cell cancer, Ewing's sarcoma, eye and

orbit cancer, female genital cancer, focal nodular hyperplasia, gallbladder cancer, gastric antrum cancer, gastric fundus cancer, gastrinoma, glioblastoma, glucagonoma, heart cancer, hemangiblastomas, hemangioendothelioma, hemangiomas, hepatic adenoma, hepatic adenomatosis, hepatobiliary cancer, hepatocellular carcinoma, Hodgkin's disease, ileum cancer, insulinoma, intaepithelial neoplasia, interepithelial squamous cell neoplasia, intrahepatic bile duct cancer, invasive squamous cell carcinoma, jejunum cancer, joint cancer, Kaposi's sarcoma, pelvic cancer, large cell carcinoma, large intestine cancer, leiomyosarcoma, lentigo maligna melanomas, lymphoma, male genital cancer, malignant melanoma, malignant mesothelial tumors, medulloblastoma, medulloepithelioma, meningeal cancer, mesothelial cancer, metastatic carcinoma, mouth cancer, mucoepidermoid carcinoma, multiple myeloma, muscle cancer, nasal tract cancer, nervous system cancer, neuroepithelial adenocarcinoma nodular melanoma, non-epithelial skin cancer, non-Hodgkin's lymphoma, oat cell carcinoma, oligodendroglial cancer, oral cavity cancer, osteosarcoma, papillary serous adenocarcinoma, penile cancer, pharynx cancer, pituitary tumors, plasmacytoma, pseudosarcoma, pulmonary blastoma, rectal cancer, renal cell carcinoma, respiratory system cancer, retinoblastoma, rhabdomyosarcoma, sarcoma, serous carcinoma, sinus cancer, skin cancer, small cell carcinoma, small intestine cancer, smooth muscle cancer, soft tissue cancer, somatostatin-secreting tumor, spine cancer, squamous cell carcinoma, striated muscle cancer, submesothelial cancer, superficial spreading melanoma, T cell leukemia, tongue cancer, undifferentiated carcinoma, ureter cancer, urethra cancer, urinary bladder cancer, urinary system cancer, uterine cervix cancer, uterine corpus cancer, uveal melanoma, vaginal cancer, verrucous carcinoma, VIPoma, vulva cancer, well differentiated carcinoma, or Wilms tumor.

[0223] In certain other embodiments, the cancer is non-Hodgkin's lymphoma, such as a B-cell lymphoma or a T-cell lymphoma. In certain embodiments, the non-Hodgkin's lymphoma is a B-cell lymphoma, such as a diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, follicular lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, marginal zone B-cell lymphoma, extranodal marginal zone B-cell lymphoma, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma, hairy cell leukemia, or primary central nervous system (CNS) lymphoma. In certain other embodiments, the non-Hodgkin's lymphoma is a T-cell lymphoma, such as a precursor T-lymphoblastic lymphoma, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, angioimmunoblastic T-cell lymphoma, extranodal natural killer/T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous

panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma, or peripheral T-cell lymphoma.

[0224] The cancer to be treated can be characterized according to the presence of a particular antigen expressed on the surface of the cancer cell. In certain embodiments, the cancer cell can express one or more of the following in addition to EpCAM: CD2, CD19, CD20, CD30, CD38, CD40, CD52, CD70, EGFR/ERBB1, IGF1R, HER3/ERBB3, HER4/ERBB4, MUC1, TROP2, cMET, SLAMF7, PSCA, MICA, MICB, TRAILR1, TRAILR2, MAGE-A3, B7.1, B7.2, CTLA4, and PD1.

[0225] In some other embodiments, when the second binding site binds EpCAM, the cancer to be treated is selected from head and neck cancer, ovarian cancer, bladder cancer, breast cancer, colorectal cancer, prostate cancer, gastric cancer, liver cancer, esophageal cancer, and lung cancer. In some other embodiments, when the second binding site binds an antigen selected from Cancer Antigen 125 (CA125), sodium/phosphate cotransporter 2B (NaPi2b), Nectin cell adhesion molecule 4 (Nectin4), Fucosyl-GM1 (monosialotetrahexosylganglioside), disintegrin and metalloproteinase domain-containing protein 8 (ADAM8), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), solute carrier family 44 member 4 (SLC44A4), and sialylated Lewis a antigen (CA19-9), the cancer to be treated is selected from ovarian cancer, endometrial cancer, pancreatic cancer, lung cancer, thyroid cancer, bladder cancer, breast cancer, colorectal cancer, small cell lung cancer, neuroblastoma, liver cancer, renal cancer, melanoma, cervical cancer, prostate cancer, osteosarcoma, brain cancer, gastric cancer, cholangiocarcinoma.

IV. COMBINATION THERAPY

[0226] Another aspect of the invention provides for combination therapy. A multi-specific binding protein described herein can be used in combination with additional therapeutic agents to treat the cancer.

[0227] Exemplary therapeutic agents that may be used as part of a combination therapy in treating cancer, include, for example, radiation, mitomycin, tretinoin, ribomustin, gemcitabine, vincristine, etoposide, cladribine, mitobronitol, methotrexate, doxorubicin, carboquone, pentostatin, nitracrine, zinostatin, cetrorelix, letrozole, raltitrexed, daunorubicin, fadrozole, fotemustine, thymalfasin, sobuzoxane, nedaplatin, cytarabine, bicalutamide, vinorelbine, vesnarinone, aminoglutethimide, amsacrine, proglumide, elliptinium acetate, ketanserin, doxifluridine, etretinate, isotretinoin, streptozocin, nimustine, vindesine,

flutamide, drogenil, butocin, carmofur, razoxane, sizofilan, carboplatin, mitolactol, tegafur, ifosfamide, prednimustine, picibanil, levamisole, teniposide, improsulfan, enocitabine, lisuride, oxymetholone, tamoxifen, progesterone, mepitiostane, epitiostanol, formestane, interferon-alpha, interferon-2 alpha, interferon-beta, interferon-gamma (IFN-γ), colony stimulating factor-1, colony stimulating factor-2, denileukin diftitox, interleukin-2, luteinizing hormone releasing factor and variations of the aforementioned agents that may exhibit differential binding to its cognate receptor, and increased or decreased serum half-life.

[0228] An additional class of agents that may be used as part of a combination therapy in treating cancer is immune checkpoint inhibitors. Exemplary immune checkpoint inhibitors include agents that inhibit one or more of (i) cytotoxic T lymphocyte-associated antigen 4 (CTLA4), (ii) programmed cell death protein 1 (PD1), (iii) PDL1, (iv) LAG3, (v) B7-H3, (vi) B7-H4, and (vii) TIM3. The CTLA4 inhibitor ipilimumab has been approved by the United States Food and Drug Administration for treating melanoma.

[0229] Yet other agents that may be used as part of a combination therapy in treating cancer are monoclonal antibody agents that target non-checkpoint targets (*e.g.*, herceptin) and non-cytotoxic agents (*e.g.*, tyrosine-kinase inhibitors).

[0230] Yet other categories of anti-cancer agents include, for example: (i) an inhibitor selected from an ALK Inhibitor, an ATR Inhibitor, an A2A Antagonist, a Base Excision Repair Inhibitor, a Bcr-Abl Tyrosine Kinase Inhibitor, a Bruton's Tyrosine Kinase Inhibitor, a CDC7 Inhibitor, a CHK1 Inhibitor, a Cyclin-Dependent Kinase Inhibitor, a DNA-PK Inhibitor, an Inhibitor of both DNA-PK and mTOR, a DNMT1 Inhibitor, a DNMT1 Inhibitor plus 2-chloro-deoxyadenosine, an HDAC Inhibitor, a Hedgehog Signaling Pathway Inhibitor, an IDO Inhibitor, a JAK Inhibitor, a mTOR Inhibitor, a MEK Inhibitor, a MELK Inhibitor, a MTH1 Inhibitor, a PARP Inhibitor, a Phosphoinositide 3-Kinase Inhibitor, an Inhibitor of both PARP1 and DHODH, a Proteasome Inhibitor, a Topoisomerase-II Inhibitor, a Tyrosine Kinase Inhibitor, a VEGFR Inhibitor, and a WEE1 Inhibitor; (ii) an agonist of OX40, CD137, CD40, GITR, CD27, HVEM, TNFRSF25, or ICOS; and (iii) a cytokine selected from IL-12, IL-15, GM-CSF, and G-CSF.

[0231] Proteins of the invention can also be used as an adjunct to surgical removal of the primary lesion.

[0232] The amount of multi-specific binding protein and additional therapeutic agent and the relative timing of administration may be selected in order to achieve a desired combined

therapeutic effect. For example, when administering a combination therapy to a patient in need of such administration, the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. Further, for example, a multi-specific binding protein may be administered during a time when the additional therapeutic agent(s) exerts its prophylactic or therapeutic effect, or *vice versa*.

V. PHARMACEUTICAL COMPOSITIONS

[0233] The present disclosure also features pharmaceutical compositions that contain a therapeutically effective amount of a protein described herein. The composition can be formulated for use in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the composition for proper formulation. Suitable formulations for use in the present disclosure are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed., 1985. For a brief review of methods for drug delivery, *see, e.g.*, Langer (Science 249:1527-1533, 1990).

[0234] Pharmaceutical compositions can contain a therapeutically effective amount of a multi-specific binding protein comprising an antigen (listed in Table 11) site.

[0235] The intravenous drug delivery formulation of the present disclosure may be contained in a bag, a pen, or a syringe. In certain embodiments, the bag may be connected to a channel comprising a tube and/or a needle. In certain embodiments, the formulation may be a lyophilized formulation or a liquid formulation. In certain embodiments, the formulation may freeze-dried (lyophilized) and contained in about 12-60 vials. In certain embodiments, the formulation may be freeze-dried and 45 mg of the freeze-dried formulation may be contained in one vial. In certain embodiments, the about 40 mg – about 100 mg of freeze-dried formulation may be contained in one vial. In certain embodiments, freeze dried formulation from 12, 27, or 45 vials are combined to obtained a therapeutic dose of the protein in the intravenous drug formulation. In certain embodiments, the formulation may be a liquid formulation and stored as about 250 mg/vial to about 1000 mg/vial. In certain embodiments, the formulation may be a liquid formulation and stored as about 600 mg/vial. In certain embodiments, the formulation may be a liquid formulation and stored as about 250 mg/vial.

[0236] The protein could exist in a liquid aqueous pharmaceutical formulation including a therapeutically effective amount of the protein in a buffered solution forming a formulation.

[0237] These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as-is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 7 and 8, such as 7 to 7.5. The resulting compositions in solid form may be packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents. The composition in solid form can also be packaged in a container for a flexible quantity.

[0238] In certain embodiments, the present disclosure provides a formulation with an extended shelf life including the protein of the present disclosure, in combination with mannitol, citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, sodium dihydrogen phosphate dihydrate, sodium chloride, polysorbate 80, water, and sodium hydroxide.

[0239] In certain embodiments, an aqueous formulation is prepared including the protein of the present disclosure in a pH-buffered solution. The buffer of this invention may have a pH ranging from about 4 to about 8, *e.g.*, from about 4.5 to about 6.0, or from about 4.8 to about 5.5, or may have a pH of about 5.0 to about 5.2. Ranges intermediate to the above recited pH's are also intended to be part of this disclosure. For example, ranges of values using a combination of any of the above recited values as upper and/or lower limits are intended to be included. Examples of buffers that will control the pH within this range include acetate (*e.g.*, sodium acetate), succinate (such as sodium succinate), gluconate, histidine, citrate and other organic acid buffers.

[0240] In certain embodiments, the formulation includes a buffer system which contains citrate and phosphate to maintain the pH in a range of about 4 to about 8. In certain embodiments the pH range may be from about 4.5 to about 6.0, or from about pH 4.8 to about 5.5, or in a pH range of about 5.0 to about 5.2. In certain embodiments, the buffer system includes citric acid monohydrate, sodium citrate, disodium phosphate dihydrate, and/or sodium dihydrogen phosphate dihydrate. In certain embodiments, the buffer system includes about 1.3 mg/mL of citric acid (*e.g.*, 1.305 mg/mL), about 0.3 mg/mL of sodium citrate (*e.g.*, 0.305 mg/mL), about 1.5 mg/mL of disodium phosphate dihydrate (*e.g.*, 1.53 mg/mL), about

0.9 mg/mL of sodium dihydrogen phosphate dihydrate (*e.g.*, 0.86), and about 6.2 mg/mL of sodium chloride (*e.g.*, 6.165 mg/mL). In certain embodiments, the buffer system includes 1-1.5 mg/mL of citric acid, 0.25 to 0.5 mg/mL of sodium citrate, 1.25 to 1.75 mg/mL of disodium phosphate dihydrate, 0.7 to 1.1 mg/mL of sodium dihydrogen phosphate dihydrate, and 6.0 to 6.4 mg/mL of sodium chloride. In certain embodiments, the pH of the formulation is adjusted with sodium hydroxide.

[0241] A polyol, which acts as a tonicifier and may stabilize the antibody, may also be included in the formulation. The polyol is added to the formulation in an amount which may vary with respect to the desired isotonicity of the formulation. In certain embodiments, the aqueous formulation may be isotonic. The amount of polyol added may also be altered with respect to the molecular weight of the polyol. For example, a lower amount of a monosaccharide (*e.g.*, mannitol) may be added, compared to a disaccharide (such as trehalose). In certain embodiments, the polyol which may be used in the formulation as a tonicity agent is mannitol. In certain embodiments, the mannitol concentration may be about 5 to about 20 mg/mL. In certain embodiments, the concentration of mannitol may be about 7.5 to 15 mg/mL. In certain embodiments, the concentration of mannitol may be about 10-14 mg/mL. In certain embodiments, the concentration of mannitol may be about 12 mg/mL. In certain embodiments, the polyol sorbitol may be included in the formulation.

[0242] A detergent or surfactant may also be added to the formulation. Exemplary detergents include nonionic detergents such as polysorbates (*e.g.*, polysorbates 20, 80 etc.) or poloxamers (*e.g.*, poloxamer 188). The amount of detergent added is such that it reduces aggregation of the formulated antibody and/or minimizes the formation of particulates in the formulation and/or reduces adsorption. In certain embodiments, the formulation may include a surfactant which is a polysorbate. In certain embodiments, the formulation may contain the detergent polysorbate 80 or Tween 80. Tween 80 is a term used to describe polyoxyethylene (20) sorbitanmonooleate (*see* Fiedler, Lexikon der Hifsstoffe, Editio Cantor Verlag Aulendorf, 4th ed., 1996). In certain embodiments, the formulation may contain between about 0.1 mg/mL and about 10 mg/mL of polysorbate 80, or between about 0.5 mg/mL and about 5 mg/mL. In certain embodiments, about 0.1% polysorbate 80 may be added in the formulation.

[0243] In embodiments, the protein product of the present disclosure is formulated as a liquid formulation. The liquid formulation may be presented at a 10 mg/mL concentration in either a USP / Ph Eur type I 50R vial closed with a rubber stopper and sealed with an

aluminum crimp seal closure. The stopper may be made of elastomer complying with USP and Ph Eur. In certain embodiments vials may be filled with 61.2 mL of the protein product solution in order to allow an extractable volume of 60 mL. In certain embodiments, the liquid formulation may be diluted with 0.9% saline solution.

[0244] In certain embodiments, the liquid formulation of the disclosure may be prepared as a 10 mg/mL concentration solution in combination with a sugar at stabilizing levels. In certain embodiments the liquid formulation may be prepared in an aqueous carrier. In certain embodiments, a stabilizer may be added in an amount no greater than that which may result in a viscosity undesirable or unsuitable for intravenous administration. In certain embodiments, the sugar may be disaccharides, *e.g.*, sucrose. In certain embodiments, the liquid formulation may also include one or more of a buffering agent, a surfactant, and a preservative.

[0245] In certain embodiments, the pH of the liquid formulation may be set by addition of a pharmaceutically acceptable acid and/or base. In certain embodiments, the pharmaceutically acceptable acid may be hydrochloric acid. In certain embodiments, the base may be sodium hydroxide.

[0246] In addition to aggregation, deamidation is a common product variant of peptides and proteins that may occur during fermentation, harvest/cell clarification, purification, drug substance/drug product storage and during sample analysis. Deamidation is the loss of NH_3 from a protein forming a succinimide intermediate that can undergo hydrolysis. The succinimide intermediate results in a 17 dalton mass decrease of the parent peptide. The subsequent hydrolysis results in an 18 dalton mass increase. Isolation of the succinimide intermediate is difficult due to instability under aqueous conditions. As such, deamidation is typically detectable as 1 dalton mass increase. Deamidation of an asparagine results in either aspartic or isoaspartic acid. The parameters affecting the rate of deamidation include pH, temperature, solvent dielectric constant, ionic strength, primary sequence, local polypeptide conformation and tertiary structure. The amino acid residues adjacent to Asn in the peptide chain affect deamidation rates. Gly and Ser following an Asn in protein sequences results in a higher susceptibility to deamidation.

[0247] In certain embodiments, the liquid formulation of the present disclosure may be preserved under conditions of pH and humidity to prevent deamination of the protein product.

[0248] The aqueous carrier of interest herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a liquid formulation. Illustrative carriers include sterile water for injection (SWFI), bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.*, phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

[0249] A preservative may be optionally added to the formulations herein to reduce bacterial action. The addition of a preservative may, for example, facilitate the production of a multi-use (multiple-dose) formulation.

[0250] Intravenous (IV) formulations may be the preferred administration route in particular instances, such as when a patient is in the hospital after transplantation receiving all drugs via the IV route. In certain embodiments, the liquid formulation is diluted with 0.9% Sodium Chloride solution before administration. In certain embodiments, the diluted drug product for injection is isotonic and suitable for administration by intravenous infusion.

[0251] In certain embodiments, a salt or buffer components may be added in an amount of 10 mM - 200 mM. The salts and/or buffers are pharmaceutically acceptable and are derived from various known acids (inorganic and organic) with "base forming" metals or amines. In certain embodiments, the buffer may be phosphate buffer. In certain embodiments, the buffer may be glycinate, carbonate, citrate buffers, in which case, sodium, potassium or ammonium ions can serve as counterion.

[0252] A preservative may be optionally added to the formulations herein to reduce bacterial action. The addition of a preservative may, for example, facilitate the production of a multi-use (multiple-dose) formulation.

[0253] The aqueous carrier of interest herein is one which is pharmaceutically acceptable (safe and non-toxic for administration to a human) and is useful for the preparation of a liquid formulation. Illustrative carriers include sterile water for injection (SWFI), bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.*, phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

[0254] The protein of the present disclosure could exist in a lyophilized formulation including the proteins and a lyoprotectant. The lyoprotectant may be sugar, *e.g.*, disaccharides. In certain embodiments, the lyoprotectant may be sucrose or maltose. The lyophilized formulation may also include one or more of a buffering agent, a surfactant, a bulking agent, and/or a preservative.

[0255] The amount of sucrose or maltose useful for stabilization of the lyophilized drug product may be in a weight ratio of at least 1:2 protein to sucrose or maltose. In certain embodiments, the protein to sucrose or maltose weight ratio may be of from 1:2 to 1:5.

[0256] In certain embodiments, the pH of the formulation, prior to lyophilization, may be set by addition of a pharmaceutically acceptable acid and/or base. In certain embodiments the pharmaceutically acceptable acid may be hydrochloric acid. In certain embodiments, the pharmaceutically acceptable base may be sodium hydroxide.

[0257] Before lyophilization, the pH of the solution containing the protein of the present disclosure may be adjusted between 6 to 8. In certain embodiments, the pH range for the lyophilized drug product may be from 7 to 8.

[0258] In certain embodiments, a salt or buffer components may be added in an amount of 10 mM - 200 mM. The salts and/or buffers are pharmaceutically acceptable and are derived from various known acids (inorganic and organic) with "base forming" metals or amines. In certain embodiments, the buffer may be phosphate buffer. In certain embodiments, the buffer may be glycinate, carbonate, citrate buffers, in which case, sodium, potassium or ammonium ions can serve as counterion.

[0259] In certain embodiments, a "bulking agent" may be added. A "bulking agent" is a compound which adds mass to a lyophilized mixture and contributes to the physical structure of the lyophilized cake (*e.g.*, facilitates the production of an essentially uniform lyophilized cake which maintains an open pore structure). Illustrative bulking agents include mannitol, glycine, polyethylene glycol and sorbitol. The lyophilized formulations of the present invention may contain such bulking agents.

[0260] A preservative may be optionally added to the formulations herein to reduce bacterial action. The addition of a preservative may, for example, facilitate the production of a multi-use (multiple-dose) formulation.

[0261] In certain embodiments, the lyophilized drug product may be constituted with an aqueous carrier. The aqueous carrier of interest herein is one which is pharmaceutically acceptable (*e.g.*, safe and non-toxic for administration to a human) and is useful for the preparation of a liquid formulation, after lyophilization. Illustrative diluents include sterile water for injection (SWFI), bacteriostatic water for injection (BWFI), a pH buffered solution (*e.g.*, phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

[0262] In certain embodiments, the lyophilized drug product of the current disclosure is reconstituted with either Sterile Water for Injection, USP (SWFI) or 0.9% Sodium Chloride Injection, USP. During reconstitution, the lyophilized powder dissolves into a solution.

[0263] In certain embodiments, the lyophilized protein product of the instant disclosure is constituted to about 4.5 mL water for injection and diluted with 0.9% saline solution (sodium chloride solution).

[0264] Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[0265] The specific dose can be a uniform dose for each patient, for example, 50-5000 mg of protein. Alternatively, a patient's dose can be tailored to the approximate body weight or surface area of the patient. Other factors in determining the appropriate dosage can include the disease or condition to be treated or prevented, the severity of the disease, the route of administration, and the age, sex and medical condition of the patient. Further refinement of the calculations necessary to determine the appropriate dosage for treatment is routinely made by those skilled in the art, especially in light of the dosage information and assays disclosed herein. The dosage can also be determined through the use of known assays for determining dosages used in conjunction with appropriate dose-response data. An individual patient's dosage can be adjusted as the progress of the disease is monitored. Blood levels of the targetable construct or complex in a patient can be measured to see if the dosage needs to be adjusted to reach or maintain an effective concentration. Pharmacogenomics may be used to determine which targetable constructs and/or complexes, and dosages thereof, are most likely to be effective for a given individual (Schmitz *et al.*, *Clinica Chimica Acta* 308: 43-53, 2001; Steimer *et al.*, *Clinica Chimica Acta* 308: 33-41, 2001).

[0266] In general, dosages based on body weight are from about 0.01 μg to about 100 mg per kg of body weight, such as about 0.01 μg to about 100 mg/kg of body weight, about 0.01 μg to about 50 mg/kg of body weight, about 0.01 μg to about 10 mg/kg of body weight, about 0.01 μg to about 1 mg/kg of body weight, about 0.01 μg to about 100 μg/kg of body weight, about 0.01 μg to about 50 μg/kg of body weight, about 0.01 μg to about 10 μg/kg of body weight, about 0.01 μg to about 1 μg/kg of body weight, about 0.01 μg to about 0.1 μg/kg of body weight, about 0.1 μg to about 100 mg/kg of body weight, about 0.1 μg to about 50

mg/kg of body weight, about 0.1 μg to about 10 mg/kg of body weight, about 0.1 μg to about 1 mg/kg of body weight, about 0.1 μg to about 100 μg/kg of body weight, about 0.1 μg to about 10 μg/kg of body weight, about 0.1 μg to about 1 μg/kg of body weight, about 1 μg to about 100 mg/kg of body weight, about 1 μg to about 50 mg/kg of body weight, about 1 μg to about 10 mg/kg of body weight, about 1 μg to about 1 mg/kg of body weight, about 1 μg to about 100 μg/kg of body weight, about 1 μg to about 50 μg/kg of body weight, about 1 μg to about 10 μg/kg of body weight, about 10 μg to about 100 mg/kg of body weight, about 10 μg to about 50 mg/kg of body weight, about 10 μg to about 10 mg/kg of body weight, about 10 μg to about 1 mg/kg of body weight, about 10 μg to about 100 μg/kg of body weight, about 10 μg to about 50 μg/kg of body weight, about 50 μg to about 100 mg/kg of body weight, about 50μg to about 50 mg/kg of body weight, about 50 μg to about 10 mg/kg of body weight, about 50 μg to about 1 mg/kg of body weight, about 50 μg to about 100 μg/kg of body weight, about 100 μg to about 100 mg/kg of body weight, about 100 μg to about 50 mg/kg of body weight, about 100 μg to about 10 mg/kg of body weight, about 100 μg to about 1 mg/kg of body weight, about 1 mg to about 100 mg/kg of body weight, about 1 mg to about 50 mg/kg of body weight, about 1 mg to about 10 mg/kg of body weight, about 10 mg to about 100 mg/kg of body weight, about 10 mg to about 50 mg/kg of body weight, about 50 mg to about 100 mg/kg of body weight.

[0267] Doses may be given once or more times daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measured residence times and concentrations of the targetable construct or complex in bodily fluids or tissues. Administration of the present invention could be intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intrapleural, intrathecal, intracavitary, by perfusion through a catheter or by direct intralesional injection. This may be administered once or more times daily, once or more times weekly, once or more times monthly, and once or more times annually.

[0268] The description above describes multiple aspects and embodiments of the invention. The patent application specifically contemplates all combinations and permutations of the aspects and embodiments.

EXAMPLES

[0269] The invention now being generally described, will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of

certain aspects and embodiments of the present invention, and which are not intended to limit the invention.

Example 1 – NKG2D binding domains bind to NKG2D

NKG2D-binding domains bind to purified recombinant NKG2D

[0270] The nucleic acid sequences of human, mouse, or cynomolgus NKG2D ectodomains were fused with nucleic acid sequences encoding human IgG1 Fc domains and introduced into mammalian cells to be expressed. After purification, NKG2D-Fc fusion proteins were adsorbed to wells of microplates. After blocking the wells with bovine serum albumin to prevent non-specific binding, NKG2D-binding domains were titrated and added to the wells pre-adsorbed with NKG2D-Fc fusion proteins. Primary antibody binding was detected using a secondary antibody which was conjugated to horseradish peroxidase and specifically recognizes a human kappa light chain to avoid Fc cross-reactivity. 3,3',5,5'-Tetramethylbenzidine (TMB), a substrate for horseradish peroxidase, was added to the wells to visualize the binding signal, whose absorbance was measured at 450 nM and corrected at 540 nM. An NKG2D-binding domain clone, an isotype control or a positive control (comprising heavy chain and light chain variable domains selected from SEQ ID NOs:101-104, or anti-mouse NKG2D clones MI-6 and CX-5 available at eBioscience) was added to each well.

[0271] The isotype control showed minimal binding to recombinant NKG2D-Fc proteins, while the positive control bound strongest to the recombinant antigens. NKG2D-binding domains produced by all clones demonstrated binding across human, mouse, and cynomolgus recombinant NKG2D-Fc proteins, although with varying affinities from clone to clone. Generally, each anti-NKG2D clone bound to human (FIG. 3) and cynomolgus (FIG. 4) recombinant NKG2D-Fc with similar affinity, but with lower affinity to mouse (FIG. 5) recombinant NKG2D-Fc.

NKG2D-binding domains bind to cells expressing NKG2D

[0272] EL4 mouse lymphoma cell lines were engineered to express human or mouse NKG2D-CD3 zeta signaling domain chimeric antigen receptors. An NKG2D-binding clone, an isotype control, or a positive control was used at a 100 nM concentration to stain extracellular NKG2D expressed on the EL4 cells. The antibody binding was detected using fluorophore-conjugated anti-human IgG secondary antibodies. Cells were analyzed by flow

cytometry, and fold-over-background (FOB) was calculated using the mean fluorescence intensity (MFI) of NKG2D-expressing cells compared to parental EL4 cells.

[0273] NKG2D-binding domains produced by all clones bound to EL4 cells expressing human and mouse NKG2D. Positive control antibodies (comprising heavy chain and light chain variable domains selected from SEQ ID NOs:101-104, or anti-mouse NKG2D clones MI-6 and CX-5 available at eBioscience) gave the best FOB binding signal. The NKG2D-binding affinity for each clone was similar between cells expressing human NKG2D (FIG. 6) and mouse (FIG. 7) NKG2D.

Example 2 – NKG2D-binding domains block natural ligand binding to NKG2D

Competition With ULBP-6

[0274] Recombinant human NKG2D-Fc proteins were adsorbed to wells of a microplate, and the wells were blocked with bovine serum albumin to reduce non-specific binding. A saturating concentration of ULBP-6-His-biotin was added to the wells, followed by addition of the NKG2D-binding domain clones. After a 2-hour incubation, wells were washed and ULBP-6-His-biotin that remained bound to the NKG2D-Fc coated wells was detected by streptavidin-conjugated to horseradish peroxidase and TMB substrate. Absorbance was measured at 450 nM and corrected at 540 nM. After subtracting background, specific binding of NKG2D-binding domains to the NKG2D-Fc proteins was calculated from the percentage of ULBP-6-His-biotin that was blocked from binding to the NKG2D-Fc proteins in wells. The positive control antibody (comprising heavy chain and light chain variable domains selected from SEQ ID NOs:101-104) and various NKG2D-binding domains blocked ULBP-6 binding to NKG2D, while isotype control showed little competition with ULBP-6 (FIG. 8).

ULBP-6 sequence is represented by SEQ ID NO:108

MAAAAIPALLLCLPLLFLLFGWSRARRDDPHSLCYDITVIPKFRPGPRWCAVQ
GQVDEKTFLHYDCGNKTVTPVSPLGKKLNVTMAWKAQNPVLREVVDILTEQ
LLDIQLENYTPKEPLTLQARMSCEQKAEGHSSGSWQFSIDGQTFLLFDSEKRM
WTTVHPGARKMKEKWENDKDVAMSFHYISMGDCIGWLEDFLMGMDSTLEP
SAGAPLAMSSGTTQLRATATTLILCCLLIILPCFILPGI (SEQ ID NO:108)

Competition With MICA

[0275] Recombinant human MICA-Fc proteins were adsorbed to wells of a microplate, and the wells were blocked with bovine serum albumin to reduce non-specific binding.

NKG2D-Fc-biotin was added to wells followed by NKG2D-binding domains. After incubation and washing, NKG2D-Fc-biotin that remained bound to MICA-Fc coated wells was detected using streptavidin-HRP and TMB substrate. Absorbance was measured at 450 nM and corrected at 540 nM. After subtracting background, specific binding of NKG2D-binding domains to the NKG2D-Fc proteins was calculated from the percentage of NKG2D-Fc-biotin that was blocked from binding to the MICA-Fc coated wells. The positive control antibody (comprising heavy chain and light chain variable domains selected from SEQ ID NOs:101-104) and various NKG2D-binding domains blocked MICA binding to NKG2D, while isotype control showed little competition with MICA (FIG. 9).

Competition With Rae-1 delta

[0276] Recombinant mouse Rae-1delta-Fc (purchased from R&D Systems) was adsorbed to wells of a microplate, and the wells were blocked with bovine serum albumin to reduce non-specific binding. Mouse NKG2D-Fc-biotin was added to the wells followed by NKG2D-binding domains. After incubation and washing, NKG2D-Fc-biotin that remained bound to Rae-1delta-Fc coated wells was detected using streptavidin-HRP and TMB substrate. Absorbance was measured at 450 nM and corrected at 540 nM. After subtracting background, specific binding of NKG2D-binding domains to the NKG2D-Fc proteins was calculated from the percentage of NKG2D-Fc-biotin that was blocked from binding to the Rae-1delta-Fc coated wells. The positive control (comprising heavy chain and light chain variable domains selected from SEQ ID NOs:101-104, or anti-mouse NKG2D clones MI-6 and CX-5 available at eBioscience) and various NKG2D-binding domain clones blocked Rae-1delta binding to mouse NKG2D, while the isotype control antibody showed little competition with Rae-1delta (FIG. 10).

Example 3 – NKG2D-binding domain clones activate NKG2D

[0277] Nucleic acid sequences of human and mouse NKG2D were fused to nucleic acid sequences encoding a CD3 zeta signaling domain to obtain chimeric antigen receptor (CAR) constructs. The NKG2D-CAR constructs were then cloned into a retrovirus vector using Gibson assembly and transfected into expi293 cells for retrovirus production. EL4 cells were infected with viruses containing NKG2D-CAR together with 8 µg/mL polybrene. 24 hours after infection, the expression levels of NKG2D-CAR in the EL4 cells were analyzed by flow cytometry, and clones which express high levels of the NKG2D-CAR on the cell surface were selected.

[0278] To determine whether NKG2D-binding domains activate NKG2D, they were adsorbed to wells of a microplate, and NKG2D-CAR EL4 cells were cultured on the antibody fragment-coated wells for 4 hours in the presence of brefeldin-A and monensin. Intracellular TNF-α production, an indicator for NKG2D activation, was assayed by flow cytometry. The percentage of TNF-α positive cells was normalized to the cells treated with the positive control. All NKG2D-binding domains activated both human NKG2D (FIG. 11) and mouse NKG2D (FIG. 12).

Example 4 – NKG2D-binding domains activate NK cells

Primary human NK cells

[0279] Peripheral blood mononuclear cells (PBMCs) were isolated from human peripheral blood buffy coats using density gradient centrifugation. NK cells ($CD3^-CD56^+$) were isolated using negative selection with magnetic beads from PBMCs, and the purity of the isolated NK cells was typically >95%. Isolated NK cells were then cultured in media containing 100 ng/mL IL-2 for 24-48 hours before they were transferred to the wells of a microplate to which the NKG2D-binding domains were adsorbed, and cultured in the media containing fluorophore-conjugated anti-CD107a antibody, brefeldin-A, and monensin. Following culture, NK cells were assayed by flow cytometry using fluorophore-conjugated antibodies against CD3, CD56 and IFN-γ. CD107a and IFN-γ staining were analyzed in $CD3^-CD56^+$ cells to assess NK cell activation. The increase in CD107a/IFN-γ double-positive cells is indicative of better NK cell activation through engagement of two activating receptors rather than one receptor. NKG2D-binding domains and the positive control (*e.g.*, heavy chain variable domain represent by SEQ ID NO:101 or SEQ ID NO:103, and light chain variable domain represented by SEQ ID NO:102 or SEQ ID NO:104) showed a higher percentage of NK cells becoming $CD107a^+$ and IFN-γ^+ than the isotype control (FIG. 13 & FIG. 14 represent data from two independent experiments, each using a different donor's PBMC for NK cell preparation).

Primary mouse NK cells

[0280] Spleens were obtained from C57Bl/6 mice and crushed through a 70 μm cell strainer to obtain single cell suspension. Cells were pelleted and resuspended in ACK lysis buffer (purchased from Thermo Fisher Scientific #A1049201; 155 mM ammonium chloride, 10 mM potassium bicarbonate, 0.01 mM EDTA) to remove red blood cells. The remaining cells were cultured with 100 ng/mL hIL-2 for 72 hours before being harvested and prepared

for NK cell isolation. NK cells ($CD3^-NK1.1^+$) were then isolated from spleen cells using a negative depletion technique with magnetic beads with typically >90% purity. Purified NK cells were cultured in media containing 100 ng/mL mIL-15 for 48 hours before they were transferred to the wells of a microplate to which the NKG2D-binding domains were adsorbed, and cultured in the media containing fluorophore-conjugated anti-CD107a antibody, brefeldin-A, and monensin. Following culture in NKG2D-binding domain-coated wells, NK cells were assayed by flow cytometry using fluorophore-conjugated antibodies against CD3, NK1.1 and IFN-γ. CD107a and IFN-γ staining were analyzed in $CD3^-NK1.1^+$ cells to assess NK cell activation. The increase in CD107a/IFN-γ double-positive cells is indicative of better NK cell activation through engagement of two activating receptors rather than one receptor. NKG2D-binding domains and the positive control (selected from anti-mouse NKG2D clones MI-6 and CX-5 available at eBioscience) showed a higher percentage of NK cells becoming $CD107a^+$ and IFN-γ^+ than the isotype control (FIG. 15 & FIG. 16 represent data from two independent experiments, each using a different mouse for NK cell preparation).

Example 5 – NKG2D-binding domains enable cytotoxicity of target tumor cells

[0281] Human and mouse primary NK cell activation assays demonstrated increased cytotoxicity markers on NK cells after incubation with NKG2D-binding domains. To address whether this translates into increased tumor cell lysis, a cell-based assay was utilized where each NKG2D-binding domain was developed into a monospecific antibody. The Fc region was used as one targeting arm, while the Fab fragment regions (NKG2D-binding domain) acted as another targeting arm to activate NK cells. THP-1 cells, which are of human origin and express high levels of Fc receptors, were used as a tumor target and a Perkin Elmer DELFIA Cytotoxicity Kit was used. THP-1 cells were labeled with BATDA reagent, and resuspended at 10^5/mL in culture media. Labeled THP-1 cells were then combined with NKG2D antibodies and isolated mouse NK cells in wells of a microtiter plate at 37 °C for 3 hours. After incubation, 20 µL of the culture supernatant was removed, mixed with 200 µL of Europium solution and incubated with shaking for 15 minutes in the dark. Fluorescence was measured over time by a PheraStar plate reader equipped with a time-resolved fluorescence module (Excitation 337 nM, Emission 620 nM) and specific lysis was calculated according to the kit instructions.

[0282] The positive control, ULBP-6 - a natural ligand for NKG2D – conjugated to Fc, showed increased specific lysis of THP-1 target cells by mouse NK cells. NKG2D antibodies

also increased specific lysis of THP-1 target cells, while isotype control antibody showed reduced specific lysis. The dotted line indicates specific lysis of THP-1 cells by mouse NK cells without antibody added (FIG. 17).

Example 6 – NKG2D antibodies show high thermostability

[0283] Melting temperatures of NKG2D-binding domains were assayed using differential scanning fluorimetry. The extrapolated apparent melting temperatures are high relative to typical IgG1 antibodies (FIG. 18).

Example 7 – Synergistic activation of human NK cells by cross-linking NKG2D and CD16

Primary human NK cell activation assay

[0284] Peripheral blood mononuclear cells (PBMCs) were isolated from peripheral human blood buffy coats using density gradient centrifugation. NK cells were purified from PBMCs using negative magnetic beads (StemCell # 17955). NK cells were >90% $CD3^-$ $CD56^+$ as determined by flow cytometry. Cells were then expanded 48 hours in media containing 100 ng/mL hIL-2 (Peprotech #200-02) before use in activation assays. Antibodies were coated onto a 96-well flat-bottom plate at a concentration of 2 µg/mL (anti-CD16, Biolegend # 302013) and 5 µg/mL (anti-NKG2D, R&D #MAB139) in 100 µL sterile PBS overnight at 4 °C followed by washing the wells thoroughly to remove excess antibody. For the assessment of degranulation IL-2-activated NK cells were resuspended at 5×10^5 cells/mL in culture media supplemented with 100 ng/mL human IL-2 (hIL2) and 1 µg/mL APC-conjugated anti-CD107a mAb (Biolegend # 328619). 1×10^5 cells/well were then added onto antibody coated plates. The protein transport inhibitors Brefeldin A (BFA, Biolegend # 420601) and Monensin (Biolegend # 420701) were added at a final dilution of 1:1000 and 1:270, respectively. Plated cells were incubated for 4 hours at 37 °C in 5% CO_2. For intracellular staining of IFN-γ, NK cells were labeled with anti-CD3 (Biolegend #300452) and anti-CD56 mAb (Biolegend # 318328), and subsequently fixed, permeabilized and labeled with anti-IFN-γ mAb (Biolegend # 506507). NK cells were analyzed for expression of CD107a and IFN-γ by flow cytometry after gating on live $CD56^+CD3^-$cells.

[0285] To investigate the relative potency of receptor combination, crosslinking of NKG2D or CD16, and co-crosslinking of both receptors by plate-bound stimulation was performed. As shown in Figure 19 (FIGs. 19A-19C), combined stimulation of CD16 and

NKG2D resulted in highly elevated levels of CD107a (degranulation) (FIG. 19A) and/or IFN-γ production (FIG. 19B). Dotted lines represent an additive effect of individual stimulations of each receptor.

CD107a levels and intracellular IFN-γ production of IL-2-activated NK cells were analyzed after 4 hours of plate-bound stimulation with anti-CD16, anti-NKG2D or a combination of both monoclonal antibodies. Graphs indicate the mean (n = 2) ± Sd. FIG. 19A demonstrates levels of CD107a; FIG. 19B demonstrates levels of IFN-γ; FIG. 19C demonstrates levels of CD107a and IFN-γ. Data shown in FIGs. 19A-19C are representative of five independent experiments using five different healthy donors.

Example 8 – Trispecific binding protein (TriNKET)-mediated enhanced cytotoxicity of target cells

Assessment of TriNKET or mAb binding to cell expressed human cancer antigens

[0286] Human cancer cell lines expressing EPCAM were used to assess tumor antigen binding of TriNKETs derived from EPCAM targeting clone MT110 in F4 and F3' formats. The human cell lines H747, HCC827 and HCT116 were used to assess binding of TriNKETs and mAb to cell expressed EPCAM. TriNKETs or mAb were diluted and incubated with the respective cells. Binding was detected using a fluorophore conjugated anti-human IgG secondary antibody. Cells were analyzed by flow cytometry, binding MFI to cell expressed EPCAM was normalized to human recombinant IgG1 stained controls to obtain fold over background values.

[0287] FIG. 37 shows binding of trispecific binding proteins (TriNKETs) of the present disclosure (A49-F4-TriNKET-MT110 and A49-F3'-TriNKET-MT110) and parental monoclonal antibody (mAb) to EpCAM expressing H747 human colorectal cancer cells. FIG. 38 shows binding of trispecific binding proteins (TriNKETs) of the present disclosure (A49-F4-TriNKET-MT110 and A49-F3'-TriNKET-MT110) and parental monoclonal antibody (mAb) to EpCAM expressing HCC827 human lung cancer cells. FIG. 39 shows binding of trispecific binding proteins (TriNKETs) of the present disclosure (A49-F4-TriNKET-MT110 and A49-F3'-TriNKET-MT110) and parental monoclonal antibody (mAb) to EpCAM expressing HCT116 human colorectal cancer cells. Overall binding was stronger with F4-TriNKET compared to F3'-TriNKET that incorporate MT110 EPCAM binder.

Primary human NK cell cytotoxicity assay

[0288] PBMCs were isolated from human peripheral blood buffy coats using density gradient centrifugation. Isolated PBMCs were washed and prepared for NK cell isolation. NK cells were isolated using a negative selection technique with magnetic beads. Purity of isolated NK cells achieved was typically greater than 90% $CD3^-$ $CD56^+$. Isolated NK cells were incubated overnight without cytokine, and used the following day in cytotoxicity assays.

DELFIA cytotoxicity assay

[0289] Human cancer cell lines expressing a target of interest were harvested from culture, washed with HBS, and resuspended in growth media at 10^6 cells/mL for labeling with BATDA reagent (Perkin Elmer, AD0116). Manufacturer instructions were followed for labeling of the target cells. After labeling, cells were washed 3 times with HBS and resuspended at $0.5x10^5$ cells/mL in culture media. To prepare the background wells, an aliquot of the labeled cells was put aside, and the cells were spun out of the media. 100 µL of the media was carefully added to wells in triplicate to avoid disturbing the pelleted cells. 100 µL of BATDA-labeled cells were added to each well of the 96-well plate. Wells were saved for spontaneous release from target cells and prepared for lysis of target cells by addition of 1% Triton-X. Monoclonal antibodies or TriNKETs against the tumor target of interest were diluted in culture media, and 50 µL of diluted mAb or TriNKET was added to each well. Rested NK cells were harvested from culture, washed, and resuspended at $1.0x10^5$-$2.0x10^6$ cell/mL in culture media, depending on the desired effector to target cell ratio. 50 µL of NK cells were added to each well of the plate to provide a total of 200 µL culture volume. The plate was incubated at 37 °C with 5% CO_2 for 2-4 hours before developing the assay.

[0290] After culturing for 2-3 hours, the plate was removed from the incubator and the cells were pelleted by centrifugation at 200xg for 5 minutes. 20 µL of culture supernatant was transferred to a clean microplate provided from the manufacturer, and 200 µL of room temperature Europium solution was added to each well. The plate was protected from light and incubated on a plate shaker at 250 rpm for 15 minutes. The plate was read using a SpectraMax® i3X instrument (Molecular Devices), and percent specific lysis was calculated (% Specific lysis = (Experimental release – Spontaneous release) / (Maximum release – Spontaneous release)) x 100).

[0291] FIG. 40A and FIG. 40B TriNKET-mediated cytotoxicity of rested human NK cells from two different healthy donors against H747 human cancer cells. FIG. 41A and FIG.

41B TriNKET-mediated cytotoxicity of rested human NK cells from two different healthy donors against HCC827 human cancer cells. FIG. 42A and FIG. 42B TriNKET-mediated cytotoxicity of rested human NK cells from two different healthy donors against MCF7 human cancer cells. FIG. 43A and FIG. 43B TriNKET-mediated cytotoxicity of rested human NK cells from two different healthy donors against HCT116 human cancer cells. EPCAM-targeting F4-TriNKET killed target cells more effectively than the parental mAb targeting EPCAM. F4-TriNKET also killed target cells more potently than F3'-TriNKET, which may be a reflection of the stronger binding of F4-TriNKET to target cells.

INCORPORATION BY REFERENCE

[0292] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

EQUIVALENTS

[0293] The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

[0294] Other embodiments as described herein are defined in the following paragraphs:

1. A protein comprising:

(a) a first antigen-binding site that binds Natural killer group 2 member D (NKG2D);

(b) a second antigen-binding site that binds an antigen selected from the group consisting of: EpCAM, Cancer Antigen 125 (CA125), sodium/phosphate cotransporter 2B (NaPi2b), Nectin cell adhesion molecule 4 (Nectin4), Fucosyl-GM1 (monosialotetrahexosylganglioside), disintegrin and metalloproteinase domain-containing protein 8 (ADAM8), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), solute carrier family 44 member 4 (SLC44A4), and sialylated Lewis a antigen (CA19-9); and

(c) an antibody Fc domain or a portion thereof sufficient to bind cluster of differentiation 16 (CD16), or a third antigen-binding site that binds CD16.

2. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds EpCAM; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

3. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a tumor associated antigen selected from Cancer Antigen 125 (CA125), sodium/phosphate cotransporter 2B (NaPi2b), Nectin cell adhesion molecule 4 (Nectin4), Fucosyl-GM1 (monosialotetrahexosylganglioside), disintegrin and metalloproteinase domain-containing protein 8 (ADAM8), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), solute carrier family 44 member 4 (SLC44A4), and sialylated Lewis a antigen (CA19-9); and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

4. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a tumor associated antigen selected from sodium-dependent phosphate transport protein 2b (NaPi2b); and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

5. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a tumor associated antigen Nectin4; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

6. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a multiple myeloma associated antigen Fucosyl-GM1; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

7. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a T-cell associated tumor antigen selected from SLC44A4; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

8. The protein of any one of paragraphs 1-7, wherein the first antigen-binding site binds to NKG2D in humans, non-human primates, and rodents.

9. The protein of any one of paragraphs 1-8, wherein the first antigen-binding site comprises a heavy chain variable domain and a light chain variable domain.

10. A protein according to paragraph 9, wherein the heavy chain variable domain and the light chain variable domain are present on the same polypeptide.

11. A protein according to paragraph 9 or 10, wherein the second antigen-binding site comprises a heavy chain variable domain and a light chain variable domain.

12. A protein according to paragraph 11, wherein the heavy chain variable domain and the light chain variable domain of the second antigen-binding site are present on the same polypeptide.

13. A protein according to paragraph 11 or 12, wherein the light chain variable domain of the first antigen-binding site has an amino acid sequence identical to the amino acid sequence of the light chain variable domain of the second antigen-binding site.

14. A protein comprising:

(a) a first antigen-binding site comprising an Fab fragment that binds NKG2D;

b) a second antigen-binding site comprising a single-chain variable fragment (scFv) that binds EpCAM; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

15. The protein of paragraph 14, wherein the scFv is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or the third antigen-binding site that binds CD16, via a hinge comprising Ala-Ser or Gly-Ala-Ser, wherein the scFv comprises a heavy chain variable domain and a light chain variable domain.

16. The protein of paragraph 15, wherein the scFv is linked to the antibody Fc domain.

17. The protein of paragraph 14 or 15, wherein the heavy chain variable domain of the scFv forms a disulfide bridge with the light chain variable domain of the scFv.

18. The protein of paragraph 17, wherein the disulfide bridge is formed between C44 from the heavy chain variable domain and C100 from the light chain variable domain.

19. The protein of paragraph 18, wherein the scFv is linked to the antibody Fc domain, wherein the light chain variable domain of the scFv is positioned at the N-terminus of the heavy chain variable domain of the scFv, and is linked to the heavy chain variable domain of the scFv via a flexible linker $(GlyGlyGlyGlySer)_4$ $((G4S)_4)$, and the Fab is linked to the antibody Fc domain.

20. A protein according to any one of paragraphs 15-19, wherein the heavy chain variable domain of the scFv is linked to the light chain variable domain of the scFv via a flexible linker.

21. The protein of paragraph 20, wherein the flexible linker comprises $(GlyGlyGlyGlySer)_4$ ($(G4S)_4$).

22. A protein according to any one of paragraphs 15-21, wherein the heavy chain variable domain of the scFv is positioned at the N-terminus or the C-terminus of the light chain variable domain of the scFv.

23. The protein of paragraph 22, wherein the light chain variable domain of the scFv is positioned at the N-terminus of the heavy chain variable domain of the scFv.

24. A protein according to any one of paragraphs 14 to 23, wherein the Fab fragment is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16 or the third antigen-binding site that binds CD16.

25. The protein of paragraph 24, wherein the heavy chain portion of the Fab fragment comprises a heavy chain variable domain and a CH1 domain, and wherein the heavy chain variable domain is linked to the CH1 domain.

26. A protein according to paragraph 24 or 25, wherein the Fab fragment is linked to the antibody Fc domain.

27. A protein according to any one of paragraphs 14 to 26 comprising a sequence selected from SEQ ID NO:208 and SEQ ID NO:209.

28. A protein according to any one of paragraphs 15-27 comprising an scFv linked to an antibody Fc domain, wherein the scFv linked to the antibody Fc domain is represented by a sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

29. A protein according to any one of paragraphs 15-27 comprising a sequence selected from SEQ ID NO:212 and SEQ ID NO:213.

30. A protein according to any one of paragraphs 15-26 comprising a sequence at least 90% identical to an amino acid sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

31. A protein according to any one of paragraphs 15-26 comprising a sequence at least 95% identical to an amino acid sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

32. A protein according to any one of paragraphs 15-26 comprising a sequence at least 99% identical to an amino acid sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

33. A protein according to any one of paragraphs 15-32 comprising a sequence at least 90% identical to an amino acid sequence selected from SEQ ID NO:212 and SEQ ID NO:213.

34. A protein according to any one of paragraphs 15-32 comprising a sequence at least 95% identical to an amino acid sequence selected from SEQ ID NO:212 and SEQ ID NO:213.

35. A protein according to any one of paragraphs 15-32 comprising a sequence at least 99% identical to an amino acid sequence selected from SEQ ID NO:212 and SEQ ID NO:213.

36. A protein comprising:

(a) a first antigen-binding site comprising a single-chain variable fragment (scFv) that binds NKG2D;

(b) a second antigen-binding site that binds EpCAM; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

37. A protein according to paragraph 36 further comprising an additional antigen-binding site that binds EpCAM.

38. The protein according to paragraph 36 or 37, wherein the second antigen-binding site that binds EpCAM is an Fab fragment.

39. The protein according to paragraph 37 or 38, wherein the second and the additional antigen-binding site that bind EpCAM are Fab fragments.

40. The protein according to paragraph 36 or 37, wherein the second and the additional antigen-binding site that bind EpCAM are scFvs.

41. The protein according to any one of paragraphs 36-40, wherein the heavy chain variable domain of the scFv that binds NKG2D is positioned at the N-terminus or the C-terminus of the light chain variable domain of the scFv.

42. The protein according to paragraph 41, wherein the light chain variable domain is positioned at the N-terminus of the heavy chain variable domain of the scFv that binds NKG2D.

43. The protein according to any one of paragraphs 36-42, wherein the scFv that binds to NKG2D is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

44. The protein according to paragraph 43, wherein the scFv that binds to NKG2D is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16 *via* a hinge comprising Ala-Ser or Gly-Ala-Ser.

45. The protein according to paragraph 43, wherein the scFv that binds to NKG2D is linked to the C-terminus of the antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16 *via* a flexible linker comprising SGSGGGGS (SEQ ID NO: 207).

46. The protein according to paragraph 45, wherein the C-terminus of the antibody Fc domain is linked to the N-terminus of the light chain variable domain of the scFv that binds NKG2D.

47. The protein according to any one of paragraphs 36-46, wherein within the scFv that binds NKG2D, a disulfide bridge is formed between the heavy chain variable domain of the scFv and the light chain variable domain of the scFv.

48. The protein according to paragraph 47, wherein the disulfide bridge is formed between C44 from the heavy chain variable domain and C100 from the light chain variable domain.

49. The protein according to any one of paragraphs 36-48, wherein, within the scFv that binds NKG2D, the heavy chain variable domain is linked to the light chain variable domain via a flexible linker.

50. The protein according to paragraph 49, wherein the flexible linker comprises $(GlyGlyGlyGlySer)_4$ $(G4S)_4$).

51. The protein according to any one of paragraphs 40 to 50, wherein the second and the additional antigen-binding site scFvs are linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or the third antigen-binding site that binds CD16, *via* a hinge comprising Ala-Ser.

52. The protein according to any one of paragraphs 40 to 51, wherein the second and the additional antigen-binding site scFvs are linked to the antibody Fc domain *via* a hinge comprising Ala-Ser.

53. The protein according to paragraph 51 or 52, wherein a disulfide bridge is formed between the heavy chain variable domain and the light chain variable domain of the second antigen-binding site and/or the additional antigen-binding site.

54. The protein according to paragraph 53, wherein the disulfide bridge is formed between C44 from the heavy chain variable domain and C100 from the light chain variable domain.

55. The protein according to any one of paragraphs 36 to 54, wherein the scFv that binds NKG2D comprises a light chain variable domain positioned at the N-terminus of a heavy chain variable domain, wherein the light chain variable domain is linked to the heavy chain variable domain of the scFv via a flexible linker $(GlyGlyGlyGlySer)_4$ $(G4S)_4$), and the scFv that binds NKG2D is linked to the antibody Fc domain *via* a hinge comprising Ala-Ser or Gly-Ala-Ser.

56. A protein comprising an amino acid sequence of SEQ ID NO:203.

57. A protein comprising an amino acid sequence of SEQ ID NO:203 and SEQ ID NO:204.

58. A protein comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:203.

59. A protein comprising an amino acid sequence at least 95% identical to an amino acid sequence of SEQ ID NO:203.

60. A protein comprising an amino acid sequence at least 99% identical to an amino acid sequence of SEQ ID NO:203.

61. A protein according to any one of the preceding paragraphs, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to an amino acid sequence selected from: SEQ ID NO:1, SEQ ID NO:41, SEQ ID NO:49, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:69, SEQ ID NO:77, SEQ ID NO:85, and SEQ ID NO:93.

62. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:41 and a light chain variable domain at least 90% identical to SEQ ID NO:42.

63. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:49 and a light chain variable domain at least 90% identical to SEQ ID NO:50.

64. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:57 and a light chain variable domain at least 90% identical to SEQ ID NO:58.

65. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:59 and a light chain variable domain at least 90% identical to SEQ ID NO:60.

66. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:61 and a light chain variable domain at least 90% identical to SEQ ID NO:62.

67. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:69 and a light chain variable domain at least 90% identical to SEQ ID NO:70.

68. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:77 and a light chain variable domain at least 90% identical to SEQ ID NO:78.

69. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:85 and a light chain variable domain at least 90% identical to SEQ ID NO:86.

70. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:93 and a light chain variable domain at least 90% identical to SEQ ID NO:94.

71. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:101 and a light chain variable domain at least 90% identical to SEQ ID NO:102.

72. A protein according to any one of paragraphs 1-60, wherein the first antigen-binding site comprises a heavy chain variable domain at least 90% identical to SEQ ID NO:103 and a light chain variable domain at least 90% identical to SEQ ID NO:104.

73. The protein of any one of paragraphs 1-10, wherein the first antigen-binding site is a single-domain antibody.

74. The protein of paragraph 73, wherein the single-domain antibody is a V_HH fragment or a V_{NAR} fragment.

75. A protein of any one of paragraphs 1-10 or 73-74, wherein the second antigen-binding site comprises a heavy chain variable domain and a light chain variable domain.

76. A protein of paragraph 75, wherein the heavy chain variable domain and the light chain variable domain of the second antigen-binding site are present on the same polypeptide.

77. A protein of any of paragraphs 1, 2, or 61-72, wherein the second antigen-binding site binds EpCAM, the heavy chain variable domain of the second antigen-binding site comprises

an amino acid sequence at least 90% identical to SEQ ID NO:115 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:119.

78. A protein of paragraph 77, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:116;

a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:117; and

a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:118.

79. A protein of paragraph 78, wherein the light chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:120;

a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:121;

and a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:122.

80. A protein of any one of paragraphs 1, 2, or 61-72, wherein the second antigen-binding site binds EpCAM, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:123 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:127.

81. A protein of paragraph 80, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:124;

a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:125; and

a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:126.

82. A protein according to paragraph 81, wherein the light chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:128;

a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:129; and

a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:130.

83. A protein of any one of paragraphs 1, 2, or 61-72, wherein the second antigen-binding site binds EpCAM, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:131 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:135.

84. A protein of paragraph 83, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:132;

a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:133; and

a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:134.

85. A protein of paragraph 84, wherein the light chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:136;

a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:137; and

a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:138.

86. A protein of any one of paragraphs 1, 2, or 61-72, wherein the second antigen-binding site binds EpCAM, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:139 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:143.

87. A protein of paragraph 86, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:140;

a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:141; and

a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:142.

88. A protein of paragraph 87, wherein the light chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:144;

a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:145; and

a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:146.

89. A protein of any one of paragraphs 1, 3, or 61-72, wherein the second antigen-binding site binds CA125, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:155 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:159.

90. A protein of any one of paragraphs 1, 3, or 61-72, wherein the second antigen-binding site binds CA125, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:163 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:167.

91. A protein of any one of paragraphs 1, 4, or 61-72, wherein the second antigen-binding site binds NaPi2b, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:171 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:175.

92. A protein of any one of paragraphs 1, 5, or 61-72, wherein the second antigen-binding site binds Nectin4, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:179 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:183.

93. A protein of any one of paragraphs 1, 6, or 61-72, wherein the second antigen-binding site binds fucosyl-GM1, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:187 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:191.

94. A protein of any one of paragraphs 1, 7, or 61-72, wherein the second antigen-binding site binds SLC44A4, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:195 and the light

chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:199.

95. A protein according to any one of paragraphs 1-94, wherein the antibody Fc domain comprises hinge and CH2 domains of a human IgG1 antibody.

96. A protein of paragraph 95, wherein the Fc domain comprises an amino acid sequence at least 90% identical to amino acids 234-332 of a human IgG1 antibody.

97. A protein of paragraph 96, wherein the Fc domain comprises amino acid sequence at least 90% identical to the Fc domain of human IgG1 and differs at one or more positions selected from the group consisting of Q347, Y349, L351, S354, E356, E357, K360, Q362, S364, T366, L368, K370, N390, K392, T394, D399, S400, D401, F405, Y407, K409, T411, K439.

98. A protein according to any one of paragraphs 1-96, wherein the protein binds to NKG2D with a K_D of 10 nM or weaker affinity.

99. A formulation comprising a protein according to any one of the preceding paragraphs and a pharmaceutically acceptable carrier.

100. A cell comprising one or more nucleic acids expressing a protein according to any one of paragraphs 1-98.

101. A method of directly and/or indirectly enhancing tumor cell death, the method comprising exposing a tumor and natural killer cells to a protein according to any one of paragraphs 1-98.

102. A method of treating cancer, wherein the method comprises administering a protein according to any one of paragraphs 1-98 or a formulation according to paragraph 99 to a patient.

103. The method of paragraph 102, wherein when the second binding site binds EpCAM, the cancer is selected from the group consisting of head and neck cancer, ovarian cancer, bladder cancer, breast cancer, colorectal cancer, prostate cancer, gastric cancer, liver cancer, esophageal cancer, and lung cancer.

[0295] Still further embodiments are within the scope of the following claims.

[0296] In a first aspect, the invention relates to a protein comprising:

(a) a first antigen-binding site that binds Natural killer group 2 member D (NKG2D);

(b) a second antigen-binding site that binds an antigen selected from the group consisting of: EpCAM, Cancer Antigen 125 (CA125), sodium/phosphate cotransporter 2B (NaPi2b), Fucosyl-GM1 (monosialotetrahexosylganglioside), disintegrin and metalloproteinase domain-containing protein 8 (ADAM8), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), solute carrier family 44 member 4 (SLC44A4), and sialylated Lewis a antigen (CA19-9); and

(c) an antibody Fc domain or a portion thereof sufficient to bind cluster of differentiation 16 (CD16), or a third antigen-binding site that binds CD16.

[0297] In a second aspect, the invention relates to a protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a tumor associated antigen selected from Cancer Antigen 125 (CA125), sodium/phosphate cotransporter 2B (NaPi2b), Fucosyl-GM1 (monosialotetrahexosylganglioside), disintegrin and metalloproteinase domain-containing protein 8 (ADAM8), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), solute carrier family 44 member 4 (SLC44A4), and sialylated Lewis a antigen (CA19-9); and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

[0298] In a third aspect, the invention relates to a protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a tumor associated antigen selected from Cancer Antigen 125 (CA125), sodium/phosphate cotransporter 2B (NaPi2b), Fucosyl-GM1 (monosialotetrahexosylganglioside), disintegrin and

metalloproteinase domain-containing protein 8 (ADAM8), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), solute carrier family 44 member 4 (SLC44A4), and sialylated Lewis a antigen (CA19-9); and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

[0299] In a fourth aspect, the invention relates to a protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a tumor associated antigen selected from sodium-dependent phosphate transport protein 2b (NaPi2b); and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

[0300] In a fifth aspect, the invention relates to a protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a multiple myeloma associated antigen Fucosyl-GM1; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

[0301] In a sixth aspect, the invention relates to a protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a T-cell associated tumor antigen SLC44A4; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

[0302] In a sixth aspect, the invention relates to a protein comprising:

(a) a first antigen-binding site comprising an Fab fragment that binds NKG2D;

b) a second antigen-binding site comprising a single-chain variable fragment (scFv) that binds EpCAM; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

[0303] In a seventh aspect, the invention relates to a protein comprising:

(a) a first antigen-binding site comprising a single-chain variable fragment (scFv) that binds NKG2D;

(b) a second antigen-binding site that binds EpCAM; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

[0304] In an eighth aspect, the invention relates to a protein comprising an amino acid sequence of SEQ ID NO:203.

[0305] In a nineth aspect, the invention relates to a protein comprising an amino acid sequence of SEQ ID NO:203 and SEQ ID NO:204.

[0306] In a tenth aspect, the invention relates to a protein comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:203.

[0307] In a eleventh aspect, the invention relates to a protein comprising an amino acid sequence at least 95% identical to an amino acid sequence of SEQ ID NO:203.

[0308] In a twelfth aspect, the invention relates to a protein comprising an amino acid sequence at least 99% identical to an amino acid sequence of SEQ ID NO:203.

[0309] In a thirteenth aspect, the invention relates to a formulation comprising a protein according to any one of the first to twelfth aspects and a pharmaceutically acceptable carrier.

[0310] In a fourteenth aspect, the invention relates to a cell comprising one or more nucleic acids encoding a protein according to any one of the first to twelfth aspects.

[0311] In a fifteenth aspect, the invention relates to a method of directly and/or indirectly enhancing tumor cell death, the method comprising exposing the tumor cell and a natural killer cell to a protein to any one of the first to twelfth aspects.

[0312] In a sixteenth aspect, the invention relates to a method of treating cancer, wherein the method comprises administering a protein according to any one of the first to twelfth aspects or a formulation according the thirteenth aspect to a patient.

[0313] The term "comprise" and variants of the term such as "comprises" or "comprising" are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[0314] Any reference to any prior art in this specification is not, and should not be taken as an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge.

CLAIMS:

1. A protein comprising:

(a) a first antigen-binding site that binds Natural killer group 2 member D (NKG2D);

(b) a second antigen-binding site that binds an antigen selected from the group consisting of: EpCAM, Cancer Antigen 125 (CA125), sodium/phosphate cotransporter 2B (NaPi2b), Fucosyl-GM1 (monosialotetrahexosylganglioside), disintegrin and metalloproteinase domain-containing protein 8 (ADAM8), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), solute carrier family 44 member 4 (SLC44A4), and sialylated Lewis a antigen (CA19-9); and

(c) an antibody Fc domain or a portion thereof sufficient to bind cluster of differentiation 16 (CD16), or a third antigen-binding site that binds CD16.

2. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds EpCAM; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

3. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a tumor associated antigen selected from Cancer Antigen 125 (CA125), sodium/phosphate cotransporter 2B (NaPi2b), Fucosyl-GM1 (monosialotetrahexosylganglioside), disintegrin and metalloproteinase domain-containing protein 8 (ADAM8), disintegrin and metalloproteinase domain-containing protein 9 (ADAM9), solute carrier family 44 member 4 (SLC44A4), and sialylated Lewis a antigen (CA19-9); and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

4. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a tumor associated antigen selected from sodium-dependent phosphate transport protein 2b (NaPi2b); and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

5. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a multiple myeloma associated antigen Fucosyl-GM1; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

6. A protein comprising:

(a) a first antigen-binding site that binds NKG2D;

(b) a second antigen-binding site that binds a T-cell associated tumor antigen SLC44A4; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

7. The protein of any one of claims 1-6, wherein the first antigen-binding site binds to NKG2D in humans and non-human primates.

8. The protein of any one of claims 1-7, wherein the first antigen-binding site comprises a heavy chain variable domain and a light chain variable domain.

9. A protein according to claim 8, wherein the heavy chain variable domain and the light chain variable domain are present on the same polypeptide.

10. A protein according to claim 8 or 9, wherein the second antigen-binding site comprises a heavy chain variable domain and a light chain variable domain.

11. A protein according to claim 10, wherein the heavy chain variable domain and the light chain variable domain of the second antigen-binding site are present on the same polypeptide.

12. A protein according to claim 10 or 11, wherein the light chain variable domain of the first antigen-binding site has an amino acid sequence identical to the amino acid sequence of the light chain variable domain of the second antigen-binding site.

13. A protein comprising:

(a) a first antigen-binding site comprising an Fab fragment that binds NKG2D;

(b) a second antigen-binding site comprising a single-chain variable fragment (scFv) that binds EpCAM; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

14. The protein of claim 13, wherein the scFv is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or the third antigen-binding site that binds CD16, via a hinge comprising Ala-Ser or Gly-Ala-Ser, wherein the scFv comprises a heavy chain variable domain and a light chain variable domain.

15. The protein of claim 14, wherein the scFv is linked to the antibody Fc domain.

16. The protein of claim 13 or 14, wherein the heavy chain variable domain of the scFv forms a disulfide bridge with the light chain variable domain of the scFv.

17. The protein of claim 16, wherein the disulfide bridge is formed between C44 from the heavy chain variable domain and C100 from the light chain variable domain.

18. The protein of claim 17, wherein the scFv is linked to the antibody Fc domain, wherein the light chain variable domain of the scFv is positioned at the N-terminus of the heavy chain variable domain of the scFv, and is linked to the heavy chain variable

domain of the scFv via a flexible linker (GlyGlyGlyGlySer)4 ((G4S)4), and the Fab is linked to the antibody Fc domain.

19. A protein according to any one of claims 14-18, wherein the heavy chain variable domain of the scFv is linked to the light chain variable domain of the scFv via a flexible linker.

20. The protein of claim 19, wherein the flexible linker comprises (GlyGlyGlyGlySer)4 ((G4S)4).

21. A protein according to any one of claims 14-20, wherein the heavy chain variable domain of the scFv is positioned at the N-terminus or the C-terminus of the light chain variable domain of the scFv.

22. The protein of claim 21, wherein the light chain variable domain of the scFv is positioned at the N-terminus of the heavy chain variable domain of the scFv.

23. A protein according to any one of claims 13-22, wherein the Fab fragment is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16 or the third antigen-binding site that binds CD16.

24. The protein of claim 23, wherein the heavy chain portion of the Fab fragment comprises a heavy chain variable domain and a CH1 domain, and wherein the heavy chain variable domain is linked to the CH1 domain.

25. A protein according to claim 23 or 24, wherein the Fab fragment is linked to the antibody Fc domain.

26. A protein according to any one of claims 13-25 comprising an amino acid sequence selected from SEQ ID NO:208 and SEQ ID NO:209.

27. A protein according to any one of claims 14-26 comprising an scFv linked to an antibody Fc domain, wherein the scFv linked to the antibody Fc domain is represented by an amino acid sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

28. A protein according to any one of claims 14-26 comprising a sequence selected from SEQ ID NO:212 and SEQ ID NO:213.

29. A protein according to any one of claims 14-25 comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

30. A protein according to any one of claims 14-25 comprising an amino acid sequence at least 95% identical to an amino acid sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

31. A protein according to any one of claims 14-25 comprising an amino acid sequence at least 99% identical to an amino acid sequence selected from SEQ ID NO:210 and SEQ ID NO:211.

32. A protein according to any one of claims 14-31 comprising an amino acid sequence at least 90% identical to an amino acid sequence selected from SEQ ID NO:212 and SEQ ID NO:213.

33. A protein according to any one of claims 14-31 comprising an amino acid sequence at least 95% identical to an amino acid sequence selected from SEQ ID NO:212 and SEQ ID NO:213.

34. A protein according to any one of claims 14-31 comprising an amino acid sequence at least 99% identical to an amino acid sequence selected from SEQ ID NO:212 and SEQ ID NO:213.

35. A protein comprising:

(a) a first antigen-binding site comprising a single-chain variable fragment (scFv) that binds NKG2D;

(b) a second antigen-binding site that binds EpCAM; and

(c) an antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

36. A protein according to claim 35 further comprising an additional antigen-binding site that binds EpCAM.

37. The protein according to claim 35 or 36, wherein the second antigen-binding site that binds EpCAM is an Fab fragment.

38. The protein according to claim 36 or 37, wherein the second and the additional antigen-binding site that bind EpCAM are Fab fragments.

39. The protein according to claim 35 or 36, wherein the second and the additional antigen-binding site that bind EpCAM are scFvs.

40. The protein according to any one of claims 35-39, wherein the heavy chain variable domain of the scFv that binds NKG2D is positioned at the N-terminus or the C-terminus of the light chain variable domain of the scFv.

41. The protein according to claim 40, wherein the light chain variable domain is positioned at the N-terminus of the heavy chain variable domain of the scFv that binds NKG2D.

42. The protein according to any one of claims 35-41, wherein the scFv that binds to NKG2D is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16.

43. The protein according to claim 42, wherein the scFv that binds to NKG2D is linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16 via a hinge comprising Ala-Ser or Gly-Ala-Ser.

44. The protein according to claim 42, wherein the scFv that binds to NKG2D is linked to the C-terminus of the antibody Fc domain or a portion thereof sufficient to bind CD16, or a third antigen-binding site that binds CD16 via a flexible linker comprising SGSGGGGS (SEQ ID NO: 207).

45. The protein according to claim 42, wherein the C-terminus of the antibody Fc domain is linked to the N-terminus of the light chain variable domain of the scFv that binds NKG2D.

46. The protein according to any one of claims 35-45, wherein within the scFv that binds NKG2D, a disulfide bridge is formed between the heavy chain variable domain of the scFv and the light chain variable domain of the scFv.

47. The protein according to claim 46, wherein the disulfide bridge is formed between C44 from the heavy chain variable domain and C100 from the light chain variable domain.

48. The protein according to any one of claims 35-47, wherein, within the scFv that binds NKG2D, the heavy chain variable domain is linked to the light chain variable domain via a flexible linker.

49. The protein according to claim 48, wherein the flexible linker comprises (GlyGlyGlyGlySer)4 (G4S)4).

50. The protein according to any one of claims 39-49, wherein the second and the additional antigen-binding site scFvs are linked to the antibody Fc domain or a portion thereof sufficient to bind CD16, or the third antigen-binding site that binds CD16, via a hinge comprising Ala-Ser.

51. The protein according to any one of claims 39-50, wherein the second and the additional antigen-binding site scFvs are linked to the antibody Fc domain via a hinge comprising Ala-Ser.

52. The protein according to claim 50 or 51, wherein a disulfide bridge is formed between the heavy chain variable domain and the light chain variable domain of the second antigen-binding site and/or the additional antigen-binding site.

53. The protein according to claim 52, wherein the disulfide bridge is formed between C44 from the heavy chain variable domain and C100 from the light chain variable domain.

54. The protein according to any one of claims 35-53, wherein the scFv that binds NKG2D comprises a light chain variable domain positioned at the N-terminus of a heavy chain variable domain, wherein the light chain variable domain is linked to the heavy chain variable domain of the scFv via a flexible linker (GlyGlyGlyGlySer)4

(G4S)4), and the scFv that binds NKG2D is linked to the antibody Fc domain via a hinge comprising Ala-Ser or Gly-Ala-Ser.

55. A protein comprising an amino acid sequence of SEQ ID NO:203.

56. A protein comprising an amino acid sequence of SEQ ID NO:203 and SEQ ID NO:204.

57. A protein comprising an amino acid sequence at least 90% identical to an amino acid sequence of SEQ ID NO:203.

58. A protein comprising an amino acid sequence at least 95% identical to an amino acid sequence of SEQ ID NO:203.

59. A protein comprising an amino acid sequence at least 99% identical to an amino acid sequence of SEQ ID NO:203.

60. A protein according to any one of the preceding claims, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to an amino acid sequence selected from: SEQ ID NO:85, SEQ ID NO:1, SEQ ID NO:41, SEQ ID NO:49, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:61, SEQ ID NO:69, SEQ ID NO:77, and SEQ ID NO:93.

61. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:85 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:86.

62. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:41 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:42.

63. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:49 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:50.

64. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:57 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:58.

65. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:59 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:60.

66. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:61 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:62.

67. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:69 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:70.

68. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:77 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:78.

69. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:93 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:94.

70. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:101 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:102.

71. A protein according to any one of claims 1-59, wherein the first antigen-binding site comprises a heavy chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:103 and a light chain variable domain amino acid sequence at least 90% identical to SEQ ID NO:104.

72. The protein of any one of claims 1-9, wherein the first antigen-binding site is a single-domain antibody.

73. The protein of claim 72, wherein the single-domain antibody is a V_HH fragment or a V_{NAR} fragment.

74. A protein of any one of claims 1-9 or 72-73, wherein the second antigen-binding site comprises a heavy chain variable domain and a light chain variable domain.

75. A protein of claim 74, wherein the heavy chain variable domain and the light chain variable domain of the second antigen-binding site are present on the same polypeptide.

76. A protein of any of claims 1, 2, or 60-71, wherein the second antigen-binding site binds EpCAM, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:115 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:119.

77. A protein of claim 76, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:116;

a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:117; and

a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:118.

78. A protein of claim 77, wherein the light chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:120;

a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:121;

and a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:122.

79. A protein of any one of claims 1, 2, or 60-71, wherein the second antigen-binding site binds EpCAM, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:123 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:127.

80. A protein of claim 79, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:124;

a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:125; and

a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:126.

81. A protein according to claim 80, wherein the light chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:128;

a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:129; and

a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:130.

82. A protein of any one of claims 1, 2, or 60-71, wherein the second antigen-binding site binds EpCAM, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:131 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:135.

83. A protein of claim 82, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:132;

a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:133; and

a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:134.

84. A protein of claim 83, wherein the light chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:136;

a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:137; and

a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:138.

85. A protein of any one of claims 1, 2, or 60-71, wherein the second antigen-binding site binds EpCAM, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:139 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:143.

86. A protein of claim 85, wherein the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a heavy chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:140;

a heavy chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:141; and

a heavy chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:142.

87. A protein of claim 86, wherein the light chain variable domain of the second antigen-binding site comprises an amino acid sequence including:

a light chain CDR1 sequence identical to the amino acid sequence of SEQ ID NO:144;

a light chain CDR2 sequence identical to the amino acid sequence of SEQ ID NO:145; and

a light chain CDR3 sequence identical to the amino acid sequence of SEQ ID NO:146.

88. A protein of any one of claims 1, 3, or 60-71, wherein the second antigen-binding site binds CA125, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:155 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:159.

89. The protein of any one of claims 1, 3, 60-71 and 88, wherein the second antigen-binding site comprises:

a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:156;

a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:157;

a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:158;

a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:160;

a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:161; and

a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:162.

90. A protein of any one of claims 1, 3, or 60-71, wherein the second antigen-binding site binds CA125, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:163 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:167.

91. The protein of any one of claims 1, 3, 60-71 and 90, wherein the second antigen-binding site comprises:
a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:164;
a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:165;
a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:166;
a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:168;
a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:169; and
a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:170.

92. A protein of any one of claims 1, 4, or 60-71, wherein the second antigen-binding site binds NaPi2b, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:171 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:175.

93. The protein of any one of claims 1, 4, 60-71 and 92, wherein the second antigen-binding site comprises:
a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:172;
a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:173;
a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:174;
a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:176;
a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:177; and
a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:178.

94. A protein of any one of claims 1, 5, or 60-71, wherein the second antigen-binding site binds fucosyl-GM1, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:187 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:191.

95. The protein of any one of claims 1, 5, 60-71 and 94, wherein the second antigen-binding site comprises:

a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:188;

a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:189;

a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:190;

a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:192;

a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:193; and

a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:194.

96. A protein of any one of claims 1, 6, or 60-71, wherein the second antigen-binding site binds SLC44A4, the heavy chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:195 and the light chain variable domain of the second antigen-binding site comprises an amino acid sequence at least 90% identical to SEQ ID NO:199.

97. The protein of any one of claims 1, 6, 60-71 and 96, wherein the second antigen-binding site comprises:

a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO:196;

a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO:197;

a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO:198;

a light chain CDR1 comprising the amino acid sequence of SEQ ID NO:200;

a light chain CDR2 comprising the amino acid sequence of SEQ ID NO:201; and

a light chain CDR3 comprising the amino acid sequence of SEQ ID NO:202.

98. A protein according to any one of claims 1-97, wherein the antibody Fc domain comprises hinge and CH2 domains of a human IgG1 antibody.

99. A protein of claim 98, wherein the Fc domain comprises an amino acid sequence at least 90% identical to amino acids 234-332 of a human IgG1 antibody.

100. A protein of claim 99, wherein the Fc domain comprises an amino acid sequence at least 90% identical to the Fc domain of human IgG1 and differs at one or more positions selected from the group consisting of Q347, Y349, L351, S354, E356, E357, K360, Q362, S364, T366, L368, K370, N390, K392, T394, D399, S400, D401, F405, Y407, K409, T411, and K439.

101. A protein according to any one of claims 1-99, wherein the protein binds to NKG2D with a K_D of 10 nM or weaker affinity.

102. A formulation comprising a protein according to any one of the preceding claims and a pharmaceutically acceptable carrier.

103. A cell comprising one or more nucleic acids encoding a protein according to any one of claims 1-100.

104. A method of directly and/or indirectly enhancing tumor cell death, the method comprising exposing the tumor cell and a natural killer cell to a protein according to any one of claims 1-101.

105. A method of treating cancer, wherein the method comprises administering a protein according to any one of claims 1-101 or a formulation according to claim 102 to a patient.

106. The method of claim 105, wherein when the second binding site binds EpCAM, the cancer is selected from the group consisting of head and neck cancer, ovarian cancer, bladder cancer, breast cancer, colorectal cancer, prostate cancer, gastric cancer, liver cancer, esophageal cancer, and lung cancer.

107. The method of claim 105, wherein the cancer is selected from the group consisting of bladder cancer, breast cancer, ovarian cancer, pancreatic cancer, colorectal cancer, and lung cancer.

108. The method of claim 105, wherein the cancer is selected from the group consisting of ovarian cancer, endometrial cancer, pancreatic cancer, lung cancer,

thyroid cancer, bladder cancer, breast cancer, colorectal cancer, small cell lung cancer, neuroblastoma, liver cancer, renal cancer, melanoma, cervical cancer, prostate cancer, osteosarcoma, brain cancer, gastric cancer, and cholangiocarcinoma.

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FIG. 1

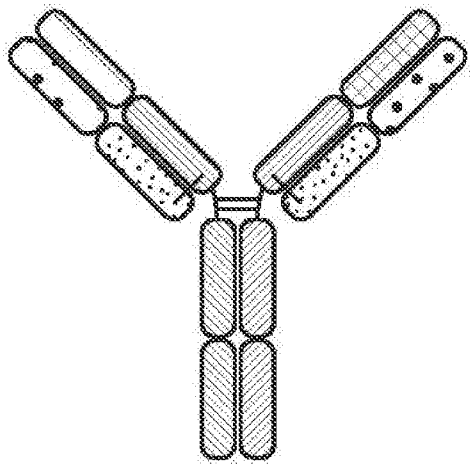

FIG. 2

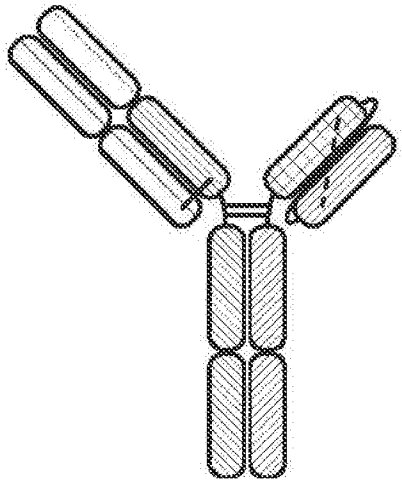

FIG. 3

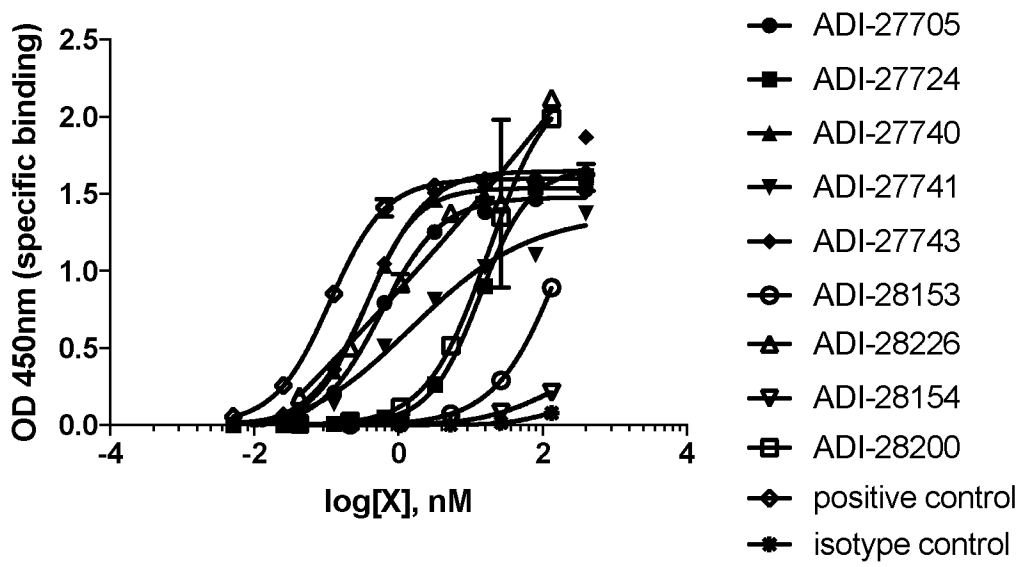

FIG. 4

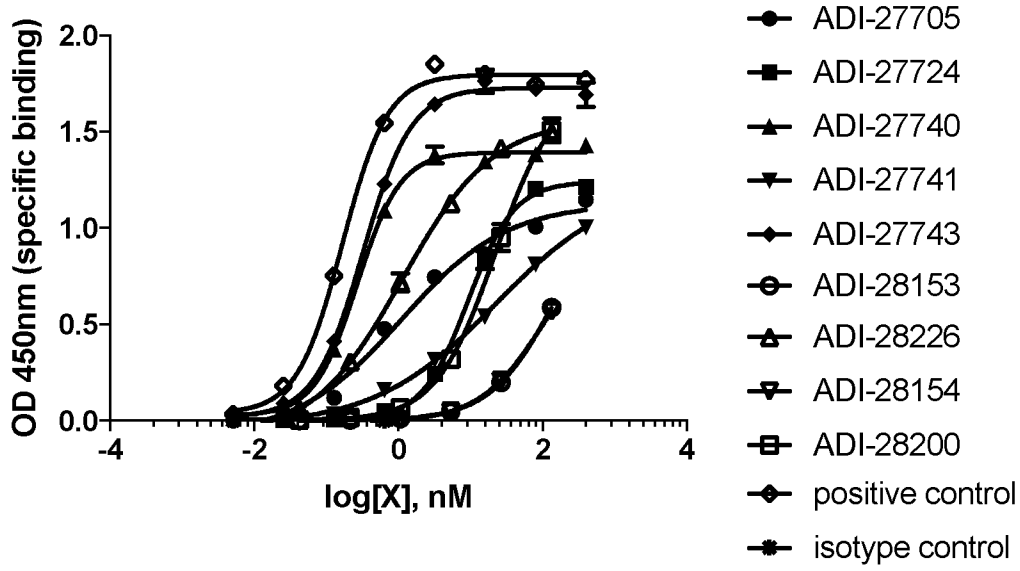

FIG. 5

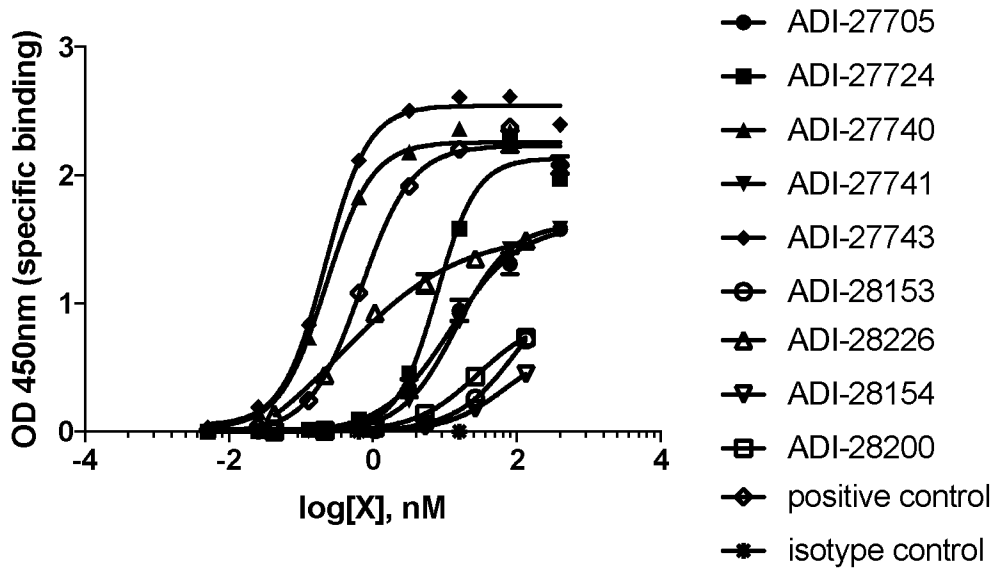

FIG. 6

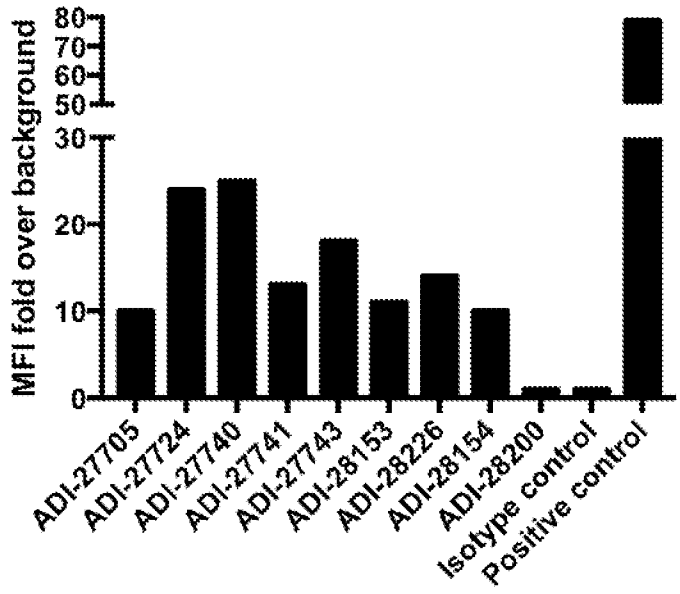

FIG. 7

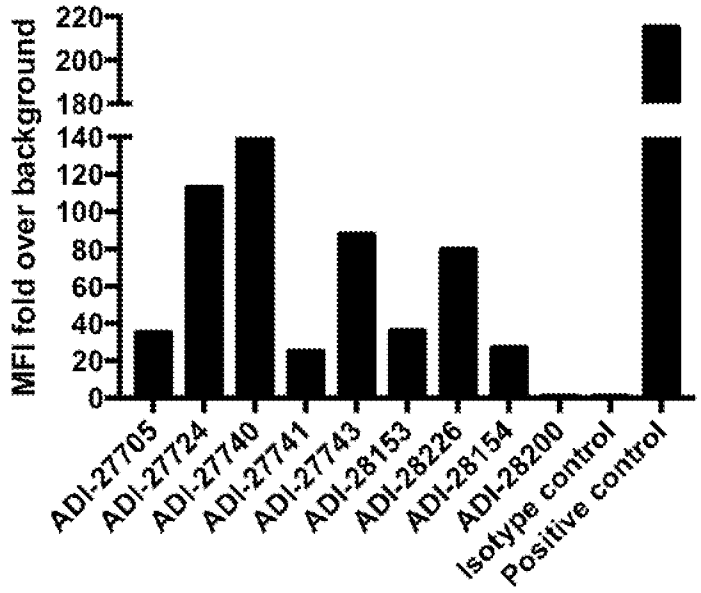

FIG. 8

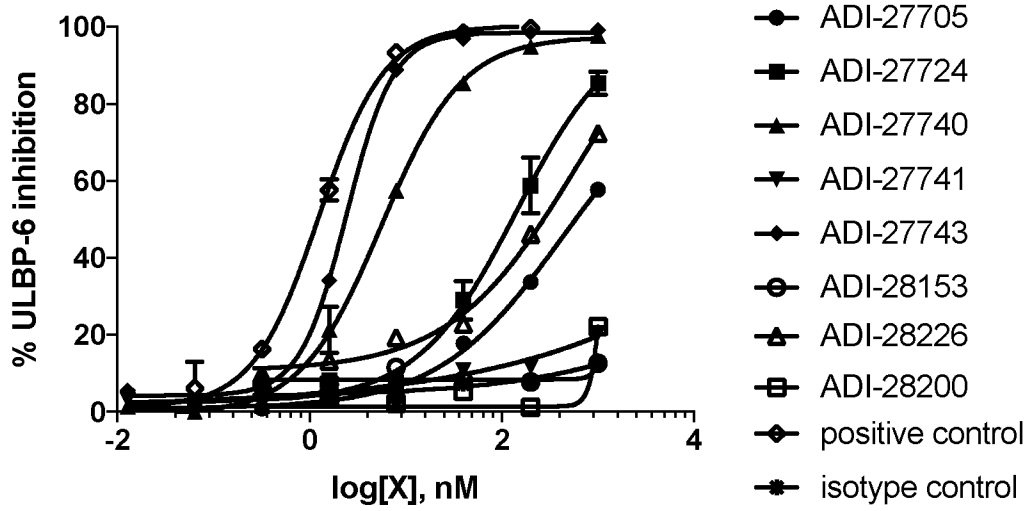

FIG. 9

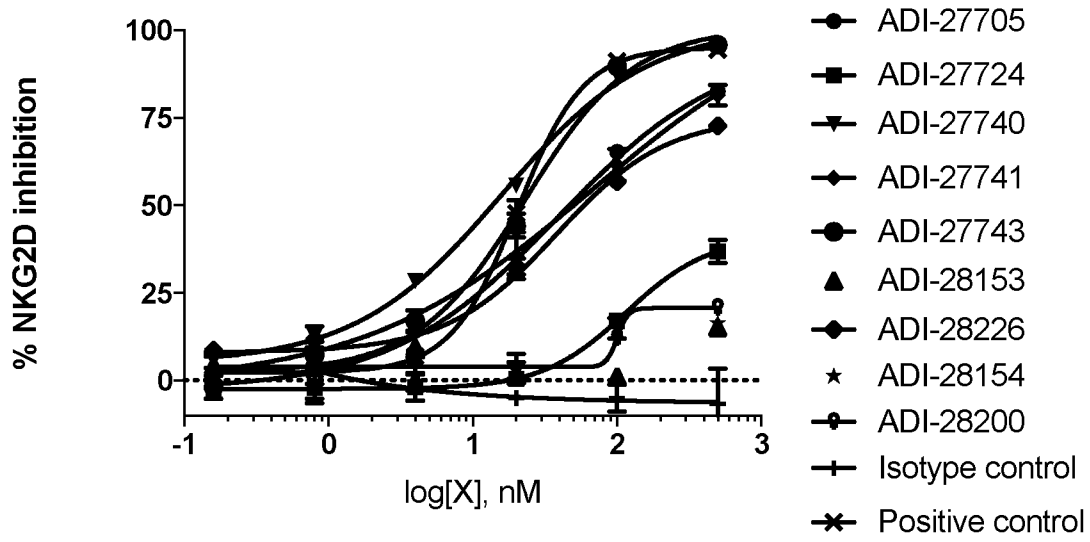

FIG. 10

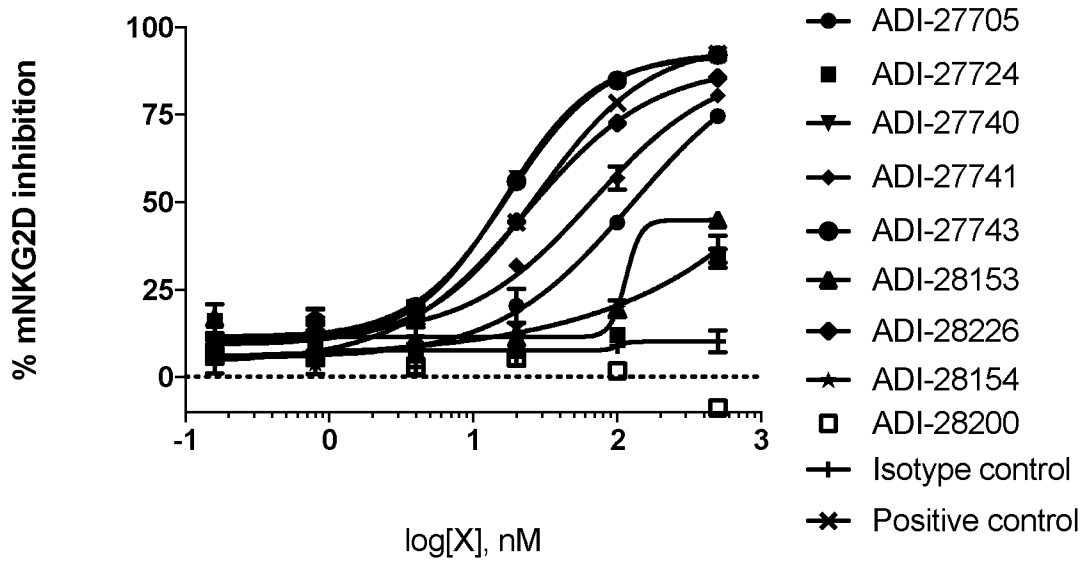

FIG. 11

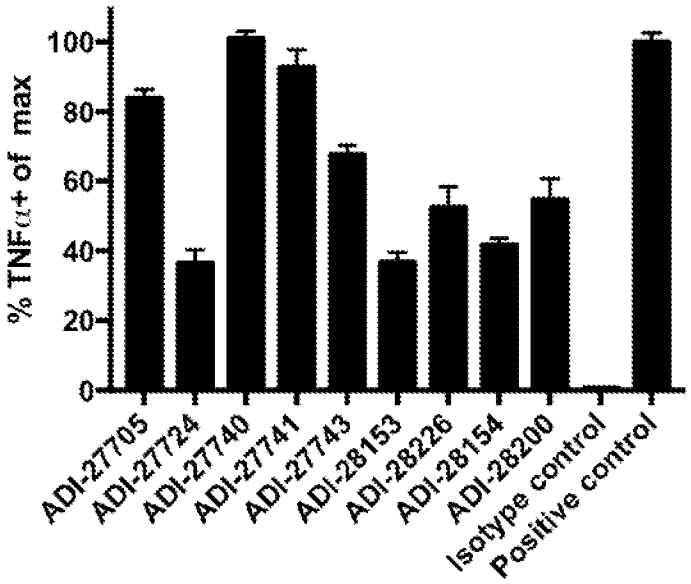

FIG. 12

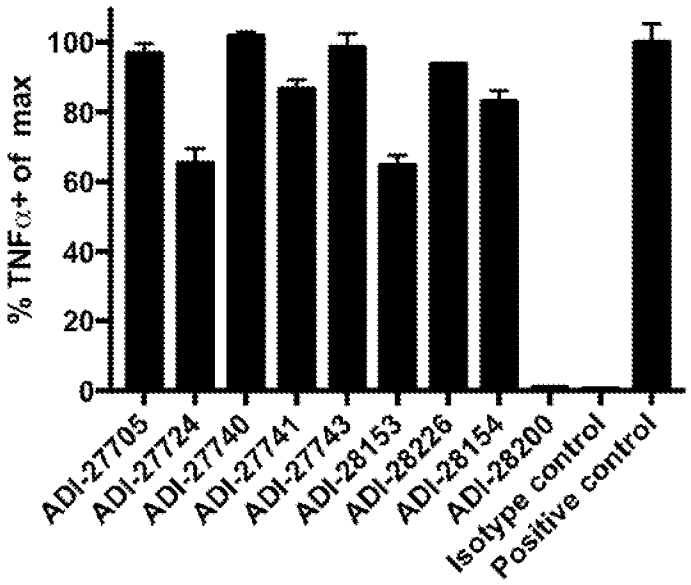

FIG. 13

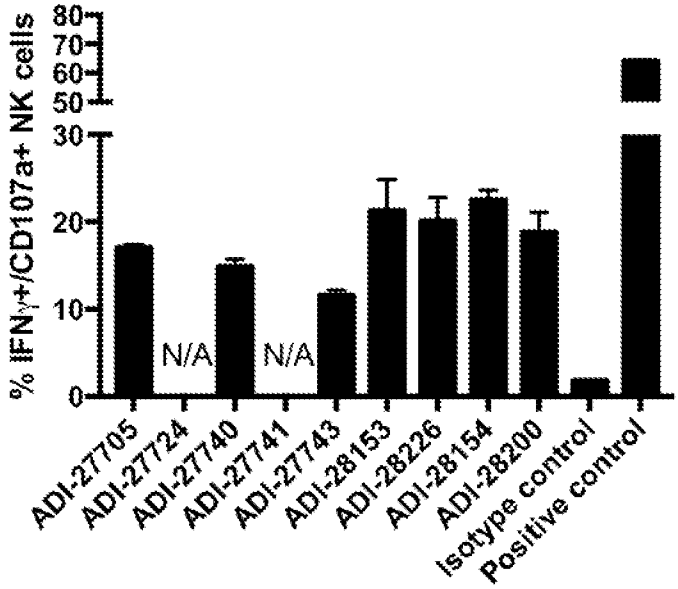

FIG. 14

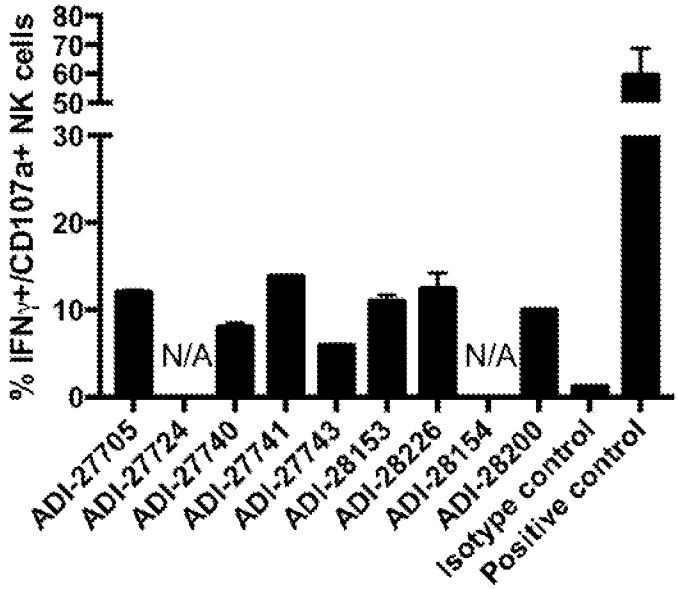

FIG. 15

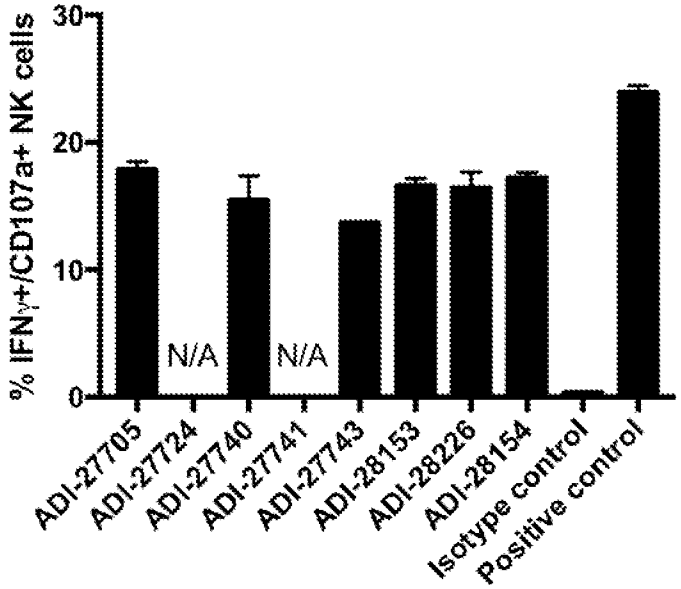

FIG. 16

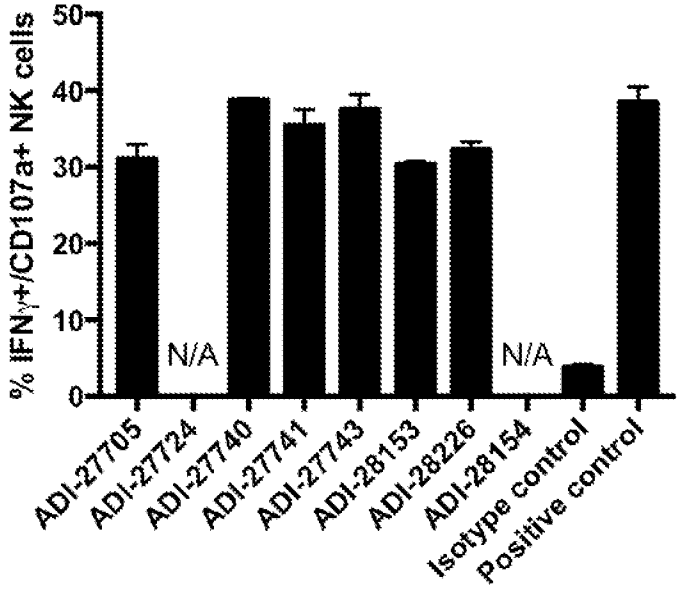

FIG. 17

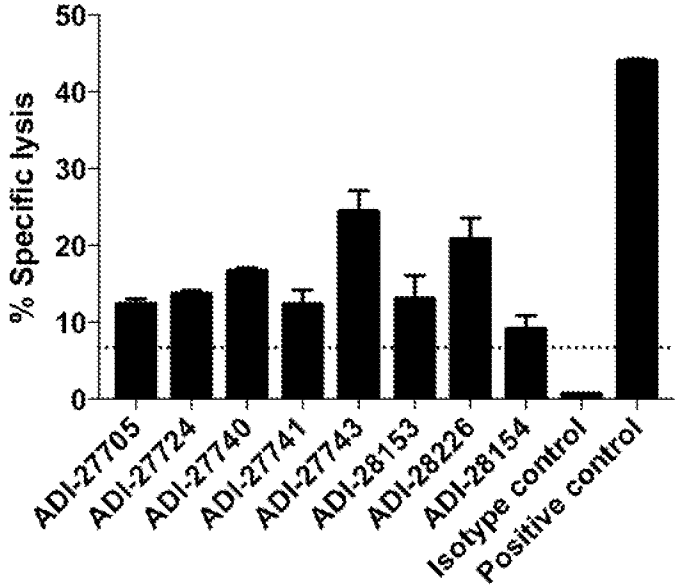

FIG. 18

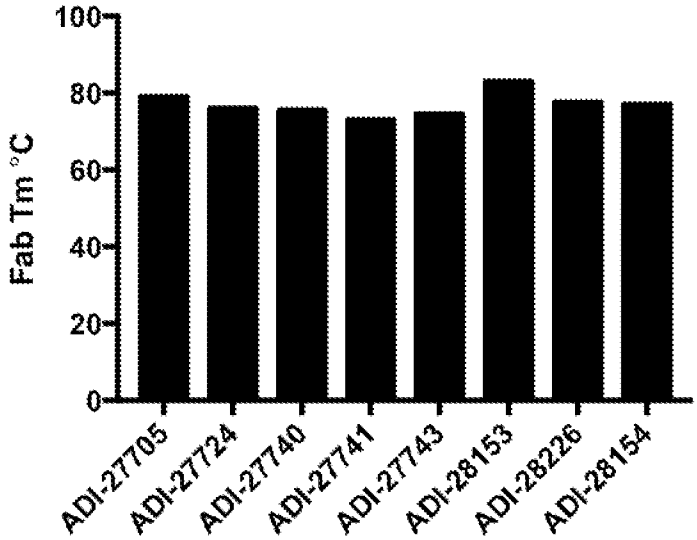

FIG. 19A

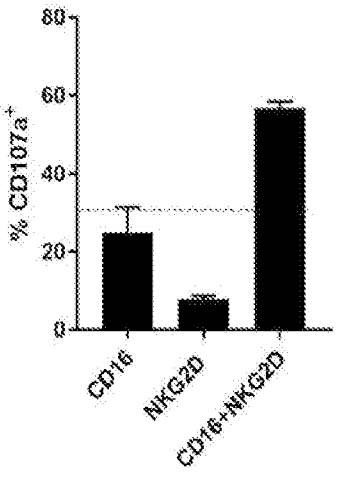

FIG. 19B

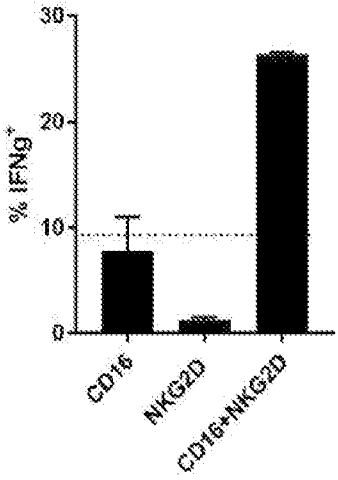

FIG. 19C

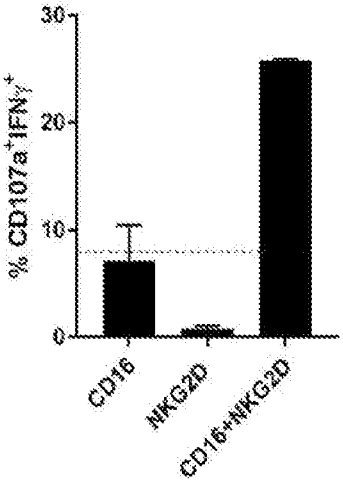

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FIG. 20

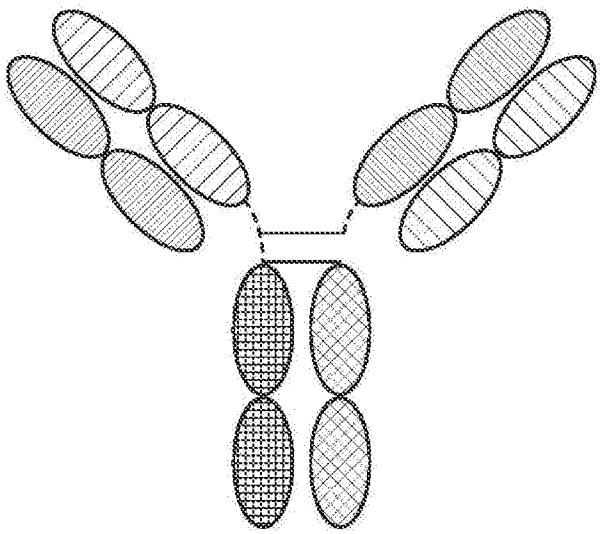

FIG. 21

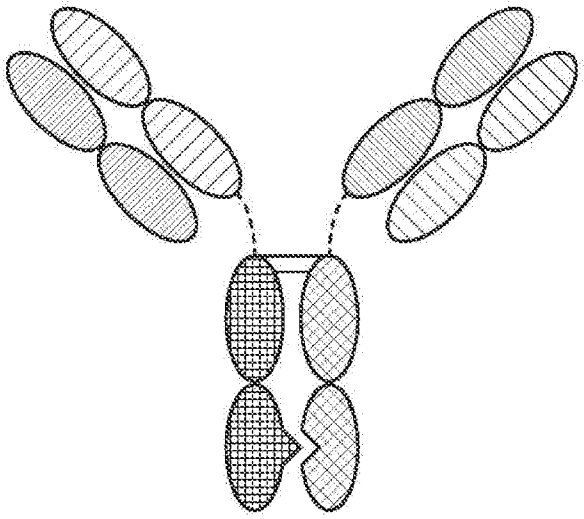

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FIG. 22

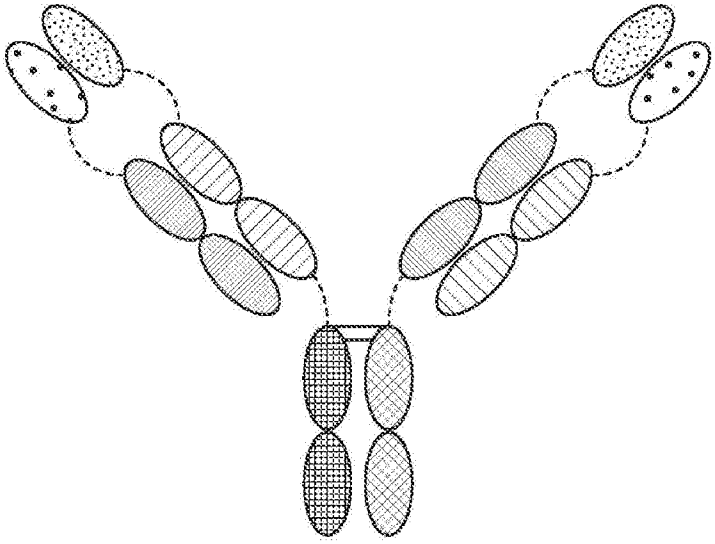

FIG. 23

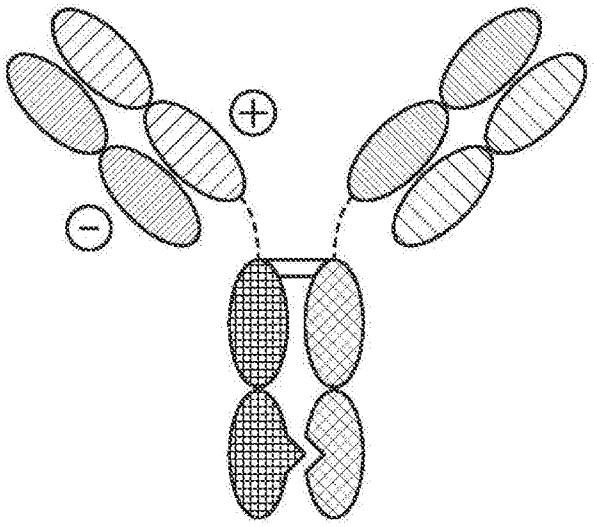

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FIG. 24

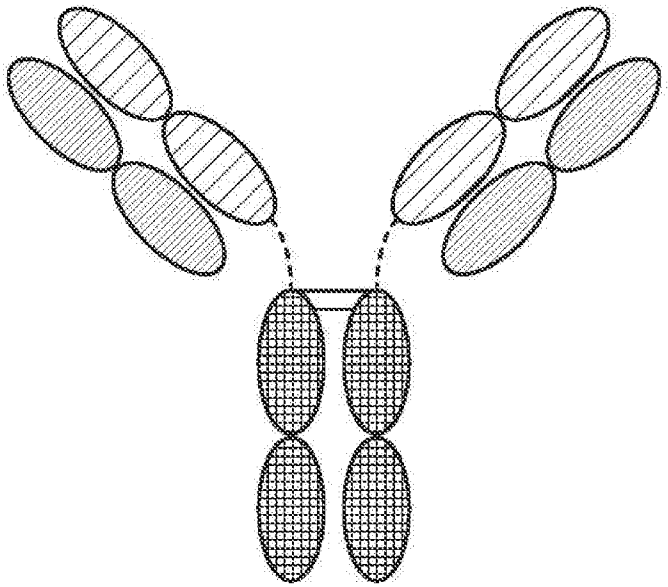

FIG. 25

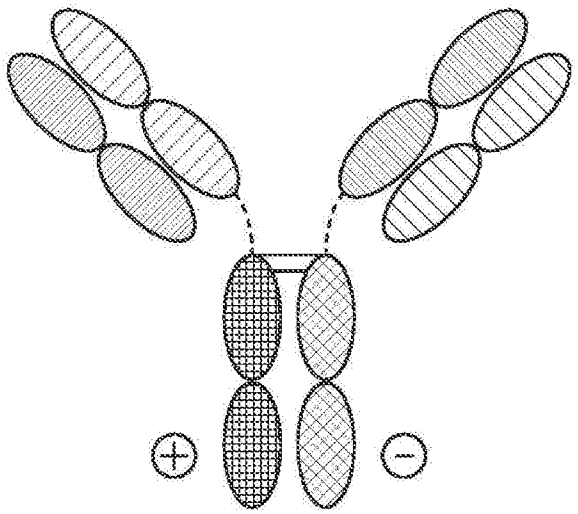

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FIG. 26

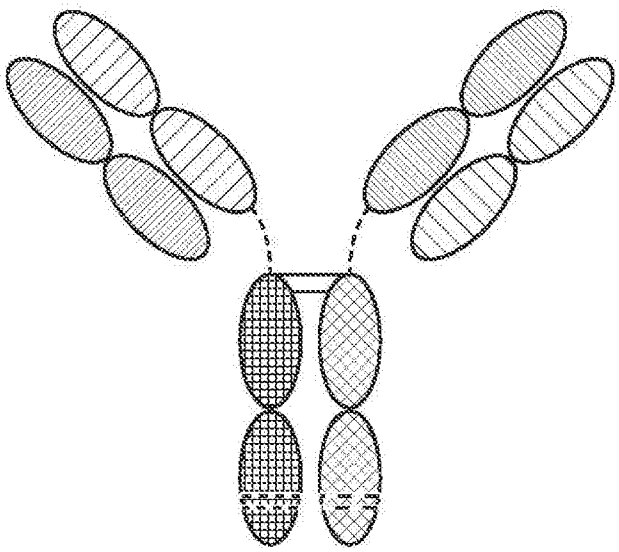

FIG. 27

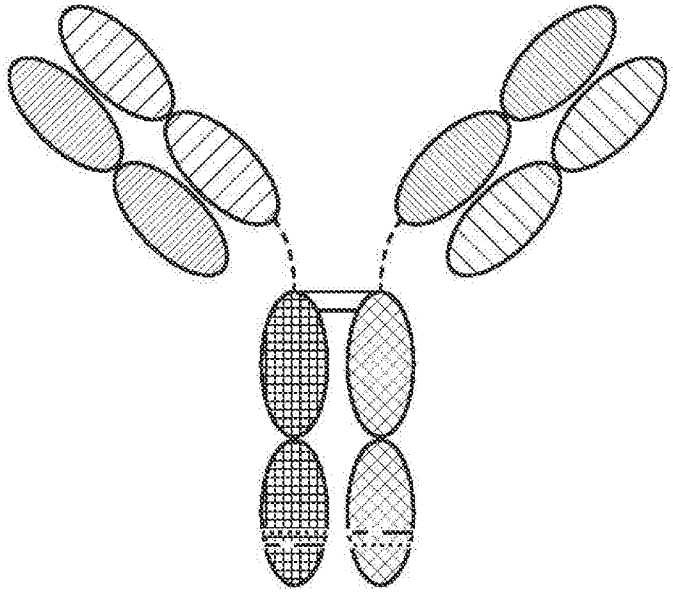

FIG. 28

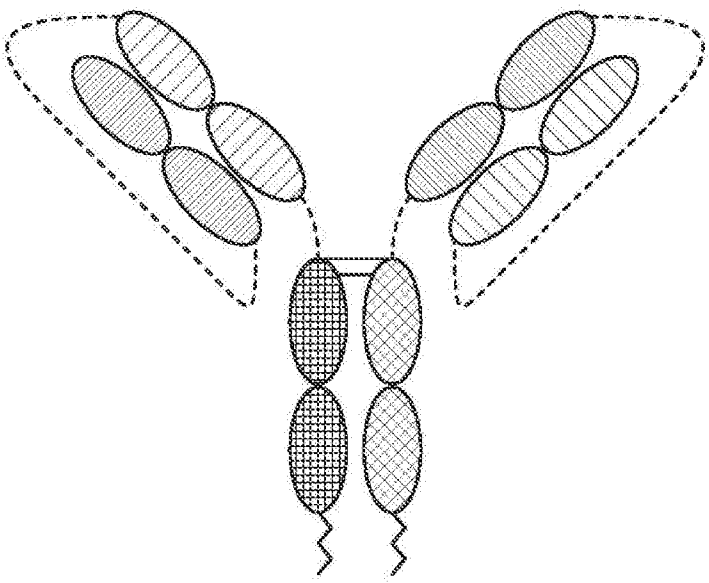

FIG. 29

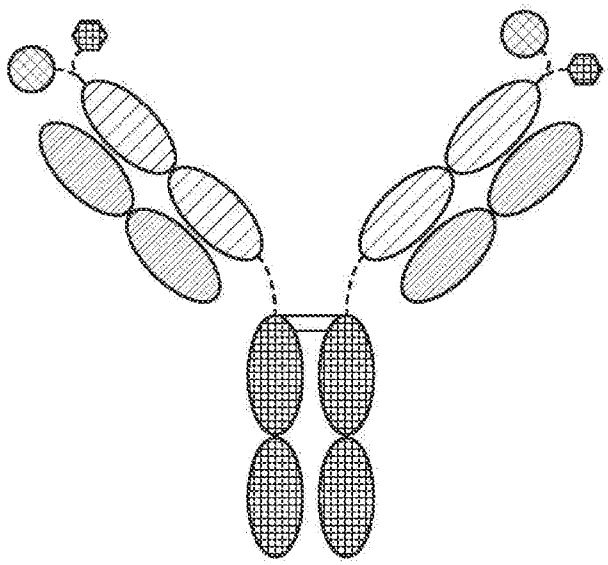

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FIG. 30A

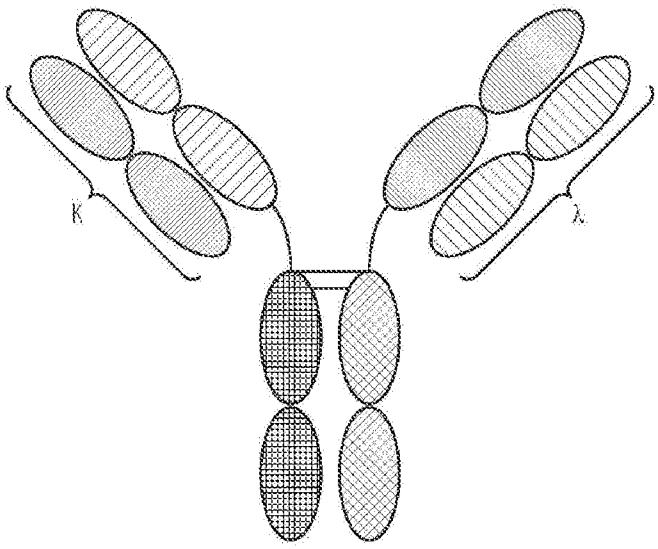

FIG. 30B

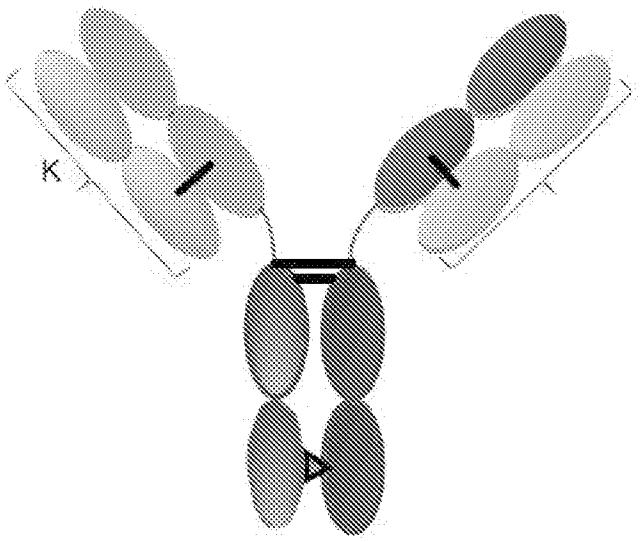

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FIG. 31

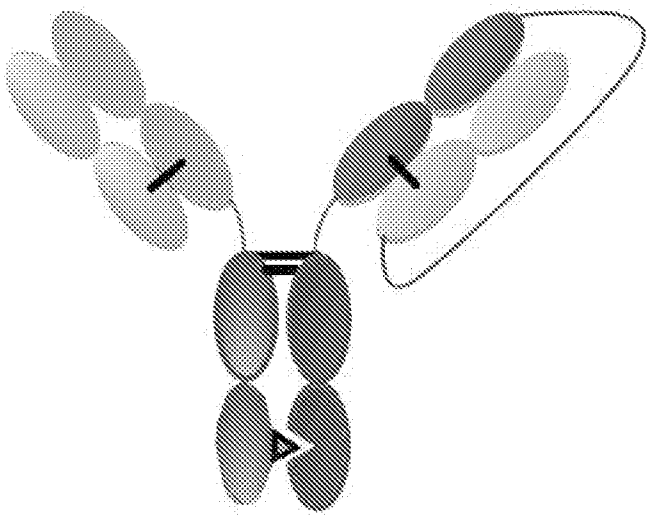

FIG. 32

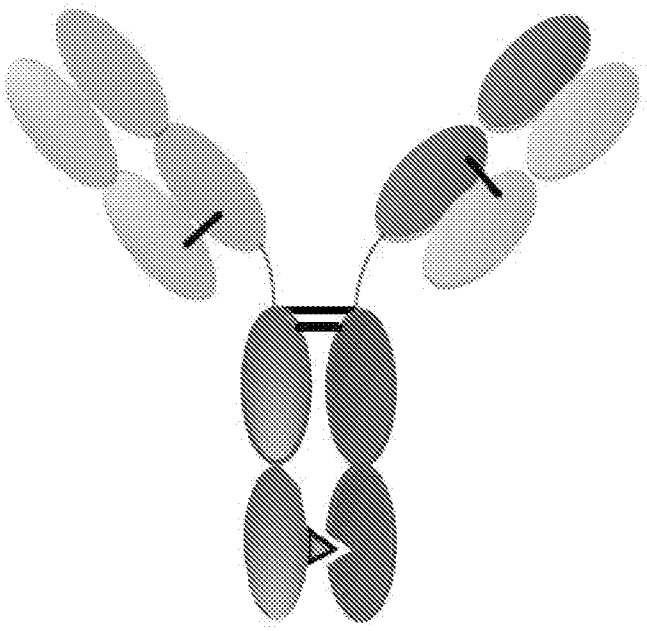

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FIG. 33

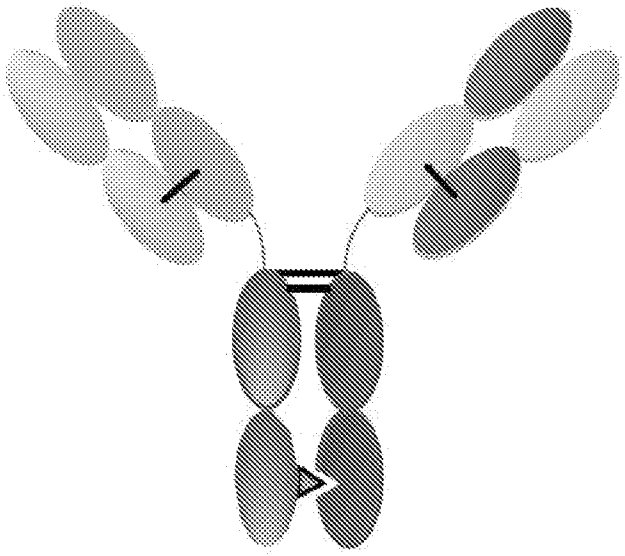


FIG. 34

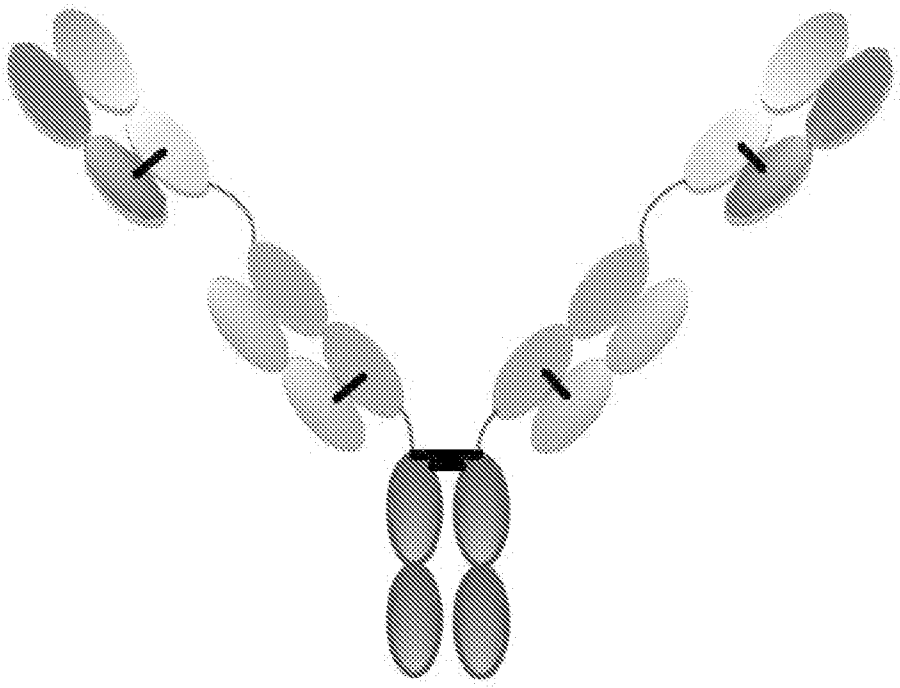


FIG. 35

F3' format

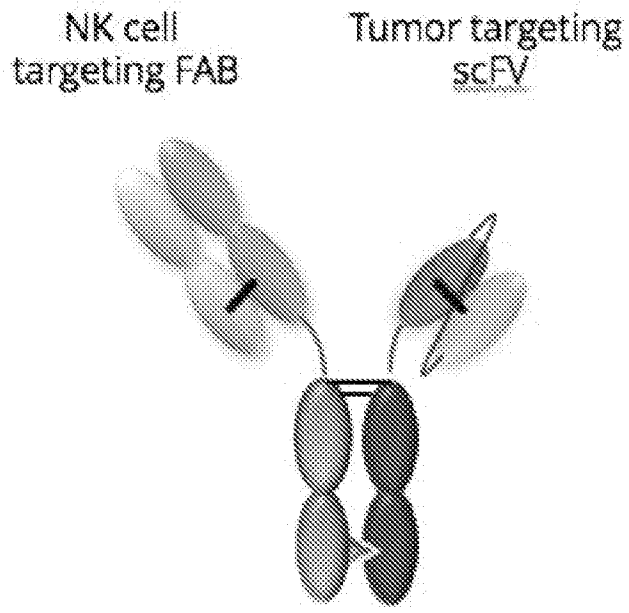


FIG. 36

F4 Format

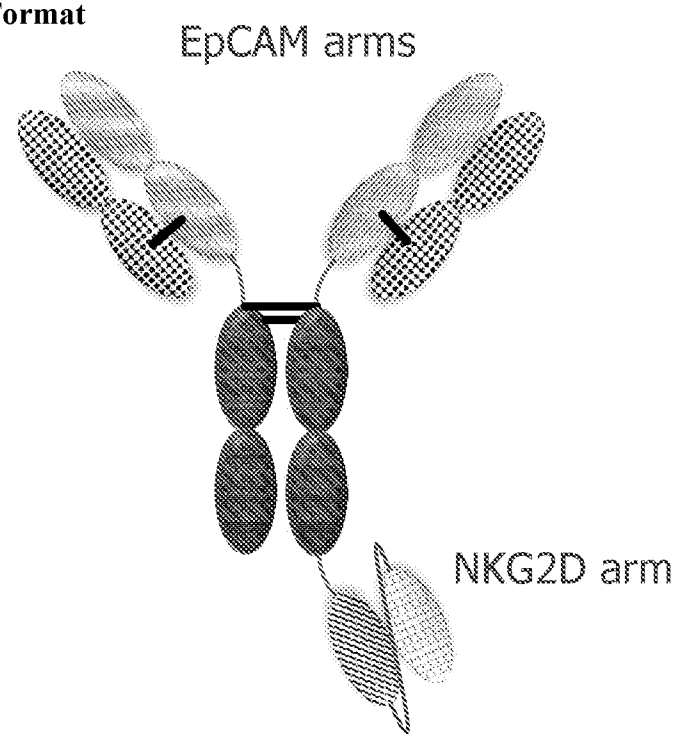


FIG. 37

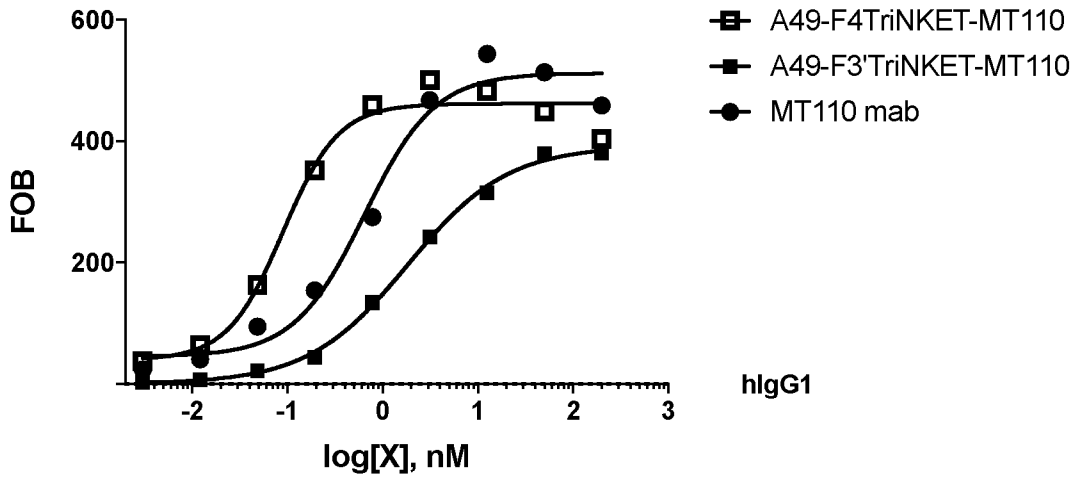


FIG. 38

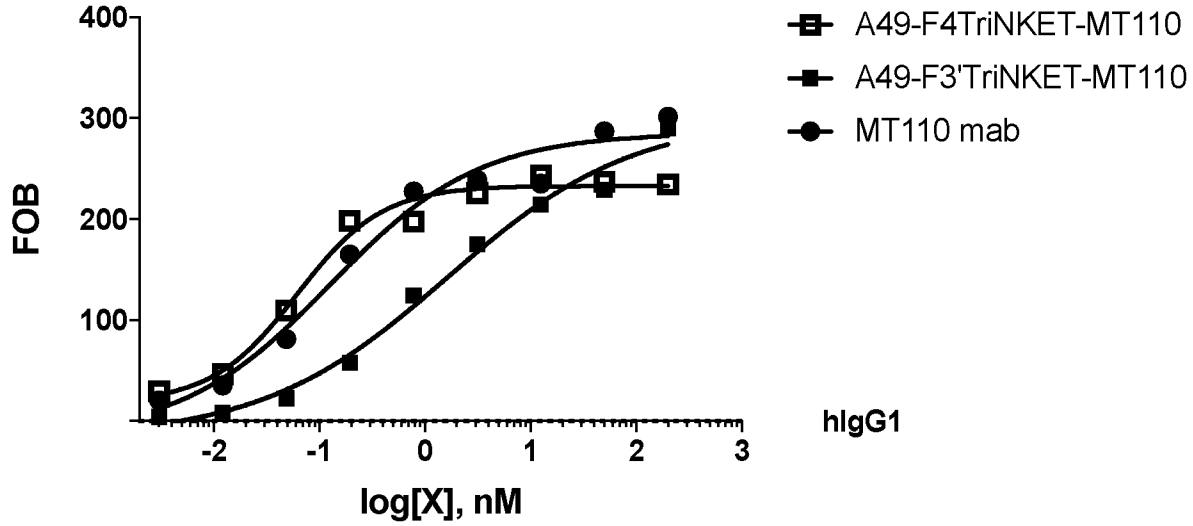


FIG. 39

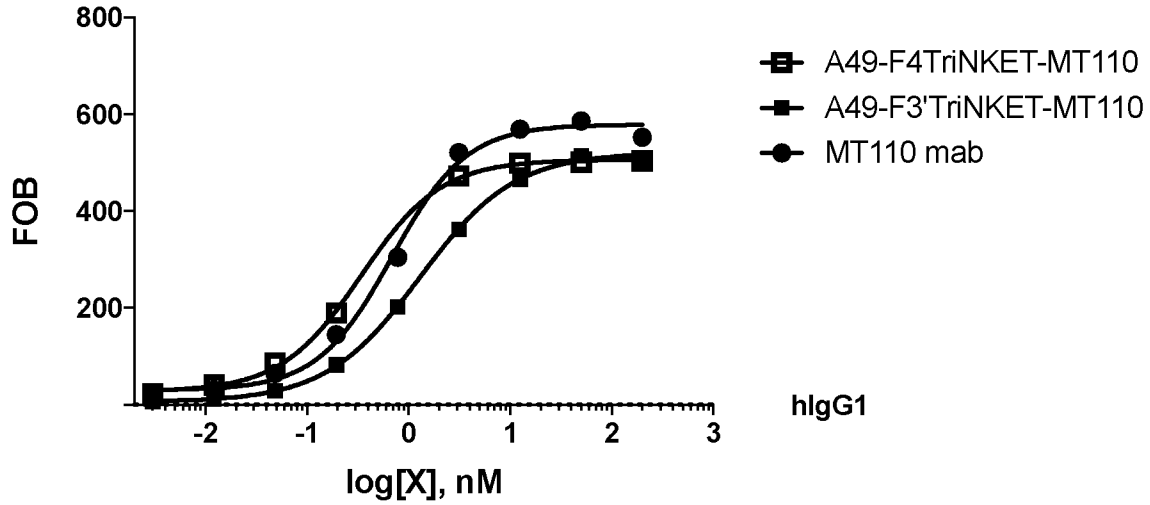


FIG. 40A

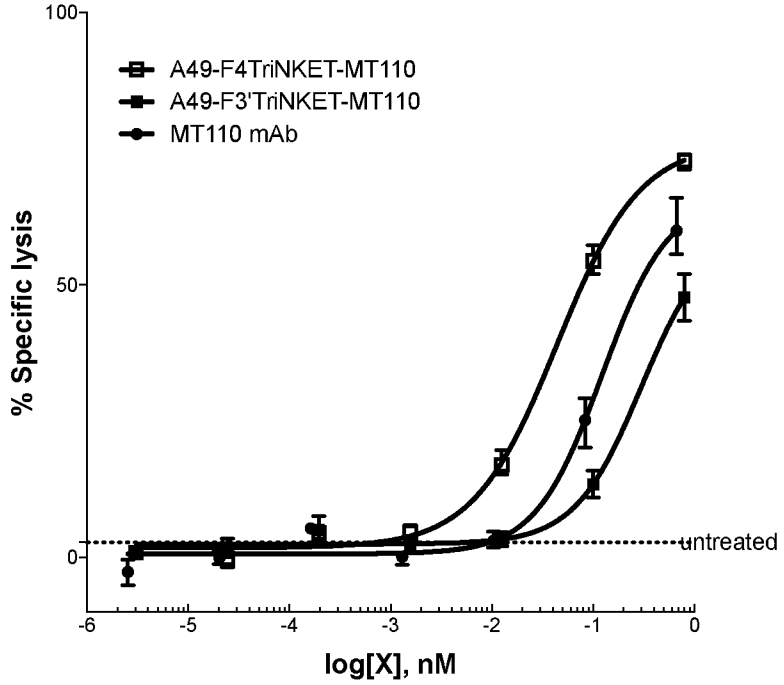


FIG. 40B

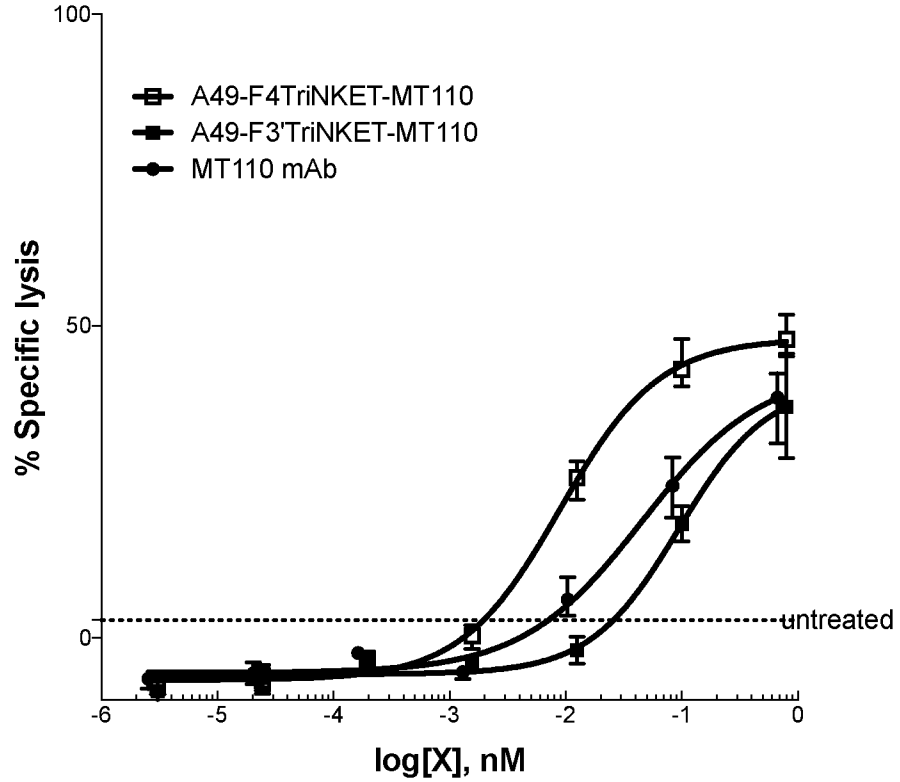


FIG. 41A

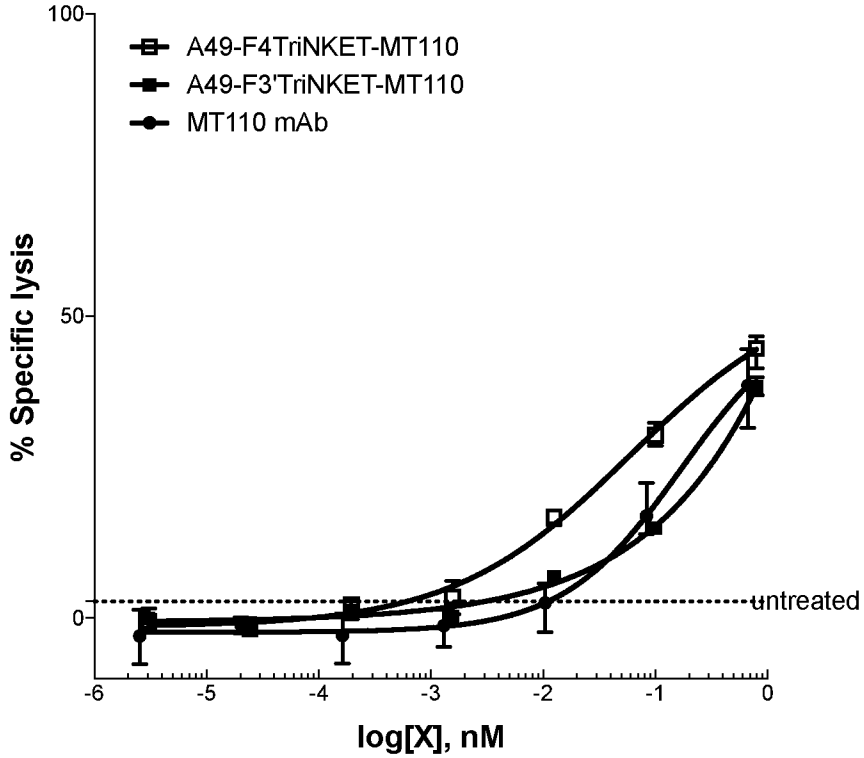


FIG. 41B

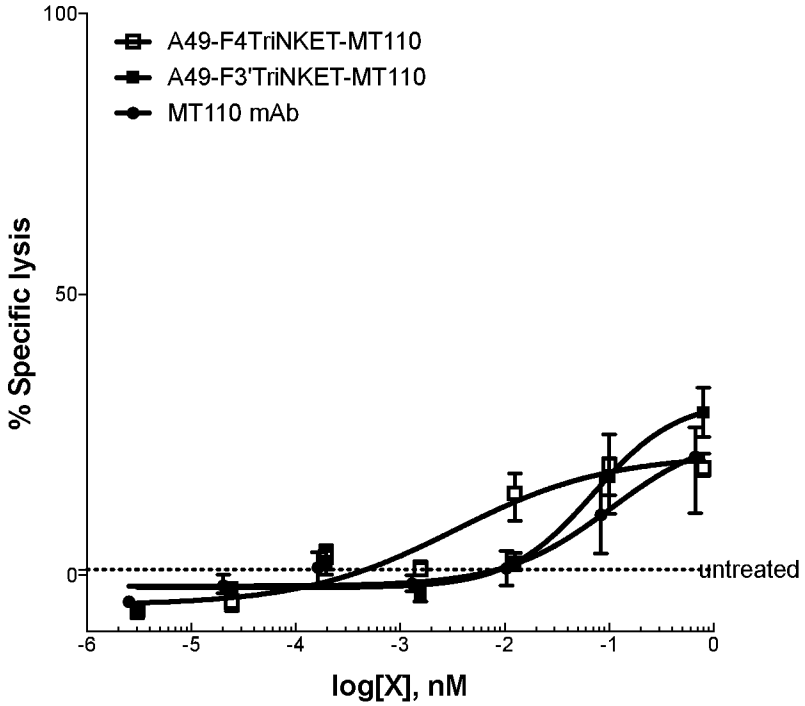


FIG. 42A

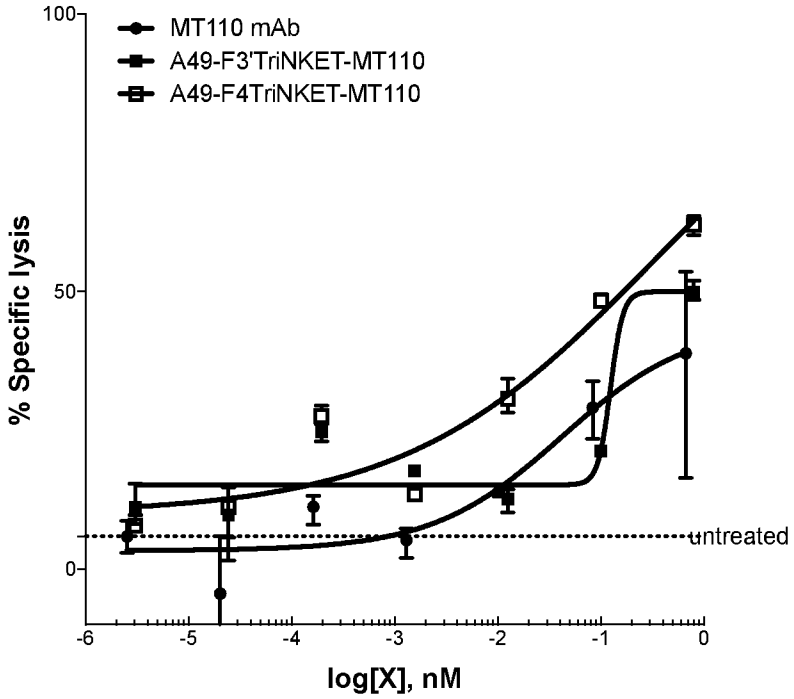
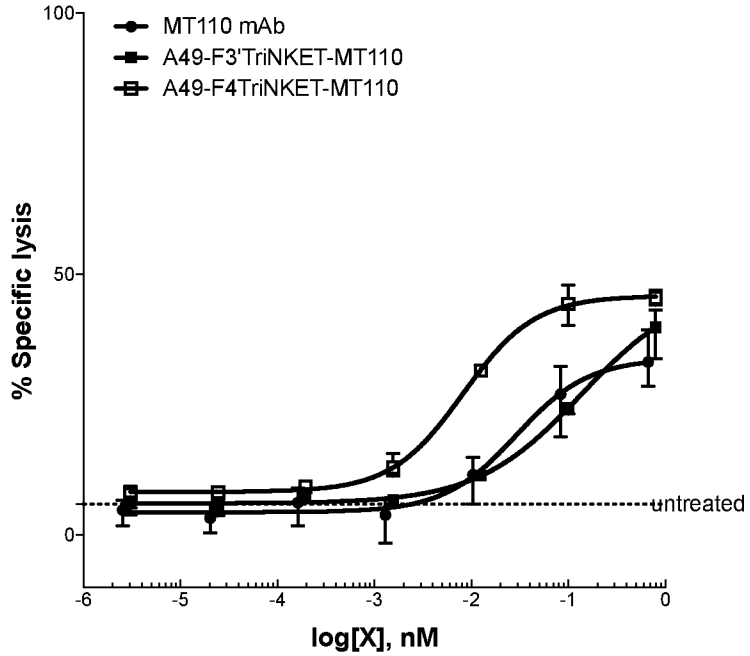


FIG. 42B



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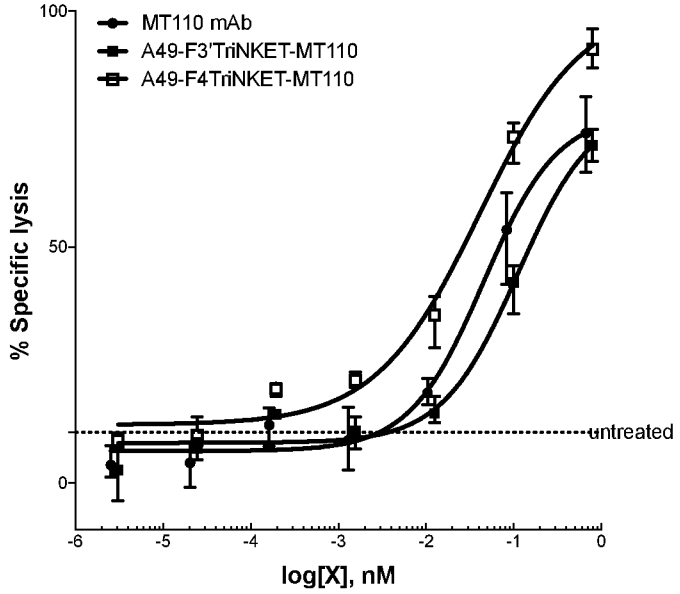
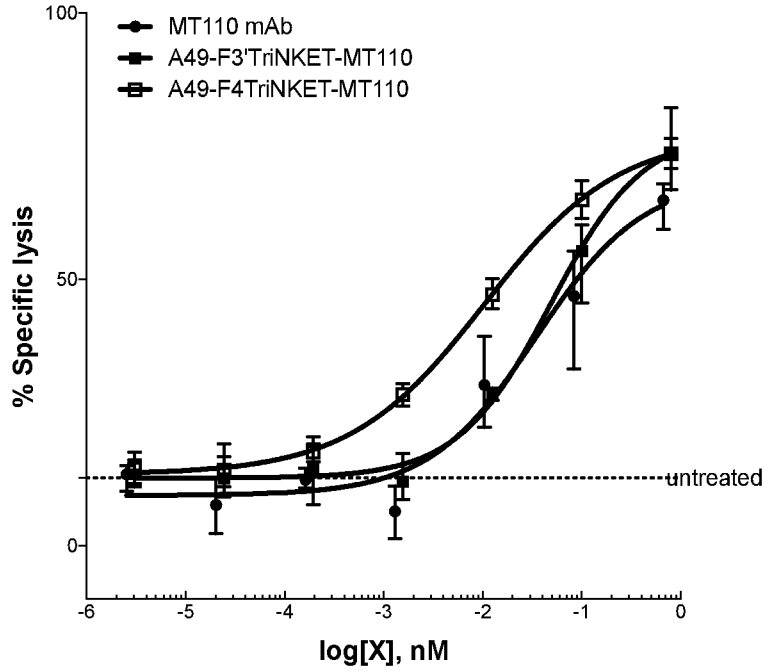


FIG. 43B



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<130> DFY-038WO

<150> 62/566,824
<151> 2017-10-02

<150> 62/555,110
<151> 2017-09-07

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<170> PatentIn version 3.5

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

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<223> Description of Artificial Sequence: Synthetic polypeptide

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

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

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

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

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

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

<210> 3
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<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

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1               5                   10                  15

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115


<210>  4
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<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
            20                  25                  30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45
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Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

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

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

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<212> PRT
<213> Artificial Sequence

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

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

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr His Ser Phe Tyr Thr
85 90 95

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

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<213> Artificial Sequence

<220>
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<400> 7

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 8
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<213> Artificial Sequence

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<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 8

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1 5 10 15

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

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

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

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

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

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

<210> 9
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<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 9

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 10
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<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 10

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

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

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

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

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

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

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

<210> 11
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 11

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Gly Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 12
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<213> Artificial Sequence

<220>
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<400> 12

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

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

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

Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

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

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

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
            100                 105                 110

Val Thr Val Ser Ser
        115
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<210> 14
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<400> 14

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1               5                  10                  15


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


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


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


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


Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Gly Ser Phe Pro Ile
                85                  90                  95


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

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1               5                  10                  15


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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

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1 5 10 15

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

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Lys Glu Val Pro Trp
85 90 95

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

<210> 17
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 17

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 18
<211> 106

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 18

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

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

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

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

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

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

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

<210> 19
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 19

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 20
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 20

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

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

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Ile Tyr Pro Thr
85 90 95

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

<210> 21
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 21

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 22
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 22

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

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

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

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

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

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

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

<210> 23
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 23

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 24
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 24

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

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

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

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

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

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

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

<210> 25
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 25

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 26
<211> 106
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 26

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

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

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

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

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

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

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

<210> 27
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 27

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 28
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 28

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

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

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Ser Ser Phe Ser Thr
85 90 95

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

<210> 29
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 29

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 30
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 30

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

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

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

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

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

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

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

<210> 31
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 31

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 32
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 32

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

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

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Ser Phe Ile Thr
85 90 95

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

<210> 33
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 33

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 34
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 34

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

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

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

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

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

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

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


<210>  35
<211>  117
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  35

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60
```

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 36
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 36

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

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

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

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

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

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

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

<210> 37
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 37

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


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


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


Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60


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


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


Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
            100                 105                 110


Val Thr Val Ser Ser
        115
```

<210> 38
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 38

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

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

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

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

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

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

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

<210> 39
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 39

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 40
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 40

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

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

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

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

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

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Thr Phe Ile Thr
85 90 95

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

<210> 41
<211> 125

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 41

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

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

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

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

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

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

Ala Arg Gly Asp Ser Ser Ile Arg His Ala Tyr Tyr Tyr Tyr Gly Met
100 105 110

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

<210> 42
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 42

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

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

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

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

Lys

<210> 43
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 43

Gly Thr Phe Ser Ser Tyr Ala Ile Ser
1 5

<210> 44
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 44

Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 45
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 45

Ala Arg Gly Asp Ser Ser Ile Arg His Ala Tyr Tyr Tyr Tyr Gly Met
1 5 10 15

Asp Val

<210> 46
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 46

Lys Ser Ser Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr Leu
1 5 10 15

Ala

<210> 47
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 47

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 48
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 48

Gln Gln Tyr Tyr Ser Thr Pro Ile Thr
1 5

<210> 49
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 49

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

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

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

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

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

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

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

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 50
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 50

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Arg Tyr
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Phe Asp Thr Trp Pro Pro
85 90 95

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

<210> 51
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 51

Gly Ser Ile Ser Ser Ser Ser Tyr Tyr Trp Gly
1 5 10

<210> 52
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 52

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

<210> 53
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 53

Ala Arg Gly Ser Asp Arg Phe His Pro Tyr Phe Asp Tyr
1 5 10

<210> 54
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 54

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

<210> 55
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 55

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 56
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 56

Gln Gln Phe Asp Thr Trp Pro Pro Thr
1 5

<210> 57
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 57

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

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

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

Gly Glu Ile Asp His Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

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

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

Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> 58
<211> 106
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 58

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

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

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

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

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

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

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

<210> 59
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 59

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

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

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

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

Gln Gly Arg Val Thr Ile Thr Ala Asp Glu Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

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

Ala Arg Arg Gly Arg Lys Ala Ser Gly Ser Phe Tyr Tyr Tyr Tyr Gly
            100                 105                 110

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


<210>  60
<211>  113
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  60

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

Glu Arg Ala Thr Ile Asn Cys Glu Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

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

Pro Pro Lys Pro Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Asn
85 90 95

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

Lys

<210> 61
<211> 126
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 61

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

Ala Arg Gly Ala Pro Asn Tyr Gly Asp Thr Thr His Asp Tyr Tyr Tyr
100 105 110

Met Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 62
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 62

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
20 25 30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asp Asp Trp Pro Phe
85 90 95

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

<210> 63
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 63

Tyr Thr Phe Thr Ser Tyr Tyr Met His
1 5

<210> 64
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 64

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

Gly

<210> 65
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 65

Ala Arg Gly Ala Pro Asn Tyr Gly Asp Thr Thr His Asp Tyr Tyr Tyr
1 5 10 15

Met Asp Val

<210> 66
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 66

Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala
1 5 10

<210> 67
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 67

Gly Ala Ser Thr Arg Ala Thr
1 5

<210> 68
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 68

Gln Gln Tyr Asp Asp Trp Pro Phe Thr
1 5

<210> 69
<211> 124
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 69

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

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

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

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

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

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

Ala Arg Asp Thr Gly Glu Tyr Tyr Asp Thr Asp Asp His Gly Met Asp
            100                 105                 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 70
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 70

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Asn
            20                  25                  30

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Asp Asp Tyr Trp Pro Pro
                85                  90                  95

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

<210> 71
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 71

Tyr Thr Phe Thr Gly Tyr Tyr Met His
1 5

<210> 72
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 72

Trp Ile Asn Pro Asn Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 73
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 73

Ala Arg Asp Thr Gly Glu Tyr Tyr Asp Thr Asp Asp His Gly Met Asp
1 5 10 15

Val

<210> 74
<211> 11

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 74

Arg Ala Ser Gln Ser Val Ser Ser Asn Leu Ala
1 5 10

<210> 75
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 75

Gly Ala Ser Thr Arg Ala Thr
1 5

<210> 76
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 76

Gln Gln Asp Asp Tyr Trp Pro Pro Thr
1 5

<210> 77
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 77

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

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

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

Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Ala Lys Asp Gly Gly Tyr Tyr Asp Ser Gly Ala Gly Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210>  78
<211>  107
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  78

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

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

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

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

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

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

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

<210> 79
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 79

Phe Thr Phe Ser Ser Tyr Ala Met Ser
1 5

<210> 80
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 80

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

Gly

<210> 81
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 81

Ala Lys Asp Gly Gly Tyr Tyr Asp Ser Gly Ala Gly Asp Tyr
1 5 10

<210> 82
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 82

Arg Ala Ser Gln Gly Ile Asp Ser Trp Leu Ala
1 5 10

<210> 83
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 83

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 84
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 84

Gln Gln Gly Val Ser Tyr Pro Arg Thr
1 5

<210> 85
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 85

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

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Gly Ala Pro Met Gly Ala Ala Ala Gly Trp Phe Asp Pro Trp
100 105 110

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

<210> 86
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 86

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

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

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

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

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

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

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

<210> 87
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 87

Phe Thr Phe Ser Ser Tyr Ser Met Asn
1 5

<210> 88
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 88

Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 89
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 89

Ala Arg Gly Ala Pro Met Gly Ala Ala Ala Gly Trp Phe Asp Pro
1 5 10 15

<210> 90
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 90

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

<210> 91
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 91

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> 92
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 92

Gln Gln Gly Val Ser Phe Pro Arg Thr
1 5

<210> 93
<211> 125

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 93

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

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

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

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

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser Thr Val Tyr
65 70 75 80

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

Ala Arg Glu Gly Ala Gly Phe Ala Tyr Gly Met Asp Tyr Tyr Tyr Met
100 105 110

Asp Val Trp Gly Lys Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> 94
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 94

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr
20 25 30

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

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

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

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

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

<210> 95
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 95

Tyr Thr Phe Thr Ser Tyr Tyr Met His
1 5

<210> 96
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 96

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

Gly

<210> 97
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 97

Ala Arg Glu Gly Ala Gly Phe Ala Tyr Gly Met Asp Tyr Tyr Tyr Met
1 5 10 15

Asp Val

<210> 98
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 98

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

<210> 99
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 99

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 100
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 100

Gln Gln Ser Asp Asn Trp Pro Phe Thr
1 5

<210> 101
<211> 121
<212> PRT
<213> Homo sapiens

<400> 101

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

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

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

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

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

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

Ala Lys Asp Arg Gly Leu Gly Asp Gly Thr Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 102
<211> 110
<212> PRT
<213> Homo sapiens

<400> 102

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

Ser Ile Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
            20                  25                  30

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

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

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

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
                85                  90                  95

Asn Gly Pro Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 103
<211> 115
<212> PRT
<213> Homo sapiens

<400> 103

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

Thr Leu Ser Leu Thr Cys Thr Val Ser Asp Asp Ser Ile Ser Ser Tyr
            20                  25                  30

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

Gly His Ile Ser Tyr Ser Gly Ser Ala Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

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

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

Asn Trp Asp Asp Ala Phe Asn Ile Trp Gly Gln Gly Thr Met Val Thr
100 105 110

Val Ser Ser
115

<210> 104
<211> 108
<212> PRT
<213> Homo sapiens

<400> 104

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

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
20 25 30

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

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

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

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Ser Pro
85 90 95

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

<210> 105
<211> 9
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 105

Gly Ser Phe Ser Gly Tyr Tyr Trp Ser
1 5

<210> 106
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 106

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

<210> 107
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 107

Ala Arg Ala Arg Gly Pro Trp Ser Phe Asp Pro
1 5 10

<210> 108
<211> 246
<212> PRT
<213> Homo sapiens

<400> 108

Met Ala Ala Ala Ala Ile Pro Ala Leu Leu Leu Cys Leu Pro Leu Leu
1 5 10 15

Phe Leu Leu Phe Gly Trp Ser Arg Ala Arg Arg Asp Asp Pro His Ser
20 25 30

Leu Cys Tyr Asp Ile Thr Val Ile Pro Lys Phe Arg Pro Gly Pro Arg
35 40 45

```
Trp Cys Ala Val Gln Gly Gln Val Asp Glu Lys Thr Phe Leu His Tyr
    50                  55                  60

Asp Cys Gly Asn Lys Thr Val Thr Pro Val Ser Pro Leu Gly Lys Lys
65                  70                  75                  80

Leu Asn Val Thr Met Ala Trp Lys Ala Gln Asn Pro Val Leu Arg Glu
                85                  90                  95

Val Val Asp Ile Leu Thr Glu Gln Leu Leu Asp Ile Gln Leu Glu Asn
            100                 105                 110

Tyr Thr Pro Lys Glu Pro Leu Thr Leu Gln Ala Arg Met Ser Cys Glu
        115                 120                 125

Gln Lys Ala Glu Gly His Ser Ser Gly Ser Trp Gln Phe Ser Ile Asp
    130                 135                 140

Gly Gln Thr Phe Leu Leu Phe Asp Ser Glu Lys Arg Met Trp Thr Thr
145                 150                 155                 160

Val His Pro Gly Ala Arg Lys Met Lys Glu Lys Trp Glu Asn Asp Lys
                165                 170                 175

Asp Val Ala Met Ser Phe His Tyr Ile Ser Met Gly Asp Cys Ile Gly
            180                 185                 190

Trp Leu Glu Asp Phe Leu Met Gly Met Asp Ser Thr Leu Glu Pro Ser
        195                 200                 205

Ala Gly Ala Pro Leu Ala Met Ser Ser Gly Thr Thr Gln Leu Arg Ala
    210                 215                 220

Thr Ala Thr Thr Leu Ile Leu Cys Cys Leu Leu Ile Ile Leu Pro Cys
225                 230                 235                 240

Phe Ile Leu Pro Gly Ile
                245
```

<210> 109

<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 109

Gly Thr Phe Ser Ser Tyr Ala Ile Ser
1 5

<210> 110
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 110

Gly Ile Ile Pro Ile Phe Gly Thr Ala Asn Tyr Ala Gln Lys Phe Gln
1 5 10 15

Gly

<210> 111
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 111

Ala Arg Arg Gly Arg Lys Ala Ser Gly Ser Phe Tyr Tyr Tyr Tyr Gly
1 5 10 15

Met Asp Val

<210> 112
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 112

Glu Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys Asn Tyr Leu
1 5 10 15

Thr

<210> 113
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 113

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 114
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 114

Gln Asn Asp Tyr Ser Tyr Pro Tyr Thr
1 5

<210> 115
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 115

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

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

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

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

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

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

Ala Arg Phe Ala Ile Lys Gly Asp Tyr Trp Gly Gln Gly Thr Leu Leu
100 105 110

Thr Val Ser Ser Glu
115

<210> 116
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 116

Gly Tyr Thr Phe Thr Asn Tyr
1 5

<210> 117
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 117

Asn Thr Tyr Thr Gly Glu

1 5

<210> 118
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 118

Phe Ala Ile Lys Gly Asp Tyr
1 5

<210> 119
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 119

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

Asp Arg Val Thr Ile Thr Cys Arg Ser Thr Lys Ser Leu Leu His Ser
20 25 30

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

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

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

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

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

Arg

<210> 120
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 120

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

<210> 121
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 121

Gln Met Ser Asn Leu Ala Ser
1 5

<210> 122
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 122

Ala Gln Asn Leu Glu Ile Pro Arg Thr
1 5

<210> 123
<211> 128
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 123

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

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

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

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

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

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

Ala Lys Asp Met Gly Trp Gly Ser Gly Trp Arg Pro Tyr Tyr Tyr Tyr
100 105 110

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

<210> 124
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 124

Gly Phe Thr Phe Ser Ser Tyr
1 5

<210> 125
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 125

Ser Tyr Asp Gly Ser Asn
1 5

<210> 126
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 126

Asp Met Gly Trp Gly Ser Gly Trp Arg Pro Tyr Tyr Tyr Tyr Gly Met
1 5 10 15

Asp Val

<210> 127
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 127

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

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

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

Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro

65 70 75 80

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

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
100 105

<210> 128
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 128

Gln Ser Ile Ser Ser Tyr Leu Asn
1 5

<210> 129
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 129

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 130
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 130

Gln Gln Ser Tyr Asp Ile Pro Tyr Thr
1 5

<210> 131

<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 131

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

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

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

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

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

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

Ala Arg Phe Ala Ile Lys Gly Asp Tyr Trp Gly Gln Gly Thr Leu Leu
100 105 110

Thr Val Ser Ser Ala
115

<210> 132
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 132

Gly Tyr Thr Phe Thr Asn Tyr
1 5

<210> 133
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 133

Asn Thr Tyr Thr Gly Glu
1 5

<210> 134
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 134

Phe Ala Ile Lys Gly Asp Tyr
1 5

<210> 135
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 135

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

Asp Arg Val Thr Ile Thr Cys Arg Ser Thr Lys Ser Leu Leu His Ser
20 25 30

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

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

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

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

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

Arg

<210> 136
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 136

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

<210> 137
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 137

Gln Met Ser Asn Leu Ala Ser
1 5

<210> 138
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 138

Ala Gln Asn Leu Glu Ile Pro Arg Thr
1 5

<210> 139
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 139

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

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

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

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
50 55 60

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

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
85 90 95

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 140
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 140

Gly Tyr Ala Phe Thr Asn Tyr
1 5

<210> 141
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 141

Phe Pro Gly Ser Gly Asn
1 5

<210> 142
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 142

Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr
1 5 10

<210> 143
<211> 114
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 143

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

Gly Asn Gln Lys Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln

35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn
85 90 95

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

Lys Gly

<210> 144
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 144

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

<210> 145
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 145

Trp Ala Ser Thr Arg Glu Ser
1 5

<210> 146
<211> 9
<212> PRT

<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 146

Gln Asn Asp Tyr Ser Tyr Pro Leu Thr
1 5

<210> 147
<211> 314
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 147

Met Ala Pro Pro Gln Val Leu Ala Phe Gly Leu Leu Leu Ala Ala Ala
1 5 10 15

Thr Ala Thr Phe Ala Ala Ala Gln Glu Glu Cys Val Cys Glu Asn Tyr
20 25 30

Lys Leu Ala Val Asn Cys Phe Val Asn Asn Asn Arg Gln Cys Gln Cys
35 40 45

Thr Ser Val Gly Ala Gln Asn Thr Val Ile Cys Ser Lys Leu Ala Ala
50 55 60

Lys Cys Leu Val Met Lys Ala Glu Met Asn Gly Ser Lys Leu Gly Arg
65 70 75 80

Arg Ala Lys Pro Glu Gly Ala Leu Gln Asn Asn Asp Gly Leu Tyr Asp
85 90 95

Pro Asp Cys Asp Glu Ser Gly Leu Phe Lys Ala Lys Gln Cys Asn Gly
100 105 110

Thr Ser Met Cys Trp Cys Val Asn Thr Ala Gly Val Arg Arg Thr Asp
115 120 125

Lys Asp Thr Glu Ile Thr Cys Ser Glu Arg Val Arg Thr Tyr Trp Ile

```
    130                 135                 140

Ile Ile Glu Leu Lys His Lys Ala Arg Glu Lys Pro Tyr Asp Ser Lys
145                 150                 155                 160

Ser Leu Arg Thr Ala Leu Gln Lys Glu Ile Thr Thr Arg Tyr Gln Leu
                165                 170                 175

Asp Pro Lys Phe Ile Thr Ser Ile Leu Tyr Glu Asn Asn Val Ile Thr
            180                 185                 190

Ile Asp Leu Val Gln Asn Ser Ser Gln Lys Thr Gln Asn Asp Val Asp
        195                 200                 205

Ile Ala Asp Val Ala Tyr Tyr Phe Glu Lys Asp Val Lys Gly Glu Ser
    210                 215                 220

Leu Phe His Ser Lys Lys Met Asp Leu Thr Val Asn Gly Glu Gln Leu
225                 230                 235                 240

Asp Leu Asp Pro Gly Gln Thr Leu Ile Tyr Tyr Val Asp Glu Lys Ala
                245                 250                 255

Pro Glu Phe Ser Met Gln Gly Leu Lys Ala Gly Val Ile Ala Val Ile
            260                 265                 270

Val Val Val Val Ile Ala Val Val Ala Gly Ile Val Val Leu Val Ile
        275                 280                 285

Ser Arg Lys Lys Arg Met Ala Lys Tyr Glu Lys Ala Glu Ile Lys Glu
    290                 295                 300

Met Gly Glu Met His Arg Glu Leu Asn Ala
305                 310
```

<210> 148
<211> 14507
<212> PRT
<213> Homo sapiens

<400> 148

```
Met Leu Lys Pro Ser Gly Leu Pro Gly Ser Ser Ser Pro Thr Arg Ser
1               5                  10                  15

Leu Met Thr Gly Ser Arg Ser Thr Lys Ala Thr Pro Glu Met Asp Ser
            20                  25                  30

Gly Leu Thr Gly Ala Thr Leu Ser Pro Lys Thr Ser Thr Gly Ala Ile
        35                  40                  45

Val Val Thr Glu His Thr Leu Pro Phe Thr Ser Pro Asp Lys Thr Leu
    50                  55                  60

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

Val Met Ser Ser Ala Leu Pro Glu Ser Thr Ser Arg Gly Met Thr His
                85                  90                  95

Ser Glu Gln Arg Thr Ser Pro Ser Leu Ser Pro Gln Val Asn Gly Thr
            100                 105                 110

Pro Ser Arg Asn Tyr Pro Ala Thr Ser Met Val Ser Gly Leu Ser Ser
        115                 120                 125

Pro Arg Thr Arg Thr Ser Ser Thr Glu Gly Asn Phe Thr Lys Glu Ala
    130                 135                 140

Ser Thr Tyr Thr Leu Thr Val Glu Thr Thr Ser Gly Pro Val Thr Glu
145                 150                 155                 160

Lys Tyr Thr Val Pro Thr Glu Thr Ser Thr Thr Glu Gly Asp Ser Thr
                165                 170                 175

Glu Thr Pro Trp Asp Thr Arg Tyr Ile Pro Val Lys Ile Thr Ser Pro
            180                 185                 190

Met Lys Thr Phe Ala Asp Ser Thr Ala Ser Lys Glu Asn Ala Pro Val
        195                 200                 205

Ser Met Thr Pro Ala Glu Thr Thr Val Thr Asp Ser His Thr Pro Gly
    210                 215                 220
```

```
Arg Thr Asn Pro Ser Phe Gly Thr Leu Tyr Ser Ser Phe Leu Asp Leu
225                 230                 235                 240

Ser Pro Lys Gly Thr Pro Asn Ser Arg Gly Glu Thr Ser Leu Glu Leu
                245                 250                 255

Ile Leu Ser Thr Thr Gly Tyr Pro Phe Ser Ser Pro Glu Pro Gly Ser
            260                 265                 270

Ala Gly His Ser Arg Ile Ser Thr Ser Ala Pro Leu Ser Ser Ser Ala
        275                 280                 285

Ser Val Leu Asp Asn Lys Ile Ser Glu Thr Ser Ile Phe Ser Gly Gln
    290                 295                 300

Ser Leu Thr Ser Pro Leu Ser Pro Gly Val Pro Glu Ala Arg Ala Ser
305                 310                 315                 320

Thr Met Pro Asn Ser Ala Ile Pro Phe Ser Met Thr Leu Ser Asn Ala
                325                 330                 335

Glu Thr Ser Ala Glu Arg Val Arg Ser Thr Ile Ser Ser Leu Gly Thr
            340                 345                 350

Pro Ser Ile Ser Thr Lys Gln Thr Ala Glu Thr Ile Leu Thr Phe His
        355                 360                 365

Ala Phe Ala Glu Thr Met Asp Ile Pro Ser Thr His Ile Ala Lys Thr
    370                 375                 380

Leu Ala Ser Glu Trp Leu Gly Ser Pro Gly Thr Leu Gly Gly Thr Ser
385                 390                 395                 400

Thr Ser Ala Leu Thr Thr Thr Ser Pro Ser Thr Thr Leu Val Ser Glu
                405                 410                 415

Glu Thr Asn Thr His His Ser Thr Ser Gly Lys Glu Thr Glu Gly Thr
            420                 425                 430
```

```
Leu Asn Thr Ser Met Thr Pro Leu Glu Thr Ser Ala Pro Gly Glu Glu
        435                 440                 445

Ser Glu Met Thr Ala Thr Leu Val Pro Thr Leu Gly Phe Thr Thr Leu
    450                 455                 460

Asp Ser Lys Ile Arg Ser Pro Ser Gln Val Ser Ser Ser His Pro Thr
465                 470                 475                 480

Arg Glu Leu Arg Thr Thr Gly Ser Thr Ser Gly Arg Gln Ser Ser Ser
                485                 490                 495

Thr Ala Ala His Gly Ser Ser Asp Ile Leu Arg Ala Thr Thr Ser Ser
            500                 505                 510

Thr Ser Lys Ala Ser Ser Trp Thr Ser Glu Ser Thr Ala Gln Gln Phe
        515                 520                 525

Ser Glu Pro Gln His Thr Gln Trp Val Glu Thr Ser Pro Ser Met Lys
    530                 535                 540

Thr Glu Arg Pro Pro Ala Ser Thr Ser Val Ala Ala Pro Ile Thr Thr
545                 550                 555                 560

Ser Val Pro Ser Val Val Ser Gly Phe Thr Thr Leu Lys Thr Ser Ser
                565                 570                 575

Thr Lys Gly Ile Trp Leu Glu Glu Thr Ser Ala Asp Thr Leu Ile Gly
            580                 585                 590

Glu Ser Thr Ala Gly Pro Thr Thr His Gln Phe Ala Val Pro Thr Gly
        595                 600                 605

Ile Ser Met Thr Gly Gly Ser Ser Thr Arg Gly Ser Gln Gly Thr Thr
    610                 615                 620

His Leu Leu Thr Arg Ala Thr Ala Ser Ser Glu Thr Ser Ala Asp Leu
625                 630                 635                 640

Thr Leu Ala Thr Asn Gly Val Pro Val Ser Val Ser Pro Ala Val Ser
                645                 650                 655
```

```
Lys Thr Ala Ala Gly Ser Ser Pro Pro Gly Gly Thr Lys Pro Ser Tyr
            660                 665                 670

Thr Met Val Ser Ser Val Ile Pro Glu Thr Ser Ser Leu Gln Ser Ser
        675                 680                 685

Ala Phe Arg Glu Gly Thr Ser Leu Gly Leu Thr Pro Leu Asn Thr Arg
    690                 695                 700

His Pro Phe Ser Ser Pro Glu Pro Asp Ser Ala Gly His Thr Lys Ile
705                 710                 715                 720

Ser Thr Ser Ile Pro Leu Leu Ser Ser Ala Ser Val Leu Glu Asp Lys
                725                 730                 735

Val Ser Ala Thr Ser Thr Phe Ser His His Lys Ala Thr Ser Ser Ile
            740                 745                 750

Thr Thr Gly Thr Pro Glu Ile Ser Thr Lys Thr Lys Pro Ser Ser Ala
        755                 760                 765

Val Leu Ser Ser Met Thr Leu Ser Asn Ala Ala Thr Ser Pro Glu Arg
    770                 775                 780

Val Arg Asn Ala Thr Ser Pro Leu Thr His Pro Ser Pro Ser Gly Glu
785                 790                 795                 800

Glu Thr Ala Gly Ser Val Leu Thr Leu Ser Thr Ser Ala Glu Thr Thr
                805                 810                 815

Asp Ser Pro Asn Ile His Pro Thr Gly Thr Leu Thr Ser Glu Ser Ser
            820                 825                 830

Glu Ser Pro Ser Thr Leu Ser Leu Pro Ser Val Ser Gly Val Lys Thr
        835                 840                 845

Thr Phe Ser Ser Ser Thr Pro Ser Thr His Leu Phe Thr Ser Gly Glu
    850                 855                 860
```

```
Glu Thr Glu Glu Thr Ser Asn Pro Ser Val Ser Gln Pro Glu Thr Ser
865                 870                 875                 880

Val Ser Arg Val Arg Thr Thr Leu Ala Ser Thr Ser Val Pro Thr Pro
                885                 890                 895

Val Phe Pro Thr Met Asp Thr Trp Pro Thr Arg Ser Ala Gln Phe Ser
            900                 905                 910

Ser Ser His Leu Val Ser Glu Leu Arg Ala Thr Ser Ser Thr Ser Val
        915                 920                 925

Thr Asn Ser Thr Gly Ser Ala Leu Pro Lys Ile Ser His Leu Thr Gly
    930                 935                 940

Thr Ala Thr Met Ser Gln Thr Asn Arg Asp Thr Phe Asn Asp Ser Ala
945                 950                 955                 960

Ala Pro Gln Ser Thr Thr Trp Pro Glu Thr Ser Pro Arg Phe Lys Thr
                965                 970                 975

Gly Leu Pro Ser Ala Thr Thr Thr Val Ser Thr Ser Ala Thr Ser Leu
            980                 985                 990

Ser Ala Thr Val Met Val Ser Lys  Phe Thr Ser Pro Ala  Thr Ser Ser
        995                 1000                1005

Met Glu  Ala Thr Ser Ile Arg  Glu Pro Ser Thr Thr  Ile Leu Thr
    1010                1015                1020

Thr Glu  Thr Thr Asn Gly Pro  Gly Ser Met Ala Val  Ala Ser Thr
    1025                1030                1035

Asn Ile  Pro Ile Gly Lys Gly  Tyr Ile Thr Glu Gly  Arg Leu Asp
    1040                1045                1050

Thr Ser  His Leu Pro Ile Gly  Thr Thr Ala Ser Ser  Glu Thr Ser
    1055                1060                1065

Met Asp  Phe Thr Met Ala Lys  Glu Ser Val Ser Met  Ser Val Ser
    1070                1075                1080
```

```
Pro Ser  Gln Ser Met Asp Ala  Ala Gly Ser Ser Thr  Pro Gly Arg
    1085                1090                1095

Thr Ser  Gln Phe Val Asp Thr  Phe Ser Asp Asp Val  Tyr His Leu
    1100                1105                1110

Thr Ser  Arg Glu Ile Thr Ile  Pro Arg Asp Gly Thr  Ser Ser Ala
    1115                1120                1125

Leu Thr  Pro Gln Met Thr Ala  Thr His Pro Pro Ser  Pro Asp Pro
    1130                1135                1140

Gly Ser  Ala Arg Ser Thr Trp  Leu Gly Ile Leu Ser  Ser Ser Pro
    1145                1150                1155

Ser Ser  Pro Thr Pro Lys Val  Thr Met Ser Ser Thr  Phe Ser Thr
    1160                1165                1170

Gln Arg  Val Thr Thr Ser Met  Ile Met Asp Thr Val  Glu Thr Ser
    1175                1180                1185

Arg Trp  Asn Met Pro Asn Leu  Pro Ser Thr Thr Ser  Leu Thr Pro
    1190                1195                1200

Ser Asn  Ile Pro Thr Ser Gly  Ala Ile Gly Lys Ser  Thr Leu Val
    1205                1210                1215

Pro Leu  Asp Thr Pro Ser Pro  Ala Thr Ser Leu Glu  Ala Ser Glu
    1220                1225                1230

Gly Gly  Leu Pro Thr Leu Ser  Thr Tyr Pro Glu Ser  Thr Asn Thr
    1235                1240                1245

Pro Ser  Ile His Leu Gly Ala  His Ala Ser Ser Glu  Ser Pro Ser
    1250                1255                1260

Thr Ile  Lys Leu Thr Met Ala  Ser Val Val Lys Pro  Gly Ser Tyr
    1265                1270                1275
```

```
Thr Pro  Leu Thr Phe Pro Ser  Ile Glu Thr His Ile  His Val Ser
    1280                1285                1290

Thr Ala  Arg Met Ala Tyr Ser  Ser Gly Ser Ser Pro  Glu Met Thr
    1295                1300                1305

Ala Pro  Gly Glu Thr Asn Thr  Gly Ser Thr Trp Asp  Pro Thr Thr
    1310                1315                1320

Tyr Ile  Thr Thr Thr Asp Pro  Lys Asp Thr Ser Ser  Ala Gln Val
    1325                1330                1335

Ser Thr  Pro His Ser Val Arg  Thr Leu Arg Thr Thr  Glu Asn His
    1340                1345                1350

Pro Lys  Thr Glu Ser Ala Thr  Pro Ala Ala Tyr Ser  Gly Ser Pro
    1355                1360                1365

Lys Ile  Ser Ser Ser Pro Asn  Leu Thr Ser Pro Ala  Thr Lys Ala
    1370                1375                1380

Trp Thr  Ile Thr Asp Thr Thr  Glu His Ser Thr Gln  Leu His Tyr
    1385                1390                1395

Thr Lys  Leu Ala Glu Lys Ser  Ser Gly Phe Glu Thr  Gln Ser Ala
    1400                1405                1410

Pro Gly  Pro Val Ser Val Val  Ile Pro Thr Ser Pro  Thr Ile Gly
    1415                1420                1425

Ser Ser  Thr Leu Glu Leu Thr  Ser Asp Val Pro Gly  Glu Pro Leu
    1430                1435                1440

Val Leu  Ala Pro Ser Glu Gln  Thr Thr Ile Thr Leu  Pro Met Ala
    1445                1450                1455

Thr Trp  Leu Ser Thr Ser Leu  Thr Glu Glu Met Ala  Ser Thr Asp
    1460                1465                1470

Leu Asp  Ile Ser Ser Pro Ser  Ser Pro Met Ser Thr  Phe Ala Ile
    1475                1480                1485
```

```
Phe Pro  Pro Met Ser Thr Pro  Ser His Glu Leu Ser  Lys Ser Glu
    1490                1495                1500

Ala Asp  Thr Ser Ala Ile Arg  Asn Thr Asp Ser Thr  Thr Leu Asp
    1505                1510                1515

Gln His  Leu Gly Ile Arg Ser  Leu Gly Arg Thr Gly  Asp Leu Thr
    1520                1525                1530

Thr Val  Pro Ile Thr Pro Leu  Thr Thr Thr Trp Thr  Ser Val Ile
    1535                1540                1545

Glu His  Ser Thr Gln Ala Gln  Asp Thr Leu Ser Ala  Thr Met Ser
    1550                1555                1560

Pro Thr  His Val Thr Gln Ser  Leu Lys Asp Gln Thr  Ser Ile Pro
    1565                1570                1575

Ala Ser  Ala Ser Pro Ser His  Leu Thr Glu Val Tyr  Pro Glu Leu
    1580                1585                1590

Gly Thr  Gln Gly Arg Ser Ser  Ser Glu Ala Thr Thr  Phe Trp Lys
    1595                1600                1605

Pro Ser  Thr Asp Thr Leu Ser  Arg Glu Ile Glu Thr  Gly Pro Thr
    1610                1615                1620

Asn Ile  Gln Ser Thr Pro Pro  Met Asp Asn Thr Thr  Thr Gly Ser
    1625                1630                1635

Ser Ser  Ser Gly Val Thr Leu  Gly Ile Ala His Leu  Pro Ile Gly
    1640                1645                1650

Thr Ser  Ser Pro Ala Glu Thr  Ser Thr Asn Met Ala  Leu Glu Arg
    1655                1660                1665

Arg Ser  Ser Thr Ala Thr Val  Ser Met Ala Gly Thr  Met Gly Leu
    1670                1675                1680
```

```
Leu Val  Thr Ser Ala Pro Gly  Arg Ser Ile Ser Gln  Ser Leu Gly
    1685                1690                1695

Arg Val  Ser Ser Val Leu Ser  Glu Ser Thr Thr Glu  Gly Val Thr
    1700                1705                1710

Asp Ser  Ser Lys Gly Ser Ser  Pro Arg Leu Asn Thr  Gln Gly Asn
    1715                1720                1725

Thr Ala  Leu Ser Ser Ser Leu  Glu Pro Ser Tyr Ala  Glu Gly Ser
    1730                1735                1740

Gln Met  Ser Thr Ser Ile Pro  Leu Thr Ser Ser Pro  Thr Thr Pro
    1745                1750                1755

Asp Val  Glu Phe Ile Gly Gly  Ser Thr Phe Trp Thr  Lys Glu Val
    1760                1765                1770

Thr Thr  Val Met Thr Ser Asp  Ile Ser Lys Ser Ser  Ala Arg Thr
    1775                1780                1785

Glu Ser  Ser Ser Ala Thr Leu  Met Ser Thr Ala Leu  Gly Ser Thr
    1790                1795                1800

Glu Asn  Thr Gly Lys Glu Lys  Leu Arg Thr Ala Ser  Met Asp Leu
    1805                1810                1815

Pro Ser  Pro Thr Pro Ser Met  Glu Val Thr Pro Trp  Ile Ser Leu
    1820                1825                1830

Thr Leu  Ser Asn Ala Pro Asn  Thr Thr Asp Ser Leu  Asp Leu Ser
    1835                1840                1845

His Gly  Val His Thr Ser Ser  Ala Gly Thr Leu Ala  Thr Asp Arg
    1850                1855                1860

Ser Leu  Asn Thr Gly Val Thr  Arg Ala Ser Arg Leu  Glu Asn Gly
    1865                1870                1875

Ser Asp  Thr Ser Ser Lys Ser  Leu Ser Met Gly Asn  Ser Thr His
    1880                1885                1890
```

```
Thr Ser  Met Thr Tyr Thr Glu  Lys Ser Glu Val Ser  Ser Ser Ile
    1895                1900                1905

His Pro  Arg Pro Glu Thr Ser  Ala Pro Gly Ala Glu  Thr Thr Leu
    1910                1915                1920

Thr Ser  Thr Pro Gly Asn Arg  Ala Ile Ser Leu Thr  Leu Pro Phe
    1925                1930                1935

Ser Ser  Ile Pro Val Glu Glu  Val Ile Ser Thr Gly  Ile Thr Ser
    1940                1945                1950

Gly Pro  Asp Ile Asn Ser Ala  Pro Met Thr His Ser  Pro Ile Thr
    1955                1960                1965

Pro Pro  Thr Ile Val Trp Thr  Ser Thr Gly Thr Ile  Glu Gln Ser
    1970                1975                1980

Thr Gln  Pro Leu His Ala Val  Ser Ser Glu Lys Val  Ser Val Gln
    1985                1990                1995

Thr Gln  Ser Thr Pro Tyr Val  Asn Ser Val Ala Val  Ser Ala Ser
    2000                2005                2010

Pro Thr  His Glu Asn Ser Val  Ser Ser Gly Ser Ser  Thr Ser Ser
    2015                2020                2025

Pro Tyr  Ser Ser Ala Ser Leu  Glu Ser Leu Asp Ser  Thr Ile Ser
    2030                2035                2040

Arg Arg  Asn Ala Ile Thr Ser  Trp Leu Trp Asp Leu  Thr Thr Ser
    2045                2050                2055

Leu Pro  Thr Thr Thr Trp Pro  Ser Thr Ser Leu Ser  Glu Ala Leu
    2060                2065                2070

Ser Ser  Gly His Ser Gly Val  Ser Asn Pro Ser Ser  Thr Thr Thr
    2075                2080                2085
```

```
Glu Phe  Pro Leu Phe Ser Ala  Ala Ser Thr Ser Ala  Ala Lys Gln
    2090                 2095                 2100

Arg Asn  Pro Glu Thr Glu Thr  His Gly Pro Gln Asn  Thr Ala Ala
    2105                 2110                 2115

Ser Thr  Leu Asn Thr Asp Ala  Ser Ser Val Thr Gly  Leu Ser Glu
    2120                 2125                 2130

Thr Pro  Val Gly Ala Ser Ile  Ser Ser Glu Val Pro  Leu Pro Met
    2135                 2140                 2145

Ala Ile  Thr Ser Arg Ser Asp  Val Ser Gly Leu Thr  Ser Glu Ser
    2150                 2155                 2160

Thr Ala  Asn Pro Ser Leu Gly  Thr Ala Ser Ser Ala  Gly Thr Lys
    2165                 2170                 2175

Leu Thr  Arg Thr Ile Ser Leu  Pro Thr Ser Glu Ser  Leu Val Ser
    2180                 2185                 2190

Phe Arg  Met Asn Lys Asp Pro  Trp Thr Val Ser Ile  Pro Leu Gly
    2195                 2200                 2205

Ser His  Pro Thr Thr Asn Thr  Glu Thr Ser Ile Pro  Val Asn Ser
    2210                 2215                 2220

Ala Gly  Pro Pro Gly Leu Ser  Thr Val Ala Ser Asp  Val Ile Asp
    2225                 2230                 2235

Thr Pro  Ser Asp Gly Ala Glu  Ser Ile Pro Thr Val  Ser Phe Ser
    2240                 2245                 2250

Pro Ser  Pro Asp Thr Glu Val  Thr Thr Ile Ser His  Phe Pro Glu
    2255                 2260                 2265

Lys Thr  Thr His Ser Phe Arg  Thr Ile Ser Ser Leu  Thr His Glu
    2270                 2275                 2280

Leu Thr  Ser Arg Val Thr Pro  Ile Pro Gly Asp Trp  Met Ser Ser
    2285                 2290                 2295
```

```
Ala Met  Ser Thr Lys Pro Thr  Gly Ala Ser Pro Ser  Ile Thr Leu
    2300                2305                2310

Gly Glu  Arg Arg Thr Ile Thr  Ser Ala Ala Pro Thr  Thr Ser Pro
    2315                2320                2325

Ile Val  Leu Thr Ala Ser Phe  Thr Glu Thr Ser Thr  Val Ser Leu
    2330                2335                2340

Asp Asn  Glu Thr Thr Val Lys  Thr Ser Asp Ile Leu  Asp Ala Arg
    2345                2350                2355

Lys Thr  Asn Glu Leu Pro Ser  Asp Ser Ser Ser Ser  Ser Asp Leu
    2360                2365                2370

Ile Asn  Thr Ser Ile Ala Ser  Ser Thr Met Asp Val  Thr Lys Thr
    2375                2380                2385

Ala Ser  Ile Ser Pro Thr Ser  Ile Ser Gly Met Thr  Ala Ser Ser
    2390                2395                2400

Ser Pro  Ser Leu Phe Ser Ser  Asp Arg Pro Gln Val  Pro Thr Ser
    2405                2410                2415

Thr Thr  Glu Thr Asn Thr Ala  Thr Ser Pro Ser Val  Ser Ser Asn
    2420                2425                2430

Thr Tyr  Ser Leu Asp Gly Gly  Ser Asn Val Gly Gly  Thr Pro Ser
    2435                2440                2445

Thr Leu  Pro Pro Phe Thr Ile  Thr His Pro Val Glu  Thr Ser Ser
    2450                2455                2460

Ala Leu  Leu Ala Trp Ser Arg  Pro Val Arg Thr Phe  Ser Thr Met
    2465                2470                2475

Val Ser  Thr Asp Thr Ala Ser  Gly Glu Asn Pro Thr  Ser Ser Asn
    2480                2485                2490
```

```
Ser Val  Val Thr Ser Val Pro  Ala Pro Gly Thr Trp  Thr Ser Val
    2495                2500                2505

Gly Ser  Thr Thr Asp Leu Pro  Ala Met Gly Phe Leu  Lys Thr Ser
    2510                2515                2520

Pro Ala  Gly Glu Ala His Ser  Leu Leu Ala Ser Thr  Ile Glu Pro
    2525                2530                2535

Ala Thr  Ala Phe Thr Pro His  Leu Ser Ala Ala Val  Val Thr Gly
    2540                2545                2550

Ser Ser  Ala Thr Ser Glu Ala  Ser Leu Leu Thr Thr  Ser Glu Ser
    2555                2560                2565

Lys Ala  Ile His Ser Ser Pro  Gln Thr Pro Thr Thr  Pro Thr Ser
    2570                2575                2580

Gly Ala  Asn Trp Glu Thr Ser  Ala Thr Pro Glu Ser  Leu Leu Val
    2585                2590                2595

Val Thr  Glu Thr Ser Asp Thr  Thr Leu Thr Ser Lys  Ile Leu Val
    2600                2605                2610

Thr Asp  Thr Ile Leu Phe Ser  Thr Val Ser Thr Pro  Pro Ser Lys
    2615                2620                2625

Phe Pro  Ser Thr Gly Thr Leu  Ser Gly Ala Ser Phe  Pro Thr Leu
    2630                2635                2640

Leu Pro  Asp Thr Pro Ala Ile  Pro Leu Thr Ala Thr  Glu Pro Thr
    2645                2650                2655

Ser Ser  Leu Ala Thr Ser Phe  Asp Ser Thr Pro Leu  Val Thr Ile
    2660                2665                2670

Ala Ser  Asp Ser Leu Gly Thr  Val Pro Glu Thr Thr  Leu Thr Met
    2675                2680                2685

Ser Glu  Thr Ser Asn Gly Asp  Ala Leu Val Leu Lys  Thr Val Ser
    2690                2695                2700
```

```
Asn Pro  Asp Arg Ser Ile Pro  Gly Ile Thr Ile Gln  Gly Val Thr
    2705                2710                2715

Glu Ser  Pro Leu His Pro Ser  Ser Thr Ser Pro Ser  Lys Ile Val
    2720                2725                2730

Ala Pro  Arg Asn Thr Thr Tyr  Glu Gly Ser Ile Thr  Val Ala Leu
    2735                2740                2745

Ser Thr  Leu Pro Ala Gly Thr  Thr Gly Ser Leu Val  Phe Ser Gln
    2750                2755                2760

Ser Ser  Glu Asn Ser Glu Thr  Thr Ala Leu Val Asp  Ser Ser Ala
    2765                2770                2775

Gly Leu  Glu Arg Ala Ser Val  Met Pro Leu Thr Thr  Gly Ser Gln
    2780                2785                2790

Gly Met  Ala Ser Ser Gly Gly  Ile Arg Ser Gly Ser  Thr His Ser
    2795                2800                2805

Thr Gly  Thr Lys Thr Phe Ser  Ser Leu Pro Leu Thr  Met Asn Pro
    2810                2815                2820

Gly Glu  Val Thr Ala Met Ser  Glu Ile Thr Thr Asn  Arg Leu Thr
    2825                2830                2835

Ala Thr  Gln Ser Thr Ala Pro  Lys Gly Ile Pro Val  Lys Pro Thr
    2840                2845                2850

Ser Ala  Glu Ser Gly Leu Leu  Thr Pro Val Ser Ala  Ser Ser Ser
    2855                2860                2865

Pro Ser  Lys Ala Phe Ala Ser  Leu Thr Thr Ala Pro  Pro Thr Trp
    2870                2875                2880

Gly Ile  Pro Gln Ser Thr Leu  Thr Phe Glu Phe Ser  Glu Val Pro
    2885                2890                2895
```

```
Ser Leu  Asp Thr Lys Ser Ala  Ser Leu Pro Thr Pro  Gly Gln Ser
    2900                 2905                 2910

Leu Asn  Thr Ile Pro Asp Ser  Asp Ala Ser Thr Ala  Ser Ser Ser
    2915                 2920                 2925

Leu Ser  Lys Ser Pro Glu Lys  Asn Pro Arg Ala Arg  Met Met Thr
    2930                 2935                 2940

Ser Thr  Lys Ala Ile Ser Ala  Ser Ser Phe Gln Ser  Thr Gly Phe
    2945                 2950                 2955

Thr Glu  Thr Pro Glu Gly Ser  Ala Ser Pro Ser Met  Ala Gly His
    2960                 2965                 2970

Glu Pro  Arg Val Pro Thr Ser  Gly Thr Gly Asp Pro  Arg Tyr Ala
    2975                 2980                 2985

Ser Glu  Ser Met Ser Tyr Pro  Asp Pro Ser Lys Ala  Ser Ser Ala
    2990                 2995                 3000

Met Thr  Ser Thr Ser Leu Ala  Ser Lys Leu Thr Thr  Leu Phe Ser
    3005                 3010                 3015

Thr Gly  Gln Ala Ala Arg Ser  Gly Ser Ser Ser Ser  Pro Ile Ser
    3020                 3025                 3030

Leu Ser  Thr Glu Lys Glu Thr  Ser Phe Leu Ser Pro  Thr Ala Ser
    3035                 3040                 3045

Thr Ser  Arg Lys Thr Ser Leu  Phe Leu Gly Pro Ser  Met Ala Arg
    3050                 3055                 3060

Gln Pro  Asn Ile Leu Val His  Leu Gln Thr Ser Ala  Leu Thr Leu
    3065                 3070                 3075

Ser Pro  Thr Ser Thr Leu Asn  Met Ser Gln Glu Glu  Pro Pro Glu
    3080                 3085                 3090

Leu Thr  Ser Ser Gln Thr Ile  Ala Glu Glu Glu Gly  Thr Thr Ala
    3095                 3100                 3105
```

```
Glu Thr  Gln Thr Leu Thr Phe  Thr Pro Ser Glu Thr  Pro Thr Ser
    3110                3115                3120

Leu Leu  Pro Val Ser Ser Pro  Thr Glu Pro Thr Ala  Arg Arg Lys
    3125                3130                3135

Ser Ser  Pro Glu Thr Trp Ala  Ser Ser Ile Ser Val  Pro Ala Lys
    3140                3145                3150

Thr Ser  Leu Val Glu Thr Thr  Asp Gly Thr Leu Val  Thr Thr Ile
    3155                3160                3165

Lys Met  Ser Ser Gln Ala Ala  Gln Gly Asn Ser Thr  Trp Pro Ala
    3170                3175                3180

Pro Ala  Glu Glu Thr Gly Ser  Ser Pro Ala Gly Thr  Ser Pro Gly
    3185                3190                3195

Ser Pro  Glu Met Ser Thr Thr  Leu Lys Ile Met Ser  Ser Lys Glu
    3200                3205                3210

Pro Ser  Ile Ser Pro Glu Ile  Arg Ser Thr Val Arg  Asn Ser Pro
    3215                3220                3225

Trp Lys  Thr Pro Glu Thr Thr  Val Pro Met Glu Thr  Thr Val Glu
    3230                3235                3240

Pro Val  Thr Leu Gln Ser Thr  Ala Leu Gly Ser Gly  Ser Thr Ser
    3245                3250                3255

Ile Ser  His Leu Pro Thr Gly  Thr Thr Ser Pro Thr  Lys Ser Pro
    3260                3265                3270

Thr Glu  Asn Met Leu Ala Thr  Glu Arg Val Ser Leu  Ser Pro Ser
    3275                3280                3285

Pro Pro  Glu Ala Trp Thr Asn  Leu Tyr Ser Gly Thr  Pro Gly Gly
    3290                3295                3300
```

```
Thr Arg  Gln Ser Leu Ala Thr  Met Ser Ser Val Ser  Leu Glu Ser
    3305                 3310                 3315

Pro Thr  Ala Arg Ser Ile Thr  Gly Thr Gly Gln Gln  Ser Ser Pro
    3320                 3325                 3330

Glu Leu  Val Ser Lys Thr Thr  Gly Met Glu Phe Ser  Met Trp His
    3335                 3340                 3345

Gly Ser  Thr Gly Gly Thr Thr  Gly Asp Thr His Val  Ser Leu Ser
    3350                 3355                 3360

Thr Ser  Ser Asn Ile Leu Glu  Asp Pro Val Thr Ser  Pro Asn Ser
    3365                 3370                 3375

Val Ser  Ser Leu Thr Asp Lys  Ser Lys His Lys Thr  Glu Thr Trp
    3380                 3385                 3390

Val Ser  Thr Thr Ala Ile Pro  Ser Thr Val Leu Asn  Asn Lys Ile
    3395                 3400                 3405

Met Ala  Ala Glu Gln Gln Thr  Ser Arg Ser Val Asp  Glu Ala Tyr
    3410                 3415                 3420

Ser Ser  Thr Ser Ser Trp Ser  Asp Gln Thr Ser Gly  Ser Asp Ile
    3425                 3430                 3435

Thr Leu  Gly Ala Ser Pro Asp  Val Thr Asn Thr Leu  Tyr Ile Thr
    3440                 3445                 3450

Ser Thr  Ala Gln Thr Thr Ser  Leu Val Ser Leu Pro  Ser Gly Asp
    3455                 3460                 3465

Gln Gly  Ile Thr Ser Leu Thr  Asn Pro Ser Gly Gly  Lys Thr Ser
    3470                 3475                 3480

Ser Ala  Ser Ser Val Thr Ser  Pro Ser Ile Gly Leu  Glu Thr Leu
    3485                 3490                 3495

Arg Ala  Asn Val Ser Ala Val  Lys Ser Asp Ile Ala  Pro Thr Ala
    3500                 3505                 3510
```

```
Gly His  Leu Ser Gln Thr Ser  Ser Pro Ala Glu Val  Ser Ile Leu
    3515                3520                3525

Asp Val  Thr Thr Ala Pro Thr  Pro Gly Ile Ser Thr  Thr Ile Thr
    3530                3535                3540

Thr Met  Gly Thr Asn Ser Ile  Ser Thr Thr Thr Pro  Asn Pro Glu
    3545                3550                3555

Val Gly  Met Ser Thr Met Asp  Ser Thr Pro Ala Thr  Glu Arg Arg
    3560                3565                3570

Thr Thr  Ser Thr Glu His Pro  Ser Thr Trp Ser Ser  Thr Ala Ala
    3575                3580                3585

Ser Asp  Ser Trp Thr Val Thr  Asp Met Thr Ser Asn  Leu Lys Val
    3590                3595                3600

Ala Arg  Ser Pro Gly Thr Ile  Ser Thr Met His Thr  Thr Ser Phe
    3605                3610                3615

Leu Ala  Ser Ser Thr Glu Leu  Asp Ser Met Ser Thr  Pro His Gly
    3620                3625                3630

Arg Ile  Thr Val Ile Gly Thr  Ser Leu Val Thr Pro  Ser Ser Asp
    3635                3640                3645

Ala Ser  Ala Val Lys Thr Glu  Thr Ser Thr Ser Glu  Arg Thr Leu
    3650                3655                3660

Ser Pro  Ser Asp Thr Thr Ala  Ser Thr Pro Ile Ser  Thr Phe Ser
    3665                3670                3675

Arg Val  Gln Arg Met Ser Ile  Ser Val Pro Asp Ile  Leu Ser Thr
    3680                3685                3690

Ser Trp  Thr Pro Ser Ser Thr  Glu Ala Glu Asp Val  Pro Val Ser
    3695                3700                3705
```

```
Met Val  Ser Thr Asp His Ala  Ser Thr Lys Thr Asp  Pro Asn Thr
    3710                 3715                 3720

Pro Leu  Ser Thr Phe Leu Phe  Asp Ser Leu Ser Thr  Leu Asp Trp
    3725                 3730                 3735

Asp Thr  Gly Arg Ser Leu Ser  Ser Ala Thr Ala Thr  Thr Ser Ala
    3740                 3745                 3750

Pro Gln  Gly Ala Thr Thr Pro  Gln Glu Leu Thr Leu  Glu Thr Met
    3755                 3760                 3765

Ile Ser  Pro Ala Thr Ser Gln  Leu Pro Phe Ser Ile  Gly His Ile
    3770                 3775                 3780

Thr Ser  Ala Val Thr Pro Ala  Ala Met Ala Arg Ser  Ser Gly Val
    3785                 3790                 3795

Thr Phe  Ser Arg Pro Asp Pro  Thr Ser Lys Lys Ala  Glu Gln Thr
    3800                 3805                 3810

Ser Thr  Gln Leu Pro Thr Thr  Thr Ser Ala His Pro  Gly Gln Val
    3815                 3820                 3825

Pro Arg  Ser Ala Ala Thr Thr  Leu Asp Val Ile Pro  His Thr Ala
    3830                 3835                 3840

Lys Thr  Pro Asp Ala Thr Phe  Gln Arg Gln Gly Gln  Thr Ala Leu
    3845                 3850                 3855

Thr Thr  Glu Ala Arg Ala Thr  Ser Asp Ser Trp Asn  Glu Lys Glu
    3860                 3865                 3870

Lys Ser  Thr Pro Ser Ala Pro  Trp Ile Thr Glu Met  Met Asn Ser
    3875                 3880                 3885

Val Ser  Glu Asp Thr Ile Lys  Glu Val Thr Ser Ser  Ser Ser Val
    3890                 3895                 3900

Leu Arg  Thr Leu Asn Thr Leu  Asp Ile Asn Leu Glu  Ser Gly Thr
    3905                 3910                 3915
```

```
Thr Ser  Ser Pro Ser Trp Lys  Ser Ser Pro Tyr Glu  Arg Ile Ala
    3920                3925                3930

Pro Ser  Glu Ser Thr Thr Asp  Lys Glu Ala Ile His  Pro Ser Thr
    3935                3940                3945

Asn Thr  Val Glu Thr Thr Gly  Trp Val Thr Ser Ser  Glu His Ala
    3950                3955                3960

Ser His  Ser Thr Ile Pro Ala  His Ser Ala Ser Ser  Lys Leu Thr
    3965                3970                3975

Ser Pro  Val Val Thr Thr Ser  Thr Arg Glu Gln Ala  Ile Val Ser
    3980                3985                3990

Met Ser  Thr Thr Thr Trp Pro  Glu Ser Thr Arg Ala  Arg Thr Glu
    3995                4000                4005

Pro Asn  Ser Phe Leu Thr Ile  Glu Leu Arg Asp Val  Ser Pro Tyr
    4010                4015                4020

Met Asp  Thr Ser Ser Thr Thr  Gln Thr Ser Ile Ile  Ser Ser Pro
    4025                4030                4035

Gly Ser  Thr Ala Ile Thr Lys  Gly Pro Arg Thr Glu  Ile Thr Ser
    4040                4045                4050

Ser Lys  Arg Ile Ser Ser Ser  Phe Leu Ala Gln Ser  Met Arg Ser
    4055                4060                4065

Ser Asp  Ser Pro Ser Glu Ala  Ile Thr Arg Leu Ser  Asn Phe Pro
    4070                4075                4080

Ala Met  Thr Glu Ser Gly Gly  Met Ile Leu Ala Met  Gln Thr Ser
    4085                4090                4095

Pro Pro  Gly Ala Thr Ser Leu  Ser Ala Pro Thr Leu  Asp Thr Ser
    4100                4105                4110
```

```
Ala Thr  Ala Ser Trp Thr Gly  Thr Pro Leu Ala Thr  Thr Gln Arg
    4115                4120                4125

Phe Thr  Tyr Ser Glu Lys Thr  Thr Leu Phe Ser Lys  Gly Pro Glu
    4130                4135                4140

Asp Thr  Ser Gln Pro Ser Pro  Pro Ser Val Glu Glu  Thr Ser Ser
    4145                4150                4155

Ser Ser  Ser Leu Val Pro Ile  His Ala Thr Thr Ser  Pro Ser Asn
    4160                4165                4170

Ile Leu  Leu Thr Ser Gln Gly  His Ser Pro Ser Ser  Thr Pro Pro
    4175                4180                4185

Val Thr  Ser Val Phe Leu Ser  Glu Thr Ser Gly Leu  Gly Lys Thr
    4190                4195                4200

Thr Asp  Met Ser Arg Ile Ser  Leu Glu Pro Gly Thr  Ser Leu Pro
    4205                4210                4215

Pro Asn  Leu Ser Ser Thr Ala  Gly Glu Ala Leu Ser  Thr Tyr Glu
    4220                4225                4230

Ala Ser  Arg Asp Thr Lys Ala  Ile His His Ser Ala  Asp Thr Ala
    4235                4240                4245

Val Thr  Asn Met Glu Ala Thr  Ser Ser Glu Tyr Ser  Pro Ile Pro
    4250                4255                4260

Gly His  Thr Lys Pro Ser Lys  Ala Thr Ser Pro Leu  Val Thr Ser
    4265                4270                4275

His Ile  Met Gly Asp Ile Thr  Ser Ser Thr Ser Val  Phe Gly Ser
    4280                4285                4290

Ser Glu  Thr Thr Glu Ile Glu  Thr Val Ser Ser Val  Asn Gln Gly
    4295                4300                4305

Leu Gln  Glu Arg Ser Thr Ser  Gln Val Ala Ser Ser  Ala Thr Glu
    4310                4315                4320
```

```
Thr Ser  Thr Val Ile Thr His  Val Ser Ser Gly Asp  Ala Thr Thr
    4325                4330                4335

His Val  Thr Lys Thr Gln Ala  Thr Phe Ser Ser Gly  Thr Ser Ile
    4340                4345                4350

Ser Ser  Pro His Gln Phe Ile  Thr Ser Thr Asn Thr  Phe Thr Asp
    4355                4360                4365

Val Ser  Thr Asn Pro Ser Thr  Ser Leu Ile Met Thr  Glu Ser Ser
    4370                4375                4380

Gly Val  Thr Ile Thr Thr Gln  Thr Gly Pro Thr Gly  Ala Ala Thr
    4385                4390                4395

Gln Gly  Pro Tyr Leu Leu Asp  Thr Ser Thr Met Pro  Tyr Leu Thr
    4400                4405                4410

Glu Thr  Pro Leu Ala Val Thr  Pro Asp Phe Met Gln  Ser Glu Lys
    4415                4420                4425

Thr Thr  Leu Ile Ser Lys Gly  Pro Lys Asp Val Ser  Trp Thr Ser
    4430                4435                4440

Pro Pro  Ser Val Ala Glu Thr  Ser Tyr Pro Ser Ser  Leu Thr Pro
    4445                4450                4455

Phe Leu  Val Thr Thr Ile Pro  Pro Ala Thr Ser Thr  Leu Gln Gly
    4460                4465                4470

Gln His  Thr Ser Ser Pro Val  Ser Ala Thr Ser Val  Leu Thr Ser
    4475                4480                4485

Gly Leu  Val Lys Thr Thr Asp  Met Leu Asn Thr Ser  Met Glu Pro
    4490                4495                4500

Val Thr  Asn Ser Pro Gln Asn  Leu Asn Asn Pro Ser  Asn Glu Ile
    4505                4510                4515
```

```
Leu Ala  Thr Leu Ala Ala Thr  Thr Asp Ile Glu Thr  Ile His Pro
    4520                4525                4530

Ser Ile  Asn Lys Ala Val Thr  Asn Met Gly Thr Ala  Ser Ser Ala
    4535                4540                4545

His Val  Leu His Ser Thr Leu  Pro Val Ser Ser Glu  Pro Ser Thr
    4550                4555                4560

Ala Thr  Ser Pro Met Val Pro  Ala Ser Ser Met Gly  Asp Ala Leu
    4565                4570                4575

Ala Ser  Ile Ser Ile Pro Gly  Ser Glu Thr Thr Asp  Ile Glu Gly
    4580                4585                4590

Glu Pro  Thr Ser Ser Leu Thr  Ala Gly Arg Lys Glu  Asn Ser Thr
    4595                4600                4605

Leu Gln  Glu Met Asn Ser Thr  Thr Glu Ser Asn Ile  Ile Leu Ser
    4610                4615                4620

Asn Val  Ser Val Gly Ala Ile  Thr Glu Ala Thr Lys  Met Glu Val
    4625                4630                4635

Pro Ser  Phe Asp Ala Thr Phe  Ile Pro Thr Pro Ala  Gln Ser Thr
    4640                4645                4650

Lys Phe  Pro Asp Ile Phe Ser  Val Ala Ser Ser Arg  Leu Ser Asn
    4655                4660                4665

Ser Pro  Pro Met Thr Ile Ser  Thr His Met Thr Thr  Thr Gln Thr
    4670                4675                4680

Gly Ser  Ser Gly Ala Thr Ser  Lys Ile Pro Leu Ala  Leu Asp Thr
    4685                4690                4695

Ser Thr  Leu Glu Thr Ser Ala  Gly Thr Pro Ser Val  Val Thr Glu
    4700                4705                4710

Gly Phe  Ala His Ser Lys Ile  Thr Thr Ala Met Asn  Asn Asp Val
    4715                4720                4725
```

```
Lys Asp  Val Ser Gln Thr Asn  Pro Pro Phe Gln Asp  Glu Ala Ser
    4730                4735                4740

Ser Pro  Ser Ser Gln Ala Pro  Val Leu Val Thr Thr  Leu Pro Ser
    4745                4750                4755

Ser Val  Ala Phe Thr Pro Gln  Trp His Ser Thr Ser  Ser Pro Val
    4760                4765                4770

Ser Met  Ser Ser Val Leu Thr  Ser Ser Leu Val Lys  Thr Ala Gly
    4775                4780                4785

Lys Val  Asp Thr Ser Leu Glu  Thr Val Thr Ser Ser  Pro Gln Ser
    4790                4795                4800

Met Ser  Asn Thr Leu Asp Asp  Ile Ser Val Thr Ser  Ala Ala Thr
    4805                4810                4815

Thr Asp  Ile Glu Thr Thr His  Pro Ser Ile Asn Thr  Val Val Thr
    4820                4825                4830

Asn Val  Gly Thr Thr Gly Ser  Ala Phe Glu Ser His  Ser Thr Val
    4835                4840                4845

Ser Ala  Tyr Pro Glu Pro Ser  Lys Val Thr Ser Pro  Asn Val Thr
    4850                4855                4860

Thr Ser  Thr Met Glu Asp Thr  Thr Ile Ser Arg Ser  Ile Pro Lys
    4865                4870                4875

Ser Ser  Lys Thr Thr Arg Thr  Glu Thr Glu Thr Thr  Ser Ser Leu
    4880                4885                4890

Thr Pro  Lys Leu Arg Glu Thr  Ser Ile Ser Gln Glu  Ile Thr Ser
    4895                4900                4905

Ser Thr  Glu Thr Ser Thr Val  Pro Tyr Lys Glu Leu  Thr Gly Ala
    4910                4915                4920
```

```
Thr Thr  Glu Val Ser Arg Thr  Asp Val Thr Ser Ser  Ser Ser Thr
    4925                 4930                 4935

Ser Phe  Pro Gly Pro Asp Gln  Ser Thr Val Ser Leu  Asp Ile Ser
    4940                 4945                 4950

Thr Glu  Thr Asn Thr Arg Leu  Ser Thr Ser Pro Ile  Met Thr Glu
    4955                 4960                 4965

Ser Ala  Glu Ile Thr Ile Thr  Thr Gln Thr Gly Pro  His Gly Ala
    4970                 4975                 4980

Thr Ser  Gln Asp Thr Phe Thr  Met Asp Pro Ser Asn  Thr Thr Pro
    4985                 4990                 4995

Gln Ala  Gly Ile His Ser Ala  Met Thr His Gly Phe  Ser Gln Leu
    5000                 5005                 5010

Asp Val  Thr Thr Leu Met Ser  Arg Ile Pro Gln Asp  Val Ser Trp
    5015                 5020                 5025

Thr Ser  Pro Pro Ser Val Asp  Lys Thr Ser Ser Pro  Ser Ser Phe
    5030                 5035                 5040

Leu Ser  Ser Pro Ala Met Thr  Thr Pro Ser Leu Ile  Ser Ser Thr
    5045                 5050                 5055

Leu Pro  Glu Asp Lys Leu Ser  Ser Pro Met Thr Ser  Leu Leu Thr
    5060                 5065                 5070

Ser Gly  Leu Val Lys Ile Thr  Asp Ile Leu Arg Thr  Arg Leu Glu
    5075                 5080                 5085

Pro Val  Thr Ser Ser Leu Pro  Asn Phe Ser Ser Thr  Ser Asp Lys
    5090                 5095                 5100

Ile Leu  Ala Thr Ser Lys Asp  Ser Lys Asp Thr Lys  Glu Ile Phe
    5105                 5110                 5115

Pro Ser  Ile Asn Thr Glu Glu  Thr Asn Val Lys Ala  Asn Asn Ser
    5120                 5125                 5130
```

```
Gly His  Glu Ser His Ser Pro  Ala Leu Ala Asp Ser  Glu Thr Pro
    5135                5140                5145

Lys Ala  Thr Thr Gln Met Val  Ile Thr Thr Thr Val  Gly Asp Pro
    5150                5155                5160

Ala Pro  Ser Thr Ser Met Pro  Val His Gly Ser Ser  Glu Thr Thr
    5165                5170                5175

Asn Ile  Lys Arg Glu Pro Thr  Tyr Phe Leu Thr Pro  Arg Leu Arg
    5180                5185                5190

Glu Thr  Ser Thr Ser Gln Glu  Ser Ser Phe Pro Thr  Asp Thr Ser
    5195                5200                5205

Phe Leu  Leu Ser Lys Val Pro  Thr Gly Thr Ile Thr  Glu Val Ser
    5210                5215                5220

Ser Thr  Gly Val Asn Ser Ser  Ser Lys Ile Ser Thr  Pro Asp His
    5225                5230                5235

Asp Lys  Ser Thr Val Pro Pro  Asp Thr Phe Thr Gly  Glu Ile Pro
    5240                5245                5250

Arg Val  Phe Thr Ser Ser Ile  Lys Thr Lys Ser Ala  Glu Met Thr
    5255                5260                5265

Ile Thr  Thr Gln Ala Ser Pro  Pro Glu Ser Ala Ser  His Ser Thr
    5270                5275                5280

Leu Pro  Leu Asp Thr Ser Thr  Thr Leu Ser Gln Gly  Gly Thr His
    5285                5290                5295

Ser Thr  Val Thr Gln Gly Phe  Pro Tyr Ser Glu Val  Thr Thr Leu
    5300                5305                5310

Met Gly  Met Gly Pro Gly Asn  Val Ser Trp Met Thr  Thr Pro Pro
    5315                5320                5325
```

```
Val Glu  Glu Thr Ser Ser Val  Ser Ser Leu Met Ser  Ser Pro Ala
    5330                 5335                 5340

Met Thr  Ser Pro Ser Pro Val  Ser Ser Thr Ser Pro  Gln Ser Ile
    5345                 5350                 5355

Pro Ser  Ser Pro Leu Pro Val  Thr Ala Leu Pro Thr  Ser Val Leu
    5360                 5365                 5370

Val Thr  Thr Thr Asp Val Leu  Gly Thr Thr Ser Pro  Glu Ser Val
    5375                 5380                 5385

Thr Ser  Ser Pro Pro Asn Leu  Ser Ser Ile Thr His  Glu Arg Pro
    5390                 5395                 5400

Ala Thr  Tyr Lys Asp Thr Ala  His Thr Glu Ala Ala  Met His His
    5405                 5410                 5415

Ser Thr  Asn Thr Ala Val Thr  Asn Val Gly Thr Ser  Gly Ser Gly
    5420                 5425                 5430

His Lys  Ser Gln Ser Ser Val  Leu Ala Asp Ser Glu  Thr Ser Lys
    5435                 5440                 5445

Ala Thr  Pro Leu Met Ser Thr  Thr Ser Thr Leu Gly  Asp Thr Ser
    5450                 5455                 5460

Val Ser  Thr Ser Thr Pro Asn  Ile Ser Gln Thr Asn  Gln Ile Gln
    5465                 5470                 5475

Thr Glu  Pro Thr Ala Ser Leu  Ser Pro Arg Leu Arg  Glu Ser Ser
    5480                 5485                 5490

Thr Ser  Glu Lys Thr Ser Ser  Thr Thr Glu Thr Asn  Thr Ala Phe
    5495                 5500                 5505

Ser Tyr  Val Pro Thr Gly Ala  Ile Thr Gln Ala Ser  Arg Thr Glu
    5510                 5515                 5520

Ile Ser  Ser Ser Arg Thr Ser  Ile Ser Asp Leu Asp  Arg Pro Thr
    5525                 5530                 5535
```

```
Ile Ala  Pro Asp Ile Ser Thr  Gly Met Ile Thr Arg  Leu Phe Thr
    5540                5545                5550

Ser Pro  Ile Met Thr Lys Ser  Ala Glu Met Thr Val  Thr Thr Gln
    5555                5560                5565

Thr Thr  Thr Pro Gly Ala Thr  Ser Gln Gly Ile Leu  Pro Trp Asp
    5570                5575                5580

Thr Ser  Thr Thr Leu Phe Gln  Gly Gly Thr His Ser  Thr Val Ser
    5585                5590                5595

Gln Gly  Phe Pro His Ser Glu  Ile Thr Thr Leu Arg  Ser Arg Thr
    5600                5605                5610

Pro Gly  Asp Val Ser Trp Met  Thr Thr Pro Pro Val  Glu Glu Thr
    5615                5620                5625

Ser Ser  Gly Phe Ser Leu Met  Ser Pro Ser Met Thr  Ser Pro Ser
    5630                5635                5640

Pro Val  Ser Ser Thr Ser Pro  Glu Ser Ile Pro Ser  Ser Pro Leu
    5645                5650                5655

Pro Val  Thr Ala Leu Leu Thr  Ser Val Leu Val Thr  Thr Thr Asn
    5660                5665                5670

Val Leu  Gly Thr Thr Ser Pro  Glu Pro Val Thr Ser  Ser Pro Pro
    5675                5680                5685

Asn Leu  Ser Ser Pro Thr Gln  Glu Arg Leu Thr Thr  Tyr Lys Asp
    5690                5695                5700

Thr Ala  His Thr Glu Ala Met  His Ala Ser Met His  Thr Asn Thr
    5705                5710                5715

Ala Val  Ala Asn Val Gly Thr  Ser Ile Ser Gly His  Glu Ser Gln
    5720                5725                5730
```

```
Ser Ser  Val Pro Ala Asp Ser  His Thr Ser Lys Ala  Thr Ser Pro
    5735                5740                5745

Met Gly  Ile Thr Phe Ala Met  Gly Asp Thr Ser Val  Ser Thr Ser
    5750                5755                5760

Thr Pro  Ala Phe Phe Glu Thr  Arg Ile Gln Thr Glu  Ser Thr Ser
    5765                5770                5775

Ser Leu  Ile Pro Gly Leu Arg  Asp Thr Arg Thr Ser  Glu Glu Ile
    5780                5785                5790

Asn Thr  Val Thr Glu Thr Ser  Thr Val Leu Ser Glu  Val Pro Thr
    5795                5800                5805

Thr Thr  Thr Thr Glu Val Ser  Arg Thr Glu Val Ile  Thr Ser Ser
    5810                5815                5820

Arg Thr  Thr Ile Ser Gly Pro  Asp His Ser Lys Met  Ser Pro Tyr
    5825                5830                5835

Ile Ser  Thr Glu Thr Ile Thr  Arg Leu Ser Thr Phe  Pro Phe Val
    5840                5845                5850

Thr Gly  Ser Thr Glu Met Ala  Ile Thr Asn Gln Thr  Gly Pro Ile
    5855                5860                5865

Gly Thr  Ile Ser Gln Ala Thr  Leu Thr Leu Asp Thr  Ser Ser Thr
    5870                5875                5880

Ala Ser  Trp Glu Gly Thr His  Ser Pro Val Thr Gln  Arg Phe Pro
    5885                5890                5895

His Ser  Glu Glu Thr Thr Thr  Met Ser Arg Ser Thr  Lys Gly Val
    5900                5905                5910

Ser Trp  Gln Ser Pro Pro Ser  Val Glu Glu Thr Ser  Ser Pro Ser
    5915                5920                5925

Ser Pro  Val Pro Leu Pro Ala  Ile Thr Ser His Ser  Ser Leu Tyr
    5930                5935                5940
```

```
Ser Ala  Val Ser Gly Ser Ser  Pro Thr Ser Ala Leu  Pro Val Thr
    5945                5950                5955

Ser Leu  Leu Thr Ser Gly Arg  Arg Lys Thr Ile Asp  Met Leu Asp
    5960                5965                5970

Thr His  Ser Glu Leu Val Thr  Ser Ser Leu Pro Ser  Ala Ser Ser
    5975                5980                5985

Phe Ser  Gly Glu Ile Leu Thr  Ser Glu Ala Ser Thr  Asn Thr Glu
    5990                5995                6000

Thr Ile  His Phe Ser Glu Asn  Thr Ala Glu Thr Asn  Met Gly Thr
    6005                6010                6015

Thr Asn  Ser Met His Lys Leu  His Ser Ser Val Ser  Ile His Ser
    6020                6025                6030

Gln Pro  Ser Gly His Thr Pro  Pro Lys Val Thr Gly  Ser Met Met
    6035                6040                6045

Glu Asp  Ala Ile Val Ser Thr  Ser Thr Pro Gly Ser  Pro Glu Thr
    6050                6055                6060

Lys Asn  Val Asp Arg Asp Ser  Thr Ser Pro Leu Thr  Pro Glu Leu
    6065                6070                6075

Lys Glu  Asp Ser Thr Ala Leu  Val Met Asn Ser Thr  Thr Glu Ser
    6080                6085                6090

Asn Thr  Val Phe Ser Ser Val  Ser Leu Asp Ala Ala  Thr Glu Val
    6095                6100                6105

Ser Arg  Ala Glu Val Thr Tyr  Tyr Asp Pro Thr Phe  Met Pro Ala
    6110                6115                6120

Ser Ala  Gln Ser Thr Lys Ser  Pro Asp Ile Ser Pro  Glu Ala Ser
    6125                6130                6135
```

```
Ser Ser  His Ser Asn Ser Pro  Pro Leu Thr Ile Ser  Thr His Lys
    6140                6145                6150

Thr Ile  Ala Thr Gln Thr Gly  Pro Ser Gly Val Thr  Ser Leu Gly
    6155                6160                6165

Gln Leu  Thr Leu Asp Thr Ser  Thr Ile Ala Thr Ser  Ala Gly Thr
    6170                6175                6180

Pro Ser  Ala Arg Thr Gln Asp  Phe Val Asp Ser Glu  Thr Thr Ser
    6185                6190                6195

Val Met  Asn Asn Asp Leu Asn  Asp Val Leu Lys Thr  Ser Pro Phe
    6200                6205                6210

Ser Ala  Glu Glu Ala Asn Ser  Leu Ser Ser Gln Ala  Pro Leu Leu
    6215                6220                6225

Val Thr  Thr Ser Pro Ser Pro  Val Thr Ser Thr Leu  Gln Glu His
    6230                6235                6240

Ser Thr  Ser Ser Leu Val Ser  Val Thr Ser Val Pro  Thr Pro Thr
    6245                6250                6255

Leu Ala  Lys Ile Thr Asp Met  Asp Thr Asn Leu Glu  Pro Val Thr
    6260                6265                6270

Arg Ser  Pro Gln Asn Leu Arg  Asn Thr Leu Ala Thr  Ser Glu Ala
    6275                6280                6285

Thr Thr  Asp Thr His Thr Met  His Pro Ser Ile Asn  Thr Ala Val
    6290                6295                6300

Ala Asn  Val Gly Thr Thr Ser  Ser Pro Asn Glu Phe  Tyr Phe Thr
    6305                6310                6315

Val Ser  Pro Asp Ser Asp Pro  Tyr Lys Ala Thr Ser  Ala Val Val
    6320                6325                6330

Ile Thr  Ser Thr Ser Gly Asp  Ser Ile Val Ser Thr  Ser Met Pro
    6335                6340                6345
```

```
Arg Ser  Ser Ala Met Lys Lys  Ile Glu Ser Glu Thr  Thr Phe Ser
    6350                 6355                 6360

Leu Ile  Phe Arg Leu Arg Glu  Thr Ser Thr Ser Gln  Lys Ile Gly
    6365                 6370                 6375

Ser Ser  Ser Asp Thr Ser Thr  Val Phe Asp Lys Ala  Phe Thr Ala
    6380                 6385                 6390

Ala Thr  Thr Glu Val Ser Arg  Thr Glu Leu Thr Ser  Ser Ser Arg
    6395                 6400                 6405

Thr Ser  Ile Gln Gly Thr Glu  Lys Pro Thr Met Ser  Pro Asp Thr
    6410                 6415                 6420

Ser Thr  Arg Ser Val Thr Met  Leu Ser Thr Phe Ala  Gly Leu Thr
    6425                 6430                 6435

Lys Ser  Glu Glu Arg Thr Ile  Ala Thr Gln Thr Gly  Pro His Arg
    6440                 6445                 6450

Ala Thr  Ser Gln Gly Thr Leu  Thr Trp Asp Thr Ser  Ile Thr Thr
    6455                 6460                 6465

Ser Gln  Ala Gly Thr His Ser  Ala Met Thr His Gly  Phe Ser Gln
    6470                 6475                 6480

Leu Asp  Leu Ser Thr Leu Thr  Ser Arg Val Pro Glu  Tyr Ile Ser
    6485                 6490                 6495

Gly Thr  Ser Pro Pro Ser Val  Glu Lys Thr Ser Ser  Ser Ser Ser
    6500                 6505                 6510

Leu Leu  Ser Leu Pro Ala Ile  Thr Ser Pro Ser Pro  Val Pro Thr
    6515                 6520                 6525

Thr Leu  Pro Glu Ser Arg Pro  Ser Ser Pro Val His  Leu Thr Ser
    6530                 6535                 6540
```

```
Leu Pro  Thr Ser Gly Leu Val  Lys Thr Thr Asp Met  Leu Ala Ser
    6545                6550                6555

Val Ala  Ser Leu Pro Pro Asn  Leu Gly Ser Thr Ser  His Lys Ile
    6560                6565                6570

Pro Thr  Thr Ser Glu Asp Ile  Lys Asp Thr Glu Lys  Met Tyr Pro
    6575                6580                6585

Ser Thr  Asn Ile Ala Val Thr  Asn Val Gly Thr Thr  Thr Ser Glu
    6590                6595                6600

Lys Glu  Ser Tyr Ser Ser Val  Pro Ala Tyr Ser Glu  Pro Pro Lys
    6605                6610                6615

Val Thr  Ser Pro Met Val Thr  Ser Phe Asn Ile Arg  Asp Thr Ile
    6620                6625                6630

Val Ser  Thr Ser Met Pro Gly  Ser Ser Glu Ile Thr  Arg Ile Glu
    6635                6640                6645

Met Glu  Ser Thr Phe Ser Leu  Ala His Gly Leu Lys  Gly Thr Ser
    6650                6655                6660

Thr Ser  Gln Asp Pro Ile Val  Ser Thr Glu Lys Ser  Ala Val Leu
    6665                6670                6675

His Lys  Leu Thr Thr Gly Ala  Thr Glu Thr Ser Arg  Thr Glu Val
    6680                6685                6690

Ala Ser  Ser Arg Arg Thr Ser  Ile Pro Gly Pro Asp  His Ser Thr
    6695                6700                6705

Glu Ser  Pro Asp Ile Ser Thr  Glu Val Ile Pro Ser  Leu Pro Ile
    6710                6715                6720

Ser Leu  Gly Ile Thr Glu Ser  Ser Asn Met Thr Ile  Ile Thr Arg
    6725                6730                6735

Thr Gly  Pro Pro Leu Gly Ser  Thr Ser Gln Gly Thr  Phe Thr Leu
    6740                6745                6750
```

```
Asp Thr  Pro Thr Thr Ser Ser  Arg Ala Gly Thr His  Ser Met Ala
    6755                6760                6765

Thr Gln  Glu Phe Pro His Ser  Glu Met Thr Thr Val  Met Asn Lys
    6770                6775                6780

Asp Pro  Glu Ile Leu Ser Trp  Thr Ile Pro Pro Ser  Ile Glu Lys
    6785                6790                6795

Thr Ser  Phe Ser Ser Ser Leu  Met Pro Ser Pro Ala  Met Thr Ser
    6800                6805                6810

Pro Pro  Val Ser Ser Thr Leu  Pro Lys Thr Ile His  Thr Thr Pro
    6815                6820                6825

Ser Pro  Met Thr Ser Leu Leu  Thr Pro Ser Leu Val  Met Thr Thr
    6830                6835                6840

Asp Thr  Leu Gly Thr Ser Pro  Glu Pro Thr Thr Ser  Ser Pro Pro
    6845                6850                6855

Asn Leu  Ser Ser Thr Ser His  Glu Ile Leu Thr Thr  Asp Glu Asp
    6860                6865                6870

Thr Thr  Ala Ile Glu Ala Met  His Pro Ser Thr Ser  Thr Ala Ala
    6875                6880                6885

Thr Asn  Val Glu Thr Thr Ser  Ser Gly His Gly Ser  Gln Ser Ser
    6890                6895                6900

Val Leu  Ala Asp Ser Glu Lys  Thr Lys Ala Thr Ala  Pro Met Asp
    6905                6910                6915

Thr Thr  Ser Thr Met Gly His  Thr Thr Val Ser Thr  Ser Met Ser
    6920                6925                6930

Val Ser  Ser Glu Thr Thr Lys  Ile Lys Arg Glu Ser  Thr Tyr Ser
    6935                6940                6945
```

```
Leu Thr  Pro Gly Leu Arg Glu  Thr Ser Ile Ser Gln  Asn Ala Ser
    6950                 6955                 6960

Phe Ser  Thr Asp Thr Ser Ile  Val Leu Ser Glu Val  Pro Thr Gly
    6965                 6970                 6975

Thr Thr  Ala Glu Val Ser Arg  Thr Glu Val Thr Ser  Ser Gly Arg
    6980                 6985                 6990

Thr Ser  Ile Pro Gly Pro Ser  Gln Ser Thr Val Leu  Pro Glu Ile
    6995                 7000                 7005

Ser Thr  Arg Thr Met Thr Arg  Leu Phe Ala Ser Pro  Thr Met Thr
    7010                 7015                 7020

Glu Ser  Ala Glu Met Thr Ile  Pro Thr Gln Thr Gly  Pro Ser Gly
    7025                 7030                 7035

Ser Thr  Ser Gln Asp Thr Leu  Thr Leu Asp Thr Ser  Thr Thr Lys
    7040                 7045                 7050

Ser Gln  Ala Lys Thr His Ser  Thr Leu Thr Gln Arg  Phe Pro His
    7055                 7060                 7065

Ser Glu  Met Thr Thr Leu Met  Ser Arg Gly Pro Gly  Asp Met Ser
    7070                 7075                 7080

Trp Gln  Ser Ser Pro Ser Leu  Glu Asn Pro Ser Ser  Leu Pro Ser
    7085                 7090                 7095

Leu Leu  Ser Leu Pro Ala Thr  Thr Ser Pro Pro Pro  Ile Ser Ser
    7100                 7105                 7110

Thr Leu  Pro Val Thr Ile Ser  Ser Ser Pro Leu Pro  Val Thr Ser
    7115                 7120                 7125

Leu Leu  Thr Ser Ser Pro Val  Thr Thr Thr Asp Met  Leu His Thr
    7130                 7135                 7140

Ser Pro  Glu Leu Val Thr Ser  Ser Pro Pro Lys Leu  Ser His Thr
    7145                 7150                 7155
```

```
Ser Asp  Glu Arg Leu Thr Thr  Gly Lys Asp Thr Thr  Asn Thr Glu
    7160                 7165                 7170

Ala Val  His Pro Ser Thr Asn  Thr Ala Ala Ser Asn  Val Glu Ile
    7175                 7180                 7185

Pro Ser  Ser Gly His Glu Ser  Pro Ser Ser Ala Leu  Ala Asp Ser
    7190                 7195                 7200

Glu Thr  Ser Lys Ala Thr Ser  Pro Met Phe Ile Thr  Ser Thr Gln
    7205                 7210                 7215

Glu Asp  Thr Thr Val Ala Ile  Ser Thr Pro His Phe  Leu Glu Thr
    7220                 7225                 7230

Ser Arg  Ile Gln Lys Glu Ser  Ile Ser Ser Leu Ser  Pro Lys Leu
    7235                 7240                 7245

Arg Glu  Thr Gly Ser Ser Val  Glu Thr Ser Ser Ala  Ile Glu Thr
    7250                 7255                 7260

Ser Ala  Val Leu Ser Glu Val  Ser Ile Gly Ala Thr  Thr Glu Ile
    7265                 7270                 7275

Ser Arg  Thr Glu Val Thr Ser  Ser Ser Arg Thr Ser  Ile Ser Gly
    7280                 7285                 7290

Ser Ala  Glu Ser Thr Met Leu  Pro Glu Ile Ser Thr  Thr Arg Lys
    7295                 7300                 7305

Ile Ile  Lys Phe Pro Thr Ser  Pro Ile Leu Ala Glu  Ser Ser Glu
    7310                 7315                 7320

Met Thr  Ile Lys Thr Gln Thr  Ser Pro Pro Gly Ser  Thr Ser Glu
    7325                 7330                 7335

Ser Thr  Phe Thr Leu Asp Thr  Ser Thr Thr Pro Ser  Leu Val Ile
    7340                 7345                 7350
```

```
Thr His  Ser Thr Met Thr Gln  Arg Leu Pro His Ser  Glu Ile Thr
    7355                 7360                 7365

Thr Leu  Val Ser Arg Gly Ala  Gly Asp Val Pro Arg  Pro Ser Ser
    7370                 7375                 7380

Leu Pro  Val Glu Glu Thr Ser  Pro Pro Ser Ser Gln  Leu Ser Leu
    7385                 7390                 7395

Ser Ala  Met Ile Ser Pro Ser  Pro Val Ser Ser Thr  Leu Pro Ala
    7400                 7405                 7410

Ser Ser  His Ser Ser Ser Ala  Ser Val Thr Ser Leu  Leu Thr Pro
    7415                 7420                 7425

Gly Gln  Val Lys Thr Thr Glu  Val Leu Asp Ala Ser  Ala Glu Pro
    7430                 7435                 7440

Glu Thr  Ser Ser Pro Pro Ser  Leu Ser Ser Thr Ser  Val Glu Ile
    7445                 7450                 7455

Leu Ala  Thr Ser Glu Val Thr  Thr Asp Thr Glu Lys  Ile His Pro
    7460                 7465                 7470

Phe Ser  Asn Thr Ala Val Thr  Lys Val Gly Thr Ser  Ser Ser Gly
    7475                 7480                 7485

His Glu  Ser Pro Ser Ser Val  Leu Pro Asp Ser Glu  Thr Thr Lys
    7490                 7495                 7500

Ala Thr  Ser Ala Met Gly Thr  Ile Ser Ile Met Gly  Asp Thr Ser
    7505                 7510                 7515

Val Ser  Thr Leu Thr Pro Ala  Leu Ser Asn Thr Arg  Lys Ile Gln
    7520                 7525                 7530

Ser Glu  Pro Ala Ser Ser Leu  Thr Thr Arg Leu Arg  Glu Thr Ser
    7535                 7540                 7545

Thr Ser  Glu Glu Thr Ser Leu  Ala Thr Glu Ala Asn  Thr Val Leu
    7550                 7555                 7560
```

```
Ser Lys  Val Ser Thr Gly Ala  Thr Thr Glu Val Ser  Arg Thr Glu
    7565                7570                7575

Ala Ile  Ser Phe Ser Arg Thr  Ser Met Ser Gly Pro  Glu Gln Ser
    7580                7585                7590

Thr Met  Ser Gln Asp Ile Ser  Ile Gly Thr Ile Pro  Arg Ile Ser
    7595                7600                7605

Ala Ser  Ser Val Leu Thr Glu  Ser Ala Lys Met Thr  Ile Thr Thr
    7610                7615                7620

Gln Thr  Gly Pro Ser Glu Ser  Thr Leu Glu Ser Thr  Leu Asn Leu
    7625                7630                7635

Asn Thr  Ala Thr Thr Pro Ser  Trp Val Glu Thr His  Ser Ile Val
    7640                7645                7650

Ile Gln  Gly Phe Pro His Pro  Glu Met Thr Thr Ser  Met Gly Arg
    7655                7660                7665

Gly Pro  Gly Gly Val Ser Trp  Pro Ser Pro Pro Phe  Val Lys Glu
    7670                7675                7680

Thr Ser  Pro Pro Ser Ser Pro  Leu Ser Leu Pro Ala  Val Thr Ser
    7685                7690                7695

Pro His  Pro Val Ser Thr Thr  Phe Leu Ala His Ile  Pro Pro Ser
    7700                7705                7710

Pro Leu  Pro Val Thr Ser Leu  Leu Thr Ser Gly Pro  Ala Thr Thr
    7715                7720                7725

Thr Asp  Ile Leu Gly Thr Ser  Thr Glu Pro Gly Thr  Ser Ser Ser
    7730                7735                7740

Ser Ser  Leu Ser Thr Thr Ser  His Glu Arg Leu Thr  Thr Tyr Lys
    7745                7750                7755
```

```
Asp Thr  Ala His Thr Glu Ala  Val His Pro Ser Thr  Asn Thr Gly
    7760                7765                7770

Gly Thr  Asn Val Ala Thr Thr  Ser Ser Gly Tyr Lys  Ser Gln Ser
    7775                7780                7785

Ser Val  Leu Ala Asp Ser Ser  Pro Met Cys Thr Thr  Ser Thr Met
    7790                7795                7800

Gly Asp  Thr Ser Val Leu Thr  Ser Thr Pro Ala Phe  Leu Glu Thr
    7805                7810                7815

Arg Arg  Ile Gln Thr Glu Leu  Ala Ser Ser Leu Thr  Pro Gly Leu
    7820                7825                7830

Arg Glu  Ser Ser Gly Ser Glu  Gly Thr Ser Ser Gly  Thr Lys Met
    7835                7840                7845

Ser Thr  Val Leu Ser Lys Val  Pro Thr Gly Ala Thr  Thr Glu Ile
    7850                7855                7860

Ser Lys  Glu Asp Val Thr Ser  Ile Pro Gly Pro Ala  Gln Ser Thr
    7865                7870                7875

Ile Ser  Pro Asp Ile Ser Thr  Arg Thr Val Ser Trp  Phe Ser Thr
    7880                7885                7890

Ser Pro  Val Met Thr Glu Ser  Ala Glu Ile Thr Met  Asn Thr His
    7895                7900                7905

Thr Ser  Pro Leu Gly Ala Thr  Thr Gln Gly Thr Ser  Thr Leu Asp
    7910                7915                7920

Thr Ser  Ser Thr Thr Ser Leu  Thr Met Thr His Ser  Thr Ile Ser
    7925                7930                7935

Gln Gly  Phe Ser His Ser Gln  Met Ser Thr Leu Met  Arg Arg Gly
    7940                7945                7950

Pro Glu  Asp Val Ser Trp Met  Ser Pro Pro Leu Leu  Glu Lys Thr
    7955                7960                7965
```

```
Arg Pro  Ser Phe Ser Leu Met  Ser Ser Pro Ala Thr  Thr Ser Pro
    7970                7975                8980

Ser Pro  Val Ser Ser Thr Leu  Pro Glu Ser Ile Ser  Ser Ser Pro
    7985                7990                7995

Leu Pro  Val Thr Ser Leu Leu  Thr Ser Gly Leu Ala  Lys Thr Thr
    8000                8005                8010

Asp Met  Leu His Lys Ser Ser  Glu Pro Val Thr Asn  Ser Pro Ala
    8015                8020                8025

Asn Leu  Ser Ser Thr Ser Val  Glu Ile Leu Ala Thr  Ser Glu Val
    8030                8035                8040

Thr Thr  Asp Thr Glu Lys Thr  His Pro Ser Ser Asn  Arg Thr Val
    8045                8050                8055

Thr Asp  Val Gly Thr Ser Ser  Ser Gly His Glu Ser  Thr Ser Phe
    8060                8065                8070

Val Leu  Ala Asp Ser Gln Thr  Ser Lys Val Thr Ser  Pro Met Val
    8075                8080                8085

Ile Thr  Ser Thr Met Glu Asp  Thr Ser Val Ser Thr  Ser Thr Pro
    8090                8095                8100

Gly Phe  Phe Glu Thr Ser Arg  Ile Gln Thr Glu Pro  Thr Ser Ser
    8105                8110                8115

Leu Thr  Leu Gly Leu Arg Lys  Thr Ser Ser Ser Glu  Gly Thr Ser
    8120                8125                8130

Leu Ala  Thr Glu Met Ser Thr  Val Leu Ser Gly Val  Pro Thr Gly
    8135                8140                8145

Ala Thr  Ala Glu Val Ser Arg  Thr Glu Val Thr Ser  Ser Ser Arg
    8150                8155                8160
```

```
Thr Ser  Ile Ser Gly Phe Ala  Gln Leu Thr Val Ser  Pro Glu Thr
    8165                 8170                 8175

Ser Thr  Glu Thr Ile Thr Arg  Leu Pro Thr Ser Ser  Ile Met Thr
    8180                 8185                 8190

Glu Ser  Ala Glu Met Met Ile  Lys Thr Gln Thr Asp  Pro Pro Gly
    8195                 8200                 8205

Ser Thr  Pro Glu Ser Thr His  Thr Val Asp Ile Ser  Thr Thr Pro
    8210                 8215                 8220

Asn Trp  Val Glu Thr His Ser  Thr Val Thr Gln Arg  Phe Ser His
    8225                 8230                 8235

Ser Glu  Met Thr Thr Leu Val  Ser Arg Ser Pro Gly  Asp Met Leu
    8240                 8245                 8250

Trp Pro  Ser Gln Ser Ser Val  Glu Glu Thr Ser Ser  Ala Ser Ser
    8255                 8260                 8265

Leu Leu  Ser Leu Pro Ala Thr  Thr Ser Pro Ser Pro  Val Ser Ser
    8270                 8275                 8280

Thr Leu  Val Glu Asp Phe Pro  Ser Ala Ser Leu Pro  Val Thr Ser
    8285                 8290                 8295

Leu Leu  Asn Pro Gly Leu Val  Ile Thr Thr Asp Arg  Met Gly Ile
    8300                 8305                 8310

Ser Arg  Glu Pro Gly Thr Ser  Ser Thr Ser Asn Leu  Ser Ser Thr
    8315                 8320                 8325

Ser His  Glu Arg Leu Thr Thr  Leu Glu Asp Thr Val  Asp Thr Glu
    8330                 8335                 8340

Asp Met  Gln Pro Ser Thr His  Thr Ala Val Thr Asn  Val Arg Thr
    8345                 8350                 8355

Ser Ile  Ser Gly His Glu Ser  Gln Ser Ser Val Leu  Ser Asp Ser
    8360                 8365                 8370
```

```
Glu Thr  Pro Lys Ala Thr Ser  Pro Met Gly Thr Thr  Tyr Thr Met
    8375                8380                8385

Gly Glu  Thr Ser Val Ser Ile  Ser Thr Ser Asp Phe  Phe Glu Thr
    8390                8395                8400

Ser Arg  Ile Gln Ile Glu Pro  Thr Ser Ser Leu Thr  Ser Gly Leu
    8405                8410                8415

Arg Glu  Thr Ser Ser Ser Glu  Arg Ile Ser Ser Ala  Thr Glu Gly
    8420                8425                8430

Ser Thr  Val Leu Ser Glu Val  Pro Ser Gly Ala Thr  Thr Glu Val
    8435                8440                8445

Ser Arg  Thr Glu Val Ile Ser  Ser Arg Gly Thr Ser  Met Ser Gly
    8450                8455                8460

Pro Asp  Gln Phe Thr Ile Ser  Pro Asp Ile Ser Thr  Glu Ala Ile
    8465                8470                8475

Thr Arg  Leu Ser Thr Ser Pro  Ile Met Thr Glu Ser  Ala Glu Ser
    8480                8485                8490

Ala Ile  Thr Ile Glu Thr Gly  Ser Pro Gly Ala Thr  Ser Glu Gly
    8495                8500                8505

Thr Leu  Thr Leu Asp Thr Ser  Thr Thr Thr Phe Trp  Ser Gly Thr
    8510                8515                8520

His Ser  Thr Ala Ser Pro Gly  Phe Ser His Ser Glu  Met Thr Thr
    8525                8530                8535

Leu Met  Ser Arg Thr Pro Gly  Asp Val Pro Trp Pro  Ser Leu Pro
    8540                8545                8550

Ser Val  Glu Glu Ala Ser Ser  Val Ser Ser Ser Leu  Ser Ser Pro
    8555                8560                8565
```

```
Ala Met  Thr Ser Thr Ser Phe  Phe Ser Thr Leu Pro  Glu Ser Ile
    8570                8575                8580

Ser Ser  Ser Pro His Pro Val  Thr Ala Leu Leu Thr  Leu Gly Pro
    8585                8590                8595

Val Lys  Thr Thr Asp Met Leu  Arg Thr Ser Ser Glu  Pro Glu Thr
    8600                8605                8610

Ser Ser  Pro Pro Asn Leu Ser  Ser Thr Ser Ala Glu  Ile Leu Ala
    8615                8620                8625

Thr Ser  Glu Val Thr Lys Asp  Arg Glu Lys Ile His  Pro Ser Ser
    8630                8635                8640

Asn Thr  Pro Val Val Asn Val  Gly Thr Val Ile Tyr  Lys His Leu
    8645                8650                8655

Ser Pro  Ser Ser Val Leu Ala  Asp Leu Val Thr Thr  Lys Pro Thr
    8660                8665                8670

Ser Pro  Met Ala Thr Thr Ser  Thr Leu Gly Asn Thr  Ser Val Ser
    8675                8680                8685

Thr Ser  Thr Pro Ala Phe Pro  Glu Thr Met Met Thr  Gln Pro Thr
    8690                8695                8700

Ser Ser  Leu Thr Ser Gly Leu  Arg Glu Ile Ser Thr  Ser Gln Glu
    8705                8710                8715

Thr Ser  Ser Ala Thr Glu Arg  Ser Ala Ser Leu Ser  Gly Met Pro
    8720                8725                8730

Thr Gly  Ala Thr Thr Lys Val  Ser Arg Thr Glu Ala  Leu Ser Leu
    8735                8740                8745

Gly Arg  Thr Ser Thr Pro Gly  Pro Ala Gln Ser Thr  Ile Ser Pro
    8750                8755                8760

Glu Ile  Ser Thr Glu Thr Ile  Thr Arg Ile Ser Thr  Pro Leu Thr
    8765                8770                8775
```

```
Thr Thr  Gly Ser Ala Glu Met  Thr Ile Thr Pro Lys  Thr Gly His
    8780                8785                8790

Ser Gly  Ala Ser Ser Gln Gly  Thr Phe Thr Leu Asp  Thr Ser Ser
    8795                8800                8805

Arg Ala  Ser Trp Pro Gly Thr  His Ser Ala Ala Thr  His Arg Ser
    8810                8815                8820

Pro His  Ser Gly Met Thr Thr  Pro Met Ser Arg Gly  Pro Glu Asp
    8825                8830                8835

Val Ser  Trp Pro Ser Arg Pro  Ser Val Glu Lys Thr  Ser Pro Pro
    8840                8845                8850

Ser Ser  Leu Val Ser Leu Ser  Ala Val Thr Ser Pro  Ser Pro Leu
    8855                8860                8865

Tyr Ser  Thr Pro Ser Glu Ser  Ser His Ser Ser Pro  Leu Arg Val
    8870                8875                8880

Thr Ser  Leu Phe Thr Pro Val  Met Met Lys Thr Thr  Asp Met Leu
    8885                8890                8895

Asp Thr  Ser Leu Glu Pro Val  Thr Thr Ser Pro Pro  Ser Met Asn
    8900                8905                8910

Ile Thr  Ser Asp Glu Ser Leu  Ala Thr Ser Lys Ala  Thr Met Glu
    8915                8920                8925

Thr Glu  Ala Ile Gln Leu Ser  Glu Asn Thr Ala Val  Thr Gln Met
    8930                8935                8940

Gly Thr  Ile Ser Ala Arg Gln  Glu Phe Tyr Ser Ser  Tyr Pro Gly
    8945                8950                8955

Leu Pro  Glu Pro Ser Lys Val  Thr Ser Pro Val Val  Thr Ser Ser
    8960                8965                8970
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Thr Ile  Lys Asp Ile Val Ser  Thr Thr Ile Pro Ala  Ser Ser Glu
    8975                 8980                 8985

Ile Thr  Arg Ile Glu Met Glu  Ser Thr Ser Thr Leu  Thr Pro Thr
    8990                 8995                 9000

Pro Arg  Glu Thr Ser Thr Ser  Gln Glu Ile His Ser  Ala Thr Lys
    9005                 9010                 9015

Pro Ser  Thr Val Pro Tyr Lys  Ala Leu Thr Ser Ala  Thr Ile Glu
    9020                 9025                 9030

Asp Ser  Met Thr Gln Val Met  Ser Ser Ser Arg Gly  Pro Ser Pro
    9035                 9040                 9045

Asp Gln  Ser Thr Met Ser Gln  Asp Ile Ser Thr Glu  Val Ile Thr
    9050                 9055                 9060

Arg Leu  Ser Thr Ser Pro Ile  Lys Thr Glu Ser Thr  Glu Met Thr
    9065                 9070                 9075

Ile Thr  Thr Gln Thr Gly Ser  Pro Gly Ala Thr Ser  Arg Gly Thr
    9080                 9085                 9090

Leu Thr  Leu Asp Thr Ser Thr  Thr Phe Met Ser Gly  Thr His Ser
    9095                 9100                 9105

Thr Ala  Ser Gln Gly Phe Ser  His Ser Gln Met Thr  Ala Leu Met
    9110                 9115                 9120

Ser Arg  Thr Pro Gly Asp Val  Pro Trp Leu Ser His  Pro Ser Val
    9125                 9130                 9135

Glu Glu  Ala Ser Ser Ala Ser  Phe Ser Leu Ser Ser  Pro Val Met
    9140                 9145                 9150

Thr Ser  Ser Ser Pro Val Ser  Ser Thr Leu Pro Asp  Ser Ile His
    9155                 9160                 9165

Ser Ser  Ser Leu Pro Val Thr  Ser Leu Leu Thr Ser  Gly Leu Val
    9170                 9175                 9180
```

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Lys Thr  Thr Glu Leu Leu Gly  Thr Ser Ser Glu Pro  Glu Thr Ser
    9185                9190                9195

Ser Pro  Pro Asn Leu Ser Ser  Thr Ser Ala Glu Ile  Leu Ala Ile
    9200                9205                9210

Thr Glu  Val Thr Thr Asp Thr  Glu Lys Leu Glu Met  Thr Asn Val
    9215                9220                9225

Val Thr  Ser Gly Tyr Thr His  Glu Ser Pro Ser Ser  Val Leu Ala
    9230                9235                9240

Asp Ser  Val Thr Thr Lys Ala  Thr Ser Ser Met Gly  Ile Thr Tyr
    9245                9250                9255

Pro Thr  Gly Asp Thr Asn Val  Leu Thr Ser Thr Pro  Ala Phe Ser
    9260                9265                9270

Asp Thr  Ser Arg Ile Gln Thr  Lys Ser Lys Leu Ser  Leu Thr Pro
    9275                9280                9285

Gly Leu  Met Glu Thr Ser Ile  Ser Glu Glu Thr Ser  Ser Ala Thr
    9290                9295                9300

Glu Lys  Ser Thr Val Leu Ser  Ser Val Pro Thr Gly  Ala Thr Thr
    9305                9310                9315

Glu Val  Ser Arg Thr Glu Ala  Ile Ser Ser Ser Arg  Thr Ser Ile
    9320                9325                9330

Pro Gly  Pro Ala Gln Ser Thr  Met Ser Ser Asp Thr  Ser Met Glu
    9335                9340                9345

Thr Ile  Thr Arg Ile Ser Thr  Pro Leu Thr Arg Lys  Glu Ser Thr
    9350                9355                9360

Asp Met  Ala Ile Thr Pro Lys  Thr Gly Pro Ser Gly  Ala Thr Ser
    9365                9370                9375
```

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Gln Gly  Thr Phe Thr Leu Asp  Ser Ser Ser Thr Ala  Ser Trp Pro
    9380                9385                9390

Gly Thr  His Ser Ala Thr Thr  Gln Arg Phe Pro Gln  Ser Val Val
    9395                9400                9405

Thr Thr  Pro Met Ser Arg Gly  Pro Glu Asp Val Ser  Trp Pro Ser
    9410                9415                9420

Pro Leu  Ser Val Glu Lys Asn  Ser Pro Pro Ser Ser  Leu Val Ser
    9425                9430                9435

Ser Ser  Ser Val Thr Ser Pro  Ser Pro Leu Tyr Ser  Thr Pro Ser
    9440                9445                9450

Gly Ser  Ser His Ser Ser Pro  Val Pro Val Thr Ser  Leu Phe Thr
    9455                9460                9465

Ser Ile  Met Met Lys Ala Thr  Asp Met Leu Asp Ala  Ser Leu Glu
    9470                9475                9480

Pro Glu  Thr Thr Ser Ala Pro  Asn Met Asn Ile Thr  Ser Asp Glu
    9485                9490                9495

Ser Leu  Ala Ala Ser Lys Ala  Thr Thr Glu Thr Glu  Ala Ile His
    9500                9505                9510

Val Phe  Glu Asn Thr Ala Ala  Ser His Val Glu Thr  Thr Ser Ala
    9515                9520                9525

Thr Glu  Glu Leu Tyr Ser Ser  Ser Pro Gly Phe Ser  Glu Pro Thr
    9530                9535                9540

Lys Val  Ile Ser Pro Val Val  Thr Ser Ser Ser Ile  Arg Asp Asn
    9545                9550                9555

Met Val  Ser Thr Thr Met Pro  Gly Ser Ser Gly Ile  Thr Arg Ile
    9560                9565                9570

Glu Ile  Glu Ser Met Ser Ser  Leu Thr Pro Gly Leu  Arg Glu Thr
    9575                9580                9585
```

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Arg Thr  Ser Gln Asp Ile Thr  Ser Ser Thr Glu Thr  Ser Thr Val
    9590                 9595                 9600

Leu Tyr  Lys Met Pro Ser Gly  Ala Thr Pro Glu Val  Ser Arg Thr
    9605                 9610                 9615

Glu Val  Met Pro Ser Ser Arg  Thr Ser Ile Pro Gly  Pro Ala Gln
    9620                 9625                 9630

Ser Thr  Met Ser Leu Asp Ile  Ser Asp Glu Val Val  Thr Arg Leu
    9635                 9640                 9645

Ser Thr  Ser Pro Ile Met Thr  Glu Ser Ala Glu Ile  Thr Ile Thr
    9650                 9655                 9660

Thr Gln  Thr Gly Tyr Ser Leu  Ala Thr Ser Gln Val  Thr Leu Pro
    9665                 9670                 9675

Leu Gly  Thr Ser Met Thr Phe  Leu Ser Gly Thr His  Ser Thr Met
    9680                 9685                 9690

Ser Gln  Gly Leu Ser His Ser  Glu Met Thr Asn Leu  Met Ser Arg
    9695                 9700                 9705

Gly Pro  Glu Ser Leu Ser Trp  Thr Ser Pro Arg Phe  Val Glu Thr
    9710                 9715                 9720

Thr Arg  Ser Ser Ser Ser Leu  Thr Ser Leu Pro Leu  Thr Thr Ser
    9725                 9730                 9735

Leu Ser  Pro Val Ser Ser Thr  Leu Leu Asp Ser Ser  Pro Ser Ser
    9740                 9745                 9750

Pro Leu  Pro Val Thr Ser Leu  Ile Leu Pro Gly Leu  Val Lys Thr
    9755                 9760                 9765

Thr Glu  Val Leu Asp Thr Ser  Ser Glu Pro Lys Thr  Ser Ser Ser
    9770                 9775                 9780
```

```
Pro Asn  Leu Ser Ser Thr Ser  Val Glu Ile Pro Ala  Thr Ser Glu
    9785                 9790                 9795

Ile Met  Thr Asp Thr Glu Lys  Ile His Pro Ser Ser  Asn Thr Ala
    9800                 9805                 9810

Val Ala  Lys Val Arg Thr Ser  Ser Ser Val His Glu  Ser His Ser
    9815                 9820                 9825

Ser Val  Leu Ala Asp Ser Glu  Thr Thr Ile Thr Ile  Pro Ser Met
    9830                 9835                 9840

Gly Ile  Thr Ser Ala Val Asp  Asp Thr Thr Val Phe  Thr Ser Asn
    9845                 9850                 9855

Pro Ala  Phe Ser Glu Thr Arg  Arg Ile Pro Thr Glu  Pro Thr Phe
    9860                 9865                 9870

Ser Leu  Thr Pro Gly Phe Arg  Glu Thr Ser Thr Ser  Glu Glu Thr
    9875                 9880                 9885

Thr Ser  Ile Thr Glu Thr Ser  Ala Val Leu Tyr Gly  Val Pro Thr
    9890                 9895                 9900

Ser Ala  Thr Thr Glu Val Ser  Met Thr Glu Ile Met  Ser Ser Asn
    9905                 9910                 9915

Arg Ile  His Ile Pro Asp Ser  Asp Gln Ser Thr Met  Ser Pro Asp
    9920                 9925                 9930

Ile Ile  Thr Glu Val Ile Thr  Arg Leu Ser Ser Ser  Ser Met Met
    9935                 9940                 9945

Ser Glu  Ser Thr Gln Met Thr  Ile Thr Thr Gln Lys  Ser Ser Pro
    9950                 9955                 9960

Gly Ala  Thr Ala Gln Ser Thr  Leu Thr Leu Ala Thr  Thr Thr Ala
    9965                 9970                 9975

Pro Leu  Ala Arg Thr His Ser  Thr Val Pro Pro Arg  Phe Leu His
    9980                 9985                 9990
```

```
Ser Glu  Met Thr Thr Leu Met   Ser Arg Ser Pro Glu   Asn Pro Ser
    9995                10000                10005

Trp Lys   Ser Ser Leu Phe Val   Glu Lys Thr Ser Ser   Ser Ser Ser
    10010                10015                10020

Leu Leu   Ser Leu Pro Val Thr   Thr Ser Pro Ser Val   Ser Ser Thr
    10025                10030                10035

Leu Pro   Gln Ser Ile Pro Ser   Ser Ser Phe Ser Val   Thr Ser Leu
    10040                10045                10050

Leu Thr   Pro Gly Met Val Lys   Thr Thr Asp Thr Ser   Thr Glu Pro
    10055                10060                10065

Gly Thr   Ser Leu Ser Pro Asn   Leu Ser Gly Thr Ser   Val Glu Ile
    10070                10075                10080

Leu Ala   Ala Ser Glu Val Thr   Thr Asp Thr Glu Lys   Ile His Pro
    10085                10090                10095

Ser Ser   Ser Met Ala Val Thr   Asn Val Gly Thr Thr   Ser Ser Gly
    10100                10105                10110

His Glu   Leu Tyr Ser Ser Val   Ser Ile His Ser Glu   Pro Ser Lys
    10115                10120                10125

Ala Thr   Tyr Pro Val Gly Thr   Pro Ser Ser Met Ala   Glu Thr Ser
    10130                10135                10140

Ile Ser   Thr Ser Met Pro Ala   Asn Phe Glu Thr Thr   Gly Phe Glu
    10145                10150                10155

Ala Glu   Pro Phe Ser His Leu   Thr Ser Gly Phe Arg   Lys Thr Asn
    10160                10165                10170

Met Ser   Leu Asp Thr Ser Ser   Val Thr Pro Thr Asn   Thr Pro Ser
    10175                10180                10185
```

```
Ser Pro   Gly Ser Thr His Leu   Leu Gln Ser Ser Lys   Thr Asp Phe
    10190                 10195                 10200

Thr Ser   Ser Ala Lys Thr Ser   Ser Pro Asp Trp Pro   Pro Ala Ser
    10205                 10210                 10215

Gln Tyr   Thr Glu Ile Pro Val   Asp Ile Ile Thr Pro   Phe Asn Ala
    10220                 10225                 10230

Ser Pro   Ser Ile Thr Glu Ser   Thr Gly Ile Thr Ser   Phe Pro Glu
    10235                 10240                 10245

Ser Arg   Phe Thr Met Ser Val   Thr Glu Ser Thr His   His Leu Ser
    10250                 10255                 10260

Thr Asp   Leu Leu Pro Ser Ala   Glu Thr Ile Ser Thr   Gly Thr Val
    10265                 10270                 10275

Met Pro   Ser Leu Ser Glu Ala   Met Thr Ser Phe Ala   Thr Thr Gly
    10280                 10285                 10290

Val Pro   Arg Ala Ile Ser Gly   Ser Gly Ser Pro Phe   Ser Arg Thr
    10295                 10300                 10305

Glu Ser   Gly Pro Gly Asp Ala   Thr Leu Ser Thr Ile   Ala Glu Ser
    10310                 10315                 10320

Leu Pro   Ser Ser Thr Pro Val   Pro Phe Ser Ser Ser   Thr Phe Thr
    10325                 10330                 10335

Thr Thr   Asp Ser Ser Thr Ile   Pro Ala Leu His Glu   Ile Thr Ser
    10340                 10345                 10350

Ser Ser   Ala Thr Pro Tyr Arg   Val Asp Thr Ser Leu   Gly Thr Glu
    10355                 10360                 10365

Ser Ser   Thr Thr Glu Gly Arg   Leu Val Met Val Ser   Thr Leu Asp
    10370                 10375                 10380

Thr Ser   Ser Gln Pro Gly Arg   Thr Ser Ser Ser Pro   Ile Leu Asp
    10385                 10390                 10395
```

```
Thr Arg   Met Thr Glu Ser Val   Glu Leu Gly Thr Val   Thr Ser Ala
    10400                10405                10410

Tyr Gln   Val Pro Ser Leu Ser   Thr Arg Leu Thr Arg   Thr Asp Gly
    10415                10420                10425

Ile Met   Glu His Ile Thr Lys   Ile Pro Asn Glu Ala   Ala His Arg
    10430                10435                10440

Gly Thr   Ile Arg Pro Val Lys   Gly Pro Gln Thr Ser   Thr Ser Pro
    10445                10450                10455

Ala Ser   Pro Lys Gly Leu His   Thr Gly Gly Thr Lys   Arg Met Glu
    10460                10465                10470

Thr Thr   Thr Thr Ala Leu Lys   Thr Thr Thr Thr Ala   Leu Lys Thr
    10475                10480                10485

Thr Ser   Arg Ala Thr Leu Thr   Thr Ser Val Tyr Thr   Pro Thr Leu
    10490                10495                10500

Gly Thr   Leu Thr Pro Leu Asn   Ala Ser Met Gln Met   Ala Ser Thr
    10505                10510                10515

Ile Pro   Thr Glu Met Met Ile   Thr Thr Pro Tyr Val   Phe Pro Asp
    10520                10525                10530

Val Pro   Glu Thr Thr Ser Ser   Leu Ala Thr Ser Leu   Gly Ala Glu
    10535                10540                10545

Thr Ser   Thr Ala Leu Pro Arg   Thr Thr Pro Ser Val   Phe Asn Arg
    10550                10555                10560

Glu Ser   Glu Thr Thr Ala Ser   Leu Val Ser Arg Ser   Gly Ala Glu
    10565                10570                10575

Arg Ser   Pro Val Ile Gln Thr   Leu Asp Val Ser Ser   Ser Glu Pro
    10580                10585                10590
```

```
Asp Thr   Thr Ala Ser Trp Val   Ile His Pro Ala Glu   Thr Ile Pro
    10595                10600                10605

Thr Val   Ser Lys Thr Thr Pro   Asn Phe Phe His Ser   Glu Leu Asp
    10610                10615                10620

Thr Val   Ser Ser Thr Ala Thr   Ser His Gly Ala Asp   Val Ser Ser
    10625                10630                10635

Ala Ile   Pro Thr Asn Ile Ser   Pro Ser Glu Leu Asp   Ala Leu Thr
    10640                10645                10650

Pro Leu   Val Thr Ile Ser Gly   Thr Asp Thr Ser Thr   Thr Phe Pro
    10655                10660                10665

Thr Leu   Thr Lys Ser Pro His   Glu Thr Glu Thr Arg   Thr Thr Trp
    10670                10675                10680

Leu Thr   His Pro Ala Glu Thr   Ser Ser Thr Ile Pro   Arg Thr Ile
    10685                10690                10695

Pro Asn   Phe Ser His His Glu   Ser Asp Ala Thr Pro   Ser Ile Ala
    10700                10705                10710

Thr Ser   Pro Gly Ala Glu Thr   Ser Ser Ala Ile Pro   Ile Met Thr
    10715                10720                10725

Val Ser   Pro Gly Ala Glu Asp   Leu Val Thr Ser Gln   Val Thr Ser
    10730                10735                10740

Ser Gly   Thr Asp Arg Asn Met   Thr Ile Pro Thr Leu   Thr Leu Ser
    10745                10750                10755

Pro Gly   Glu Pro Lys Thr Ile   Ala Ser Leu Val Thr   His Pro Glu
    10760                10765                10770

Ala Gln   Thr Ser Ser Ala Ile   Pro Thr Ser Thr Ile   Ser Pro Ala
    10775                10780                10785

Val Ser   Arg Leu Val Thr Ser   Met Val Thr Ser Leu   Ala Ala Lys
    10790                10795                10800
```

```
Thr Ser   Thr Thr Asn Arg Ala   Leu Thr Asn Ser Pro   Gly Glu Pro
    10805                10810                10815

Ala Thr   Thr Val Ser Leu Val   Thr His Pro Ala Gln   Thr Ser Pro
    10820                10825                10830

Thr Val   Pro Trp Thr Thr Ser   Ile Phe Phe His Ser   Lys Ser Asp
    10835                10840                10845

Thr Thr   Pro Ser Met Thr Thr   Ser His Gly Ala Glu   Ser Ser Ser
    10850                10855                10860

Ala Val   Pro Thr Pro Thr Val   Ser Thr Glu Val Pro   Gly Val Val
    10865                10870                10875

Thr Pro   Leu Val Thr Ser Ser   Arg Ala Val Ile Ser   Thr Thr Ile
    10880                10885                10890

Pro Ile   Leu Thr Leu Ser Pro   Gly Glu Pro Glu Thr   Thr Pro Ser
    10895                10900                10905

Met Ala   Thr Ser His Gly Glu   Glu Ala Ser Ser Ala   Ile Pro Thr
    10910                10915                10920

Pro Thr   Val Ser Pro Gly Val   Pro Gly Val Val Thr   Ser Leu Val
    10925                10930                10935

Thr Ser   Ser Arg Ala Val Thr   Ser Thr Thr Ile Pro   Ile Leu Thr
    10940                10945                10950

Phe Ser   Leu Gly Glu Pro Glu   Thr Thr Pro Ser Met   Ala Thr Ser
    10955                10960                10965

His Gly   Thr Glu Ala Gly Ser   Ala Val Pro Thr Val   Leu Pro Glu
    10970                10975                10980

Val Pro   Gly Met Val Thr Ser   Leu Val Ala Ser Ser   Arg Ala Val
    10985                10990                10995
```

```
Thr Ser   Thr Thr Leu Pro Thr   Leu Thr Leu Ser Pro   Gly Glu Pro
    11000                 11005                 11010

Glu Thr   Thr Pro Ser Met Ala   Thr Ser His Gly Ala   Glu Ala Ser
    11015                 11020                 11025

Ser Thr   Val Pro Thr Val Ser   Pro Glu Val Pro Gly   Val Val Thr
    11030                 11035                 11040

Ser Leu   Val Thr Ser Ser Ser   Gly Val Asn Ser Thr   Ser Ile Pro
    11045                 11050                 11055

Thr Leu   Ile Leu Ser Pro Gly   Glu Leu Glu Thr Thr   Pro Ser Met
    11060                 11065                 11070

Ala Thr   Ser His Gly Ala Glu   Ala Ser Ser Ala Val   Pro Thr Pro
    11075                 11080                 11085

Thr Val   Ser Pro Gly Val Ser   Gly Val Val Thr Pro   Leu Val Thr
    11090                 11095                 11100

Ser Ser   Arg Ala Val Thr Ser   Thr Thr Ile Pro Ile   Leu Thr Leu
    11105                 11110                 11115

Ser Ser   Ser Glu Pro Glu Thr   Thr Pro Ser Met Ala   Thr Ser His
    11120                 11125                 11130

Gly Val   Glu Ala Ser Ser Ala   Val Leu Thr Val Ser   Pro Glu Val
    11135                 11140                 11145

Pro Gly   Met Val Thr Ser Leu   Val Thr Ser Ser Arg   Ala Val Thr
    11150                 11155                 11160

Ser Thr   Thr Ile Pro Thr Leu   Thr Ile Ser Ser Asp   Glu Pro Glu
    11165                 11170                 11175

Thr Thr   Thr Ser Leu Val Thr   His Ser Glu Ala Lys   Met Ile Ser
    11180                 11185                 11190

Ala Ile   Pro Thr Leu Ala Val   Ser Pro Thr Val Gln   Gly Leu Val
    11195                 11200                 11205
```

```
Thr Ser   Leu Val Thr Ser Ser   Gly Ser Glu Thr Ser   Ala Phe Ser
    11210                11215                11220

Asn Leu   Thr Val Ala Ser Ser   Gln Pro Glu Thr Ile   Asp Ser Trp
    11225                11230                11235

Val Ala   His Pro Gly Thr Glu   Ala Ser Ser Val Val   Pro Thr Leu
    11240                11245                11250

Thr Val   Ser Thr Gly Glu Pro   Phe Thr Asn Ile Ser   Leu Val Thr
    11255                11260                11265

His Pro   Ala Glu Ser Ser Ser   Thr Leu Pro Arg Thr   Thr Ser Arg
    11270                11275                11280

Phe Ser   His Ser Glu Leu Asp   Thr Met Pro Ser Thr   Val Thr Ser
    11285                11290                11295

Pro Glu   Ala Glu Ser Ser Ser   Ala Ile Ser Thr Thr   Ile Ser Pro
    11300                11305                11310

Gly Ile   Pro Gly Val Leu Thr   Ser Leu Val Thr Ser   Ser Gly Arg
    11315                11320                11325

Asp Ile   Ser Ala Thr Phe Pro   Thr Val Pro Glu Ser   Pro His Glu
    11330                11335                11340

Ser Glu   Ala Thr Ala Ser Trp   Val Thr His Pro Ala   Val Thr Ser
    11345                11350                11355

Thr Thr   Val Pro Arg Thr Thr   Pro Asn Tyr Ser His   Ser Glu Pro
    11360                11365                11370

Asp Thr   Thr Pro Ser Ile Ala   Thr Ser Pro Gly Ala   Glu Ala Thr
    11375                11380                11385

Ser Asp   Phe Pro Thr Ile Thr   Val Ser Pro Asp Val   Pro Asp Met
    11390                11395                11400
```

```
Val Thr   Ser Gln Val Thr Ser   Ser Gly Thr Asp Thr   Ser Ile Thr
    11405                11410                11415

Ile Pro   Thr Leu Thr Leu Ser   Ser Gly Glu Pro Glu   Thr Thr Thr
    11420                11425                11430

Ser Phe   Ile Thr Tyr Ser Glu   Thr His Thr Ser Ser   Ala Ile Pro
    11435                11440                11445

Thr Leu   Pro Val Ser Pro Gly   Ala Ser Lys Met Leu   Thr Ser Leu
    11450                11455                11460

Val Ile   Ser Ser Gly Thr Asp   Ser Thr Thr Thr Phe   Pro Thr Leu
    11465                11470                11475

Thr Glu   Thr Pro Tyr Glu Pro   Glu Thr Thr Ala Ile   Gln Leu Ile
    11480                11485                11490

His Pro   Ala Glu Thr Asn Thr   Met Val Pro Arg Thr   Thr Pro Lys
    11495                11500                11505

Phe Ser   His Ser Lys Ser Asp   Thr Thr Leu Pro Val   Ala Ile Thr
    11510                11515                11520

Ser Pro   Gly Pro Glu Ala Ser   Ser Ala Val Ser Thr   Thr Thr Ile
    11525                11530                11535

Ser Pro   Asp Met Ser Asp Leu   Val Thr Ser Leu Val   Pro Ser Ser
    11540                11545                11550

Gly Thr   Asp Thr Ser Thr Thr   Phe Pro Thr Leu Ser   Glu Thr Pro
    11555                11560                11565

Tyr Glu   Pro Glu Thr Thr Ala   Thr Trp Leu Thr His   Pro Ala Glu
    11570                11575                11580

Thr Ser   Thr Thr Val Ser Gly   Thr Ile Pro Asn Phe   Ser His Arg
    11585                11590                11595

Gly Ser   Asp Thr Ala Pro Ser   Met Val Thr Ser Pro   Gly Val Asp
    11600                11605                11610
```

```
Thr Arg   Ser Gly Val Pro Thr   Thr Thr Ile Pro Pro   Ser Ile Pro
    11615                11620                11625

Gly Val   Val Thr Ser Gln Val   Thr Ser Ser Ala Thr   Asp Thr Ser
    11630                11635                11640

Thr Ala   Ile Pro Thr Leu Thr   Pro Ser Pro Gly Glu   Pro Glu Thr
    11645                11650                11655

Thr Ala   Ser Ser Ala Thr His   Pro Gly Thr Gln Thr   Gly Phe Thr
    11660                11665                11670

Val Pro   Ile Arg Thr Val Pro   Ser Ser Glu Pro Asp   Thr Met Ala
    11675                11680                11685

Ser Trp   Val Thr His Pro Pro   Gln Thr Ser Thr Pro   Val Ser Arg
    11690                11695                11700

Thr Thr   Ser Ser Phe Ser His   Ser Ser Pro Asp Ala   Thr Pro Val
    11705                11710                11715

Met Ala   Thr Ser Pro Arg Thr   Glu Ala Ser Ser Ala   Val Leu Thr
    11720                11725                11730

Thr Ile   Ser Pro Gly Ala Pro   Glu Met Val Thr Ser   Gln Ile Thr
    11735                11740                11745

Ser Ser   Gly Ala Ala Thr Ser   Thr Thr Val Pro Thr   Leu Thr His
    11750                11755                11760

Ser Pro   Gly Met Pro Glu Thr   Thr Ala Leu Leu Ser   Thr His Pro
    11765                11770                11775

Arg Thr   Glu Thr Ser Lys Thr   Phe Pro Ala Ser Thr   Val Phe Pro
    11780                11785                11790

Gln Val   Ser Glu Thr Thr Ala   Ser Leu Thr Ile Arg   Pro Gly Ala
    11795                11800                11805
```

```
Glu Thr   Ser Thr Ala Leu Pro   Thr Gln Thr Thr Ser   Ser Leu Phe
    11810                 11815                 11820

Thr Leu   Leu Val Thr Gly Thr   Ser Arg Val Asp Leu   Ser Pro Thr
    11825                 11830                 11835

Ala Ser   Pro Gly Val Ser Ala   Lys Thr Ala Pro Leu   Ser Thr His
    11840                 11845                 11850

Pro Gly   Thr Glu Thr Ser Thr   Met Ile Pro Thr Ser   Thr Leu Ser
    11855                 11860                 11865

Leu Gly   Leu Leu Glu Thr Thr   Gly Leu Leu Ala Thr   Ser Ser Ser
    11870                 11875                 11880

Ala Glu   Thr Ser Thr Ser Thr   Leu Thr Leu Thr Val   Ser Pro Ala
    11885                 11890                 11895

Val Ser   Gly Leu Ser Ser Ala   Ser Ile Thr Thr Asp   Lys Pro Gln
    11900                 11905                 11910

Thr Val   Thr Ser Trp Asn Thr   Glu Thr Ser Pro Ser   Val Thr Ser
    11915                 11920                 11925

Val Gly   Pro Pro Glu Phe Ser   Arg Thr Val Thr Gly   Thr Thr Met
    11930                 11935                 11940

Thr Leu   Ile Pro Ser Glu Met   Pro Thr Pro Pro Lys   Thr Ser His
    11945                 11950                 11955

Gly Glu   Gly Val Ser Pro Thr   Thr Ile Leu Arg Thr   Thr Met Val
    11960                 11965                 11970

Glu Ala   Thr Asn Leu Ala Thr   Thr Gly Ser Ser Pro   Thr Val Ala
    11975                 11980                 11985

Lys Thr   Thr Thr Thr Phe Asn   Thr Leu Ala Gly Ser   Leu Phe Thr
    11990                 11995                 12000

Pro Leu   Thr Thr Pro Gly Met   Ser Thr Leu Ala Ser   Glu Ser Val
    12005                 12010                 12015
```

```
Thr Ser   Arg Thr Ser Tyr Asn   His Arg Ser Trp Ile   Ser Thr Thr
    12020                12025                12030

Ser Ser   Tyr Asn Arg Arg Tyr   Trp Thr Pro Ala Thr   Ser Thr Pro
    12035                12040                12045

Val Thr   Ser Thr Phe Ser Pro   Gly Ile Ser Thr Ser   Ser Ile Pro
    12050                12055                12060

Ser Ser   Thr Ala Ala Thr Val   Pro Phe Met Val Pro   Phe Thr Leu
    12065                12070                12075

Asn Phe   Thr Ile Thr Asn Leu   Gln Tyr Glu Glu Asp   Met Arg His
    12080                12085                12090

Pro Gly   Ser Arg Lys Phe Asn   Ala Thr Glu Arg Glu   Leu Gln Gly
    12095                12100                12105

Leu Leu   Lys Pro Leu Phe Arg   Asn Ser Ser Leu Glu   Tyr Leu Tyr
    12110                12115                12120

Ser Gly   Cys Arg Leu Ala Ser   Leu Arg Pro Glu Lys   Asp Ser Ser
    12125                12130                12135

Ala Thr   Ala Val Asp Ala Ile   Cys Thr His Arg Pro   Asp Pro Glu
    12140                12145                12150

Asp Leu   Gly Leu Asp Arg Glu   Arg Leu Tyr Trp Glu   Leu Ser Asn
    12155                12160                12165

Leu Thr   Asn Gly Ile Gln Glu   Leu Gly Pro Tyr Thr   Leu Asp Arg
    12170                12175                12180

Asn Ser   Leu Tyr Val Asn Gly   Phe Thr His Arg Ser   Ser Met Pro
    12185                12190                12195

Thr Thr   Ser Thr Pro Gly Thr   Ser Thr Val Asp Val   Gly Thr Ser
    12200                12205                12210
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Gly Thr   Pro Ser Ser Ser Pro   Ser Pro Thr Thr Ala   Gly Pro Leu
    12215                 12220                 12225

Leu Met   Pro Phe Thr Leu Asn   Phe Thr Ile Thr Asn   Leu Gln Tyr
    12230                 12235                 12240

Glu Glu   Asp Met Arg Arg Thr   Gly Ser Arg Lys Phe   Asn Thr Met
    12245                 12250                 12255

Glu Ser   Val Leu Gln Gly Leu   Leu Lys Pro Leu Phe   Lys Asn Thr
    12260                 12265                 12270

Ser Val   Gly Pro Leu Tyr Ser   Gly Cys Arg Leu Thr   Leu Leu Arg
    12275                 12280                 12285

Pro Glu   Lys Asp Gly Ala Ala   Thr Gly Val Asp Ala   Ile Cys Thr
    12290                 12295                 12300

His Arg   Leu Asp Pro Lys Ser   Pro Gly Leu Asn Arg   Glu Gln Leu
    12305                 12310                 12315

Tyr Trp   Glu Leu Ser Lys Leu   Thr Asn Asp Ile Glu   Glu Leu Gly
    12320                 12325                 12330

Pro Tyr   Thr Leu Asp Arg Asn   Ser Leu Tyr Val Asn   Gly Phe Thr
    12335                 12340                 12345

His Gln   Ser Ser Val Ser Thr   Thr Ser Thr Pro Gly   Thr Ser Thr
    12350                 12355                 12360

Val Asp   Leu Arg Thr Ser Gly   Thr Pro Ser Ser Leu   Ser Ser Pro
    12365                 12370                 12375

Thr Ile   Met Ala Ala Gly Pro   Leu Leu Val Pro Phe   Thr Leu Asn
    12380                 12385                 12390

Phe Thr   Ile Thr Asn Leu Gln   Tyr Gly Glu Asp Met   Gly His Pro
    12395                 12400                 12405

Gly Ser   Arg Lys Phe Asn Thr   Thr Glu Arg Val Leu   Gln Gly Leu
    12410                 12415                 12420
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Leu Gly   Pro Ile Phe Lys Asn   Thr Ser Val Gly Pro   Leu Tyr Ser
    12425                 12430                 12435

Gly Cys   Arg Leu Thr Ser Leu   Arg Ser Glu Lys Asp   Gly Ala Ala
    12440                 12445                 12450

Thr Gly   Val Asp Ala Ile Cys   Ile His His Leu Asp   Pro Lys Ser
    12455                 12460                 12465

Pro Gly   Leu Asn Arg Glu Arg   Leu Tyr Trp Glu Leu   Ser Gln Leu
    12470                 12475                 12480

Thr Asn   Gly Ile Lys Glu Leu   Gly Pro Tyr Thr Leu   Asp Arg Asn
    12485                 12490                 12495

Ser Leu   Tyr Val Asn Gly Phe   Thr His Arg Thr Ser   Val Pro Thr
    12500                 12505                 12510

Ser Ser   Thr Pro Gly Thr Ser   Thr Val Asp Leu Gly   Thr Ser Gly
    12515                 12520                 12525

Thr Pro   Phe Ser Leu Pro Ser   Pro Ala Thr Ala Gly   Pro Leu Leu
    12530                 12535                 12540

Val Leu   Phe Thr Leu Asn Phe   Thr Ile Thr Asn Leu   Lys Tyr Glu
    12545                 12550                 12555

Glu Asp   Met His Arg Pro Gly   Ser Arg Lys Phe Asn   Thr Thr Glu
    12560                 12565                 12570

Arg Val   Leu Gln Thr Leu Leu   Gly Pro Met Phe Lys   Asn Thr Ser
    12575                 12580                 12585

Val Gly   Leu Leu Tyr Ser Gly   Cys Arg Leu Thr Leu   Leu Arg Ser
    12590                 12595                 12600

Glu Lys   Asp Gly Ala Ala Thr   Gly Val Asp Ala Ile   Cys Thr His
    12605                 12610                 12615
```

```
Arg Leu   Asp Pro Lys Ser Pro   Gly Val Asp Arg Glu   Gln Leu Tyr
    12620                 12625                 12630

Trp Glu   Leu Ser Gln Leu Thr   Asn Gly Ile Lys Glu   Leu Gly Pro
    12635                 12640                 12645

Tyr Thr   Leu Asp Arg Asn Ser   Leu Tyr Val Asn Gly   Phe Thr His
    12650                 12655                 12660

Trp Ile   Pro Val Pro Thr Ser   Ser Thr Pro Gly Thr   Ser Thr Val
    12665                 12670                 12675

Asp Leu   Gly Ser Gly Thr Pro   Ser Ser Leu Pro Ser   Pro Thr Thr
    12680                 12685                 12690

Ala Gly   Pro Leu Leu Val Pro   Phe Thr Leu Asn Phe   Thr Ile Thr
    12695                 12700                 12705

Asn Leu   Lys Tyr Glu Glu Asp   Met His Cys Pro Gly   Ser Arg Lys
    12710                 12715                 12720

Phe Asn   Thr Thr Glu Arg Val   Leu Gln Ser Leu Leu   Gly Pro Met
    12725                 12730                 12735

Phe Lys   Asn Thr Ser Val Gly   Pro Leu Tyr Ser Gly   Cys Arg Leu
    12740                 12745                 12750

Thr Leu   Leu Arg Ser Glu Lys   Asp Gly Ala Ala Thr   Gly Val Asp
    12755                 12760                 12765

Ala Ile   Cys Thr His Arg Leu   Asp Pro Lys Ser Pro   Gly Val Asp
    12770                 12775                 12780

Arg Glu   Gln Leu Tyr Trp Glu   Leu Ser Gln Leu Thr   Asn Gly Ile
    12785                 12790                 12795

Lys Glu   Leu Gly Pro Tyr Thr   Leu Asp Arg Asn Ser   Leu Tyr Val
    12800                 12805                 12810

Asn Gly   Phe Thr His Gln Thr   Ser Ala Pro Asn Thr   Ser Thr Pro
    12815                 12820                 12825
```

```
Gly Thr   Ser Thr Val Asp Leu   Gly Thr Ser Gly Thr   Pro Ser Ser
    12830                 12835                 12840

Leu Pro   Ser Pro Thr Ser Ala   Gly Pro Leu Leu Val   Pro Phe Thr
    12845                 12850                 12855

Leu Asn   Phe Thr Ile Thr Asn   Leu Gln Tyr Glu Glu   Asp Met His
    12860                 12865                 12870

His Pro   Gly Ser Arg Lys Phe   Asn Thr Thr Glu Arg   Val Leu Gln
    12875                 12880                 12885

Gly Leu   Leu Gly Pro Met Phe   Lys Asn Thr Ser Val   Gly Leu Leu
    12890                 12895                 12900

Tyr Ser   Gly Cys Arg Leu Thr   Leu Leu Arg Pro Glu   Lys Asn Gly
    12905                 12910                 12915

Ala Ala   Thr Gly Met Asp Ala   Ile Cys Ser His Arg   Leu Asp Pro
    12920                 12925                 12930

Lys Ser   Pro Gly Leu Asn Arg   Glu Gln Leu Tyr Trp   Glu Leu Ser
    12935                 12940                 12945

Gln Leu   Thr His Gly Ile Lys   Glu Leu Gly Pro Tyr   Thr Leu Asp
    12950                 12955                 12960

Arg Asn   Ser Leu Tyr Val Asn   Gly Phe Thr His Arg   Ser Ser Val
    12965                 12970                 12975

Ala Pro   Thr Ser Thr Pro Gly   Thr Ser Thr Val Asp   Leu Gly Thr
    12980                 12985                 12990

Ser Gly   Thr Pro Ser Ser Leu   Pro Ser Pro Thr Thr   Ala Val Pro
    12995                 13000                 13005

Leu Leu   Val Pro Phe Thr Leu   Asn Phe Thr Ile Thr   Asn Leu Gln
    13010                 13015                 13020
```

```
Tyr Gly   Glu Asp Met Arg His   Pro Gly Ser Arg Lys   Phe Asn Thr
    13025                 13030                 13035

Thr Glu   Arg Val Leu Gln Gly   Leu Leu Gly Pro Leu   Phe Lys Asn
    13040                 13045                 13050

Ser Ser   Val Gly Pro Leu Tyr   Ser Gly Cys Arg Leu   Ile Ser Leu
    13055                 13060                 13065

Arg Ser   Glu Lys Asp Gly Ala   Ala Thr Gly Val Asp   Ala Ile Cys
    13070                 13075                 13080

Thr His   His Leu Asn Pro Gln   Ser Pro Gly Leu Asp   Arg Glu Gln
    13085                 13090                 13095

Leu Tyr   Trp Gln Leu Ser Gln   Met Thr Asn Gly Ile   Lys Glu Leu
    13100                 13105                 13110

Gly Pro   Tyr Thr Leu Asp Arg   Asn Ser Leu Tyr Val   Asn Gly Phe
    13115                 13120                 13125

Thr His   Arg Ser Ser Gly Leu   Thr Thr Ser Thr Pro   Trp Thr Ser
    13130                 13135                 13140

Thr Val   Asp Leu Gly Thr Ser   Gly Thr Pro Ser Pro   Val Pro Ser
    13145                 13150                 13155

Pro Thr   Thr Thr Gly Pro Leu   Leu Val Pro Phe Thr   Leu Asn Phe
    13160                 13165                 13170

Thr Ile   Thr Asn Leu Gln Tyr   Glu Glu Asn Met Gly   His Pro Gly
    13175                 13180                 13185

Ser Arg   Lys Phe Asn Ile Thr   Glu Ser Val Leu Gln   Gly Leu Leu
    13190                 13195                 13200

Lys Pro   Leu Phe Lys Ser Thr   Ser Val Gly Pro Leu   Tyr Ser Gly
    13205                 13210                 13215

Cys Arg   Leu Thr Leu Leu Arg   Pro Glu Lys Asp Gly   Val Ala Thr
    13220                 13225                 13230
```

```
Arg Val   Asp Ala Ile Cys Thr   His Arg Pro Asp Pro   Lys Ile Pro
    13235                 13240                 13245

Gly Leu   Asp Arg Gln Gln Leu   Tyr Trp Glu Leu Ser   Gln Leu Thr
    13250                 13255                 13260

His Ser   Ile Thr Glu Leu Gly   Pro Tyr Thr Leu Asp   Arg Asp Ser
    13265                 13270                 13275

Leu Tyr   Val Asn Gly Phe Thr   Gln Arg Ser Ser Val   Pro Thr Thr
    13280                 13285                 13290

Ser Thr   Pro Gly Thr Phe Thr   Val Gln Pro Glu Thr   Ser Glu Thr
    13295                 13300                 13305

Pro Ser   Ser Leu Pro Gly Pro   Thr Ala Thr Gly Pro   Val Leu Leu
    13310                 13315                 13320

Pro Phe   Thr Leu Asn Phe Thr   Ile Thr Asn Leu Gln   Tyr Glu Glu
    13325                 13330                 13335

Asp Met   Arg Arg Pro Gly Ser   Arg Lys Phe Asn Thr   Thr Glu Arg
    13340                 13345                 13350

Val Leu   Gln Gly Leu Leu Met   Pro Leu Phe Lys Asn   Thr Ser Val
    13355                 13360                 13365

Ser Ser   Leu Tyr Ser Gly Cys   Arg Leu Thr Leu Leu   Arg Pro Glu
    13370                 13375                 13380

Lys Asp   Gly Ala Ala Thr Arg   Val Asp Ala Val Cys   Thr His Arg
    13385                 13390                 13395

Pro Asp   Pro Lys Ser Pro Gly   Leu Asp Arg Glu Arg   Leu Tyr Trp
    13400                 13405                 13410

Lys Leu   Ser Gln Leu Thr His   Gly Ile Thr Glu Leu   Gly Pro Tyr
    13415                 13420                 13425
```

```
Thr Leu   Asp Arg His Ser Leu   Tyr Val Asn Gly Phe   Thr His Gln
    13430                 13435                 13440

Ser Ser   Met Thr Thr Thr Arg   Thr Pro Asp Thr Ser   Thr Met His
    13445                 13450                 13455

Leu Ala   Thr Ser Arg Thr Pro   Ala Ser Leu Ser Gly   Pro Met Thr
    13460                 13465                 13470

Ala Ser   Pro Leu Leu Val Leu   Phe Thr Ile Asn Phe   Thr Ile Thr
    13475                 13480                 13485

Asn Leu   Arg Tyr Glu Glu Asn   Met His His Pro Gly   Ser Arg Lys
    13490                 13495                 13500

Phe Asn   Thr Thr Glu Arg Val   Leu Gln Gly Leu Leu   Arg Pro Val
    13505                 13510                 13515

Phe Lys   Asn Thr Ser Val Gly   Pro Leu Tyr Ser Gly   Cys Arg Leu
    13520                 13525                 13530

Thr Leu   Leu Arg Pro Lys Lys   Asp Gly Ala Ala Thr   Lys Val Asp
    13535                 13540                 13545

Ala Ile   Cys Thr Tyr Arg Pro   Asp Pro Lys Ser Pro   Gly Leu Asp
    13550                 13555                 13560

Arg Glu   Gln Leu Tyr Trp Glu   Leu Ser Gln Leu Thr   His Ser Ile
    13565                 13570                 13575

Thr Glu   Leu Gly Pro Tyr Thr   Leu Asp Arg Asp Ser   Leu Tyr Val
    13580                 13585                 13590

Asn Gly   Phe Thr Gln Arg Ser   Ser Val Pro Thr Thr   Ser Ile Pro
    13595                 13600                 13605

Gly Thr   Pro Thr Val Asp Leu   Gly Thr Ser Gly Thr   Pro Val Ser
    13610                 13615                 13620

Lys Pro   Gly Pro Ser Ala Ala   Ser Pro Leu Leu Val   Leu Phe Thr
    13625                 13630                 13635
```

```
Leu Asn   Phe Thr Ile Thr Asn   Leu Arg Tyr Glu Glu   Asn Met Gln
    13640                 13645                 13650

His Pro   Gly Ser Arg Lys Phe   Asn Thr Thr Glu Arg   Val Leu Gln
    13655                 13660                 13665

Gly Leu   Leu Arg Ser Leu Phe   Lys Ser Thr Ser Val   Gly Pro Leu
    13670                 13675                 13680

Tyr Ser   Gly Cys Arg Leu Thr   Leu Leu Arg Pro Glu   Lys Asp Gly
    13685                 13690                 13695

Thr Ala   Thr Gly Val Asp Ala   Ile Cys Thr His His   Pro Asp Pro
    13700                 13705                 13710

Lys Ser   Pro Arg Leu Asp Arg   Glu Gln Leu Tyr Trp   Glu Leu Ser
    13715                 13720                 13725

Gln Leu   Thr His Asn Ile Thr   Glu Leu Gly Pro Tyr   Ala Leu Asp
    13730                 13735                 13740

Asn Asp   Ser Leu Phe Val Asn   Gly Phe Thr His Arg   Ser Ser Val
    13745                 13750                 13755

Ser Thr   Thr Ser Thr Pro Gly   Thr Pro Thr Val Tyr   Leu Gly Ala
    13760                 13765                 13770

Ser Lys   Thr Pro Ala Ser Ile   Phe Gly Pro Ser Ala   Ala Ser His
    13775                 13780                 13785

Leu Leu   Ile Leu Phe Thr Leu   Asn Phe Thr Ile Thr   Asn Leu Arg
    13790                 13795                 13800

Tyr Glu   Glu Asn Met Trp Pro   Gly Ser Arg Lys Phe   Asn Thr Thr
    13805                 13810                 13815

Glu Arg   Val Leu Gln Gly Leu   Leu Arg Pro Leu Phe   Lys Asn Thr
    13820                 13825                 13830
```

```
Ser Val   Gly Pro Leu Tyr Ser   Gly Cys Arg Leu Thr   Leu Leu Arg
    13835                 13840                 13845

Pro Glu   Lys Asp Gly Glu Ala   Thr Gly Val Asp Ala   Ile Cys Thr
    13850                 13855                 13860

His Arg   Pro Asp Pro Thr Gly   Pro Gly Leu Asp Arg   Glu Gln Leu
    13865                 13870                 13875

Tyr Leu   Glu Leu Ser Gln Leu   Thr His Ser Ile Thr   Glu Leu Gly
    13880                 13885                 13890

Pro Tyr   Thr Leu Asp Arg Asp   Ser Leu Tyr Val Asn   Gly Phe Thr
    13895                 13900                 13905

His Arg   Ser Ser Val Pro Thr   Thr Ser Thr Gly Val   Val Ser Glu
    13910                 13915                 13920

Glu Pro   Phe Thr Leu Asn Phe   Thr Ile Asn Asn Leu   Arg Tyr Met
    13925                 13930                 13935

Ala Asp   Met Gly Gln Pro Gly   Ser Leu Lys Phe Asn   Ile Thr Asp
    13940                 13945                 13950

Asn Val   Met Gln His Leu Leu   Ser Pro Leu Phe Gln   Arg Ser Ser
    13955                 13960                 13965

Leu Gly   Ala Arg Tyr Thr Gly   Cys Arg Val Ile Ala   Leu Arg Ser
    13970                 13975                 13980

Val Lys   Asn Gly Ala Glu Thr   Arg Val Asp Leu Leu   Cys Thr Tyr
    13985                 13990                 13995

Leu Gln   Pro Leu Ser Gly Pro   Gly Leu Pro Ile Lys   Gln Val Phe
    14000                 14005                 14010

His Glu   Leu Ser Gln Gln Thr   His Gly Ile Thr Arg   Leu Gly Pro
    14015                 14020                 14025

Tyr Ser   Leu Asp Lys Asp Ser   Leu Tyr Leu Asn Gly   Tyr Asn Glu
    14030                 14035                 14040
```

```
Pro Gly   Pro Asp Glu Pro Pro   Thr Thr Pro Lys Pro   Ala Thr Thr
    14045                14050                14055

Phe Leu   Pro Pro Leu Ser Glu   Ala Thr Thr Ala Met   Gly Tyr His
    14060                14065                14070

Leu Lys   Thr Leu Thr Leu Asn   Phe Thr Ile Ser Asn   Leu Gln Tyr
    14075                14080                14085

Ser Pro   Asp Met Gly Lys Gly   Ser Ala Thr Phe Asn   Ser Thr Glu
    14090                14095                14100

Gly Val   Leu Gln His Leu Leu   Arg Pro Leu Phe Gln   Lys Ser Ser
    14105                14110                14115

Met Gly   Pro Phe Tyr Leu Gly   Cys Gln Leu Ile Ser   Leu Arg Pro
    14120                14125                14130

Glu Lys   Asp Gly Ala Ala Thr   Gly Val Asp Thr Thr   Cys Thr Tyr
    14135                14140                14145

His Pro   Asp Pro Val Gly Pro   Gly Leu Asp Ile Gln   Gln Leu Tyr
    14150                14155                14160

Trp Glu   Leu Ser Gln Leu Thr   His Gly Val Thr Gln   Leu Gly Phe
    14165                14170                14175

Tyr Val   Leu Asp Arg Asp Ser   Leu Phe Ile Asn Gly   Tyr Ala Pro
    14180                14185                14190

Gln Asn   Leu Ser Ile Arg Gly   Glu Tyr Gln Ile Asn   Phe His Ile
    14195                14200                14205

Val Asn   Trp Asn Leu Ser Asn   Pro Asp Pro Thr Ser   Ser Glu Tyr
    14210                14215                14220

Ile Thr   Leu Leu Arg Asp Ile   Gln Asp Lys Val Thr   Thr Leu Tyr
    14225                14230                14235
```

```
Lys Gly   Ser Gln Leu His Asp   Thr Phe Arg Phe Cys   Leu Val Thr
    14240                 14245                 14250

Asn Leu   Thr Met Asp Ser Val   Leu Val Thr Val Lys   Ala Leu Phe
    14255                 14260                 14265

Ser Ser   Asn Leu Asp Pro Ser   Leu Val Glu Gln Val   Phe Leu Asp
    14270                 14275                 14280

Lys Thr   Leu Asn Ala Ser Phe   His Trp Leu Gly Ser   Thr Tyr Gln
    14285                 14290                 14295

Leu Val   Asp Ile His Val Thr   Glu Met Glu Ser Ser   Val Tyr Gln
    14300                 14305                 14310

Pro Thr   Ser Ser Ser Ser Thr   Gln His Phe Tyr Leu   Asn Phe Thr
    14315                 14320                 14325

Ile Thr   Asn Leu Pro Tyr Ser   Gln Asp Lys Ala Gln   Pro Gly Thr
    14330                 14335                 14340

Thr Asn   Tyr Gln Arg Asn Lys   Arg Asn Ile Glu Asp   Ala Leu Asn
    14345                 14350                 14355

Gln Leu   Phe Arg Asn Ser Ser   Ile Lys Ser Tyr Phe   Ser Asp Cys
    14360                 14365                 14370

Gln Val   Ser Thr Phe Arg Ser   Val Pro Asn Arg His   His Thr Gly
    14375                 14380                 14385

Val Asp   Ser Leu Cys Asn Phe   Ser Pro Leu Ala Arg   Arg Val Asp
    14390                 14395                 14400

Arg Val   Ala Ile Tyr Glu Glu   Phe Leu Arg Met Thr   Arg Asn Gly
    14405                 14410                 14415

Thr Gln   Leu Gln Asn Phe Thr   Leu Asp Arg Ser Ser   Val Leu Val
    14420                 14425                 14430

Asp Gly   Tyr Ser Pro Asn Arg   Asn Glu Pro Leu Thr   Gly Asn Ser
    14435                 14440                 14445
```

Asp Leu Pro Phe Trp Ala Val Ile Leu Ile Gly Leu Ala Gly Leu
14450 14455 14460

Leu Gly Val Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr
14465 14470 14475

Arg Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys
14480 14485 14490

Pro Gly Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln
14495 14500 14505

<210> 149
<211> 690
<212> PRT
<213> Homo sapiens

<400> 149

Met Ala Pro Trp Pro Glu Leu Gly Asp Ala Gln Pro Asn Pro Asp Lys
1 5 10 15

Tyr Leu Glu Gly Ala Ala Gly Gln Gln Pro Thr Ala Pro Asp Lys Ser
20 25 30

Lys Glu Thr Asn Lys Thr Asp Asn Thr Glu Ala Pro Val Thr Lys Ile
35 40 45

Glu Leu Leu Pro Ser Tyr Ser Thr Ala Thr Leu Ile Asp Glu Pro Thr
50 55 60

Glu Val Asp Asp Pro Trp Asn Leu Pro Thr Leu Gln Asp Ser Gly Ile
65 70 75 80

Lys Trp Ser Glu Arg Asp Thr Lys Gly Lys Ile Leu Cys Phe Phe Gln
85 90 95

Gly Ile Gly Arg Leu Ile Leu Leu Leu Gly Phe Leu Tyr Phe Phe Val
100 105 110

Cys Ser Leu Asp Ile Leu Ser Ser Ala Phe Gln Leu Val Gly Gly Lys

```
        115                 120                 125

Met Ala Gly Gln Phe Phe Ser Asn Ser Ser Ile Met Ser Asn Pro Leu
    130                 135                 140

Leu Gly Leu Val Ile Gly Val Leu Val Thr Val Leu Val Gln Ser Ser
145                 150                 155                 160

Ser Thr Ser Thr Ser Ile Val Val Ser Met Val Ser Ser Ser Leu Leu
                165                 170                 175

Thr Val Arg Ala Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly Thr
            180                 185                 190

Ser Ile Thr Asn Thr Ile Val Ala Leu Met Gln Val Gly Asp Arg Ser
        195                 200                 205

Glu Phe Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe Asn
    210                 215                 220

Trp Leu Ser Val Leu Val Leu Leu Pro Val Glu Val Ala Thr His Tyr
225                 230                 235                 240

Leu Glu Ile Ile Thr Gln Leu Ile Val Glu Ser Phe His Phe Lys Asn
                245                 250                 255

Gly Glu Asp Ala Pro Asp Leu Leu Lys Val Ile Thr Lys Pro Phe Thr
            260                 265                 270

Lys Leu Ile Val Gln Leu Asp Lys Lys Val Ile Ser Gln Ile Ala Met
        275                 280                 285

Asn Asp Glu Lys Ala Lys Asn Lys Ser Leu Val Lys Ile Trp Cys Lys
    290                 295                 300

Thr Phe Thr Asn Lys Thr Gln Ile Asn Val Thr Val Pro Ser Thr Ala
305                 310                 315                 320

Asn Cys Thr Ser Pro Ser Leu Cys Trp Thr Asp Gly Ile Gln Asn Trp
                325                 330                 335
```

```
Thr Met Lys Asn Val Thr Tyr Lys Glu Asn Ile Ala Lys Cys Gln His
            340                 345                 350

Ile Phe Val Asn Phe His Leu Pro Asp Leu Ala Val Gly Thr Ile Leu
        355                 360                 365

Leu Ile Leu Ser Leu Leu Val Leu Cys Gly Cys Leu Ile Met Ile Val
    370                 375                 380

Lys Ile Leu Gly Ser Val Leu Lys Gly Gln Val Ala Thr Val Ile Lys
385                 390                 395                 400

Lys Thr Ile Asn Thr Asp Phe Pro Phe Pro Phe Ala Trp Leu Thr Gly
                405                 410                 415

Tyr Leu Ala Ile Leu Val Gly Ala Gly Met Thr Phe Ile Val Gln Ser
            420                 425                 430

Ser Ser Val Phe Thr Ser Ala Leu Thr Pro Leu Ile Gly Ile Gly Val
        435                 440                 445

Ile Thr Ile Glu Arg Ala Tyr Pro Leu Thr Leu Gly Ser Asn Ile Gly
    450                 455                 460

Thr Thr Thr Thr Ala Ile Leu Ala Ala Leu Ala Ser Pro Gly Asn Ala
465                 470                 475                 480

Leu Arg Ser Ser Leu Gln Ile Ala Leu Cys His Phe Phe Phe Asn Ile
                485                 490                 495

Ser Gly Ile Leu Leu Trp Tyr Pro Ile Pro Phe Thr Arg Leu Pro Ile
            500                 505                 510

Arg Met Ala Lys Gly Leu Gly Asn Ile Ser Ala Lys Tyr Arg Trp Phe
        515                 520                 525

Ala Val Phe Tyr Leu Ile Ile Phe Phe Phe Leu Ile Pro Leu Thr Val
    530                 535                 540

Phe Gly Leu Ser Leu Ala Gly Trp Arg Val Leu Val Gly Val Gly Val
```

545 550 555 560

Pro Val Val Phe Ile Ile Ile Leu Val Leu Cys Leu Arg Leu Leu Gln
565 570 575

Ser Arg Cys Pro Arg Val Leu Pro Lys Lys Leu Gln Asn Trp Asn Phe
580 585 590

Leu Pro Leu Trp Met Arg Ser Leu Lys Pro Trp Asp Ala Val Val Ser
595 600 605

Lys Phe Thr Gly Cys Phe Gln Met Arg Cys Cys Cys Cys Cys Arg Val
610 615 620

Cys Cys Arg Ala Cys Cys Leu Leu Cys Asp Cys Pro Lys Cys Cys Arg
625 630 635 640

Cys Ser Lys Cys Cys Glu Asp Leu Glu Glu Ala Gln Glu Gly Gln Asp
645 650 655

Val Pro Val Lys Ala Pro Glu Thr Phe Asp Asn Ile Thr Ile Ser Arg
660 665 670

Glu Ala Gln Gly Glu Val Pro Ala Ser Asp Ser Lys Thr Glu Cys Thr
675 680 685

Ala Leu
690

<210> 150
<211> 510
<212> PRT
<213> Homo sapiens

<400> 150

Met Pro Leu Ser Leu Gly Ala Glu Met Trp Gly Pro Glu Ala Trp Leu
1 5 10 15

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

```
Glu Leu Glu Thr Ser Asp Val Val Thr Val Val Leu Gly Gln Asp Ala
        35                  40                  45

Lys Leu Pro Cys Phe Tyr Arg Gly Asp Ser Gly Glu Gln Val Gly Gln
    50                  55                  60

Val Ala Trp Ala Arg Val Asp Ala Gly Glu Gly Ala Gln Glu Leu Ala
65                  70                  75                  80

Leu Leu His Ser Lys Tyr Gly Leu His Val Ser Pro Ala Tyr Glu Gly
                85                  90                  95

Arg Val Glu Gln Pro Pro Pro Pro Arg Asn Pro Leu Asp Gly Ser Val
            100                 105                 110

Leu Leu Arg Asn Ala Val Gln Ala Asp Glu Gly Glu Tyr Glu Cys Arg
        115                 120                 125

Val Ser Thr Phe Pro Ala Gly Ser Phe Gln Ala Arg Leu Arg Leu Arg
    130                 135                 140

Val Leu Val Pro Pro Leu Pro Ser Leu Asn Pro Gly Pro Ala Leu Glu
145                 150                 155                 160

Glu Gly Gln Gly Leu Thr Leu Ala Ala Ser Cys Thr Ala Glu Gly Ser
                165                 170                 175

Pro Ala Pro Ser Val Thr Trp Asp Thr Glu Val Lys Gly Thr Thr Ser
            180                 185                 190

Ser Arg Ser Phe Lys His Ser Arg Ser Ala Ala Val Thr Ser Glu Phe
        195                 200                 205

His Leu Val Pro Ser Arg Ser Met Asn Gly Gln Pro Leu Thr Cys Val
    210                 215                 220

Val Ser His Pro Gly Leu Leu Gln Asp Gln Arg Ile Thr His Ile Leu
225                 230                 235                 240

His Val Ser Phe Leu Ala Glu Ala Ser Val Arg Gly Leu Glu Asp Gln
                245                 250                 255
```

```
Asn Leu Trp His Ile Gly Arg Glu Gly Ala Met Leu Lys Cys Leu Ser
            260                 265                 270

Glu Gly Gln Pro Pro Pro Ser Tyr Asn Trp Thr Arg Leu Asp Gly Pro
        275                 280                 285

Leu Pro Ser Gly Val Arg Val Asp Gly Asp Thr Leu Gly Phe Pro Pro
    290                 295                 300

Leu Thr Thr Glu His Ser Gly Ile Tyr Val Cys His Val Ser Asn Glu
305                 310                 315                 320

Phe Ser Ser Arg Asp Ser Gln Val Thr Val Asp Val Leu Asp Pro Gln
                325                 330                 335

Glu Asp Ser Gly Lys Gln Val Asp Leu Val Ser Ala Ser Val Val Val
            340                 345                 350

Val Gly Val Ile Ala Ala Leu Leu Phe Cys Leu Leu Val Val Val Val
        355                 360                 365

Val Leu Met Ser Arg Tyr His Arg Arg Lys Ala Gln Gln Met Thr Gln
    370                 375                 380

Lys Tyr Glu Glu Glu Leu Thr Leu Thr Arg Glu Asn Ser Ile Arg Arg
385                 390                 395                 400

Leu His Ser His His Thr Asp Pro Arg Ser Gln Pro Glu Glu Ser Val
                405                 410                 415

Gly Leu Arg Ala Glu Gly His Pro Asp Ser Leu Lys Asp Asn Ser Ser
            420                 425                 430

Cys Ser Val Met Ser Glu Glu Pro Glu Gly Arg Ser Tyr Ser Thr Leu
        435                 440                 445

Thr Thr Val Arg Glu Ile Glu Thr Gln Thr Glu Leu Leu Ser Pro Gly
    450                 455                 460
```

```
Ser Gly Arg Ala Glu Glu Glu Glu Asp Gln Asp Glu Gly Ile Lys Gln
465                 470                 475                 480

Ala Met Asn His Phe Val Gln Glu Asn Gly Thr Leu Arg Ala Lys Pro
                485                 490                 495

Thr Gly Asn Gly Ile Tyr Ile Asn Gly Arg Gly His Leu Val
            500                 505                 510
```

<210> 151
<211> 764
<212> PRT
<213> Homo sapiens

<400> 151

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Leu Gly Ala Thr Gly His Asn Phe Thr Leu His Leu Arg Lys Asn Arg
1               5                   10                  15

Asp Leu Leu Gly Ser Gly Tyr Thr Glu Thr Tyr Thr Ala Ala Asn Gly
            20                  25                  30

Ser Glu Val Thr Glu Gln Pro Arg Gly Gln Asp His Cys Phe Tyr Gln
        35                  40                  45

Gly His Val Glu Gly Tyr Pro Asp Ser Ala Ala Ser Leu Ser Thr Cys
    50                  55                  60

Ala Gly Leu Arg Gly Phe Phe Gln Val Gly Ser Asp Leu His Leu Ile
65                  70                  75                  80

Glu Pro Leu Asp Glu Gly Gly Glu Gly Gly Arg His Ala Val Tyr Gln
                85                  90                  95

Ala Glu His Leu Leu Gln Thr Ala Gly Thr Cys Gly Val Ser Asp Asp
            100                 105                 110

Ser Leu Gly Ser Leu Leu Gly Pro Arg Thr Ala Ala Val Phe Arg Pro
        115                 120                 125

Arg Pro Gly Asp Ser Leu Pro Ser Arg Glu Thr Arg Tyr Val Glu Leu
    130                 135                 140
```

```
Tyr Val Val Val Asp Asn Ala Glu Phe Gln Met Leu Gly Ser Glu Ala
145                 150                 155                 160

Ala Val Arg His Arg Val Leu Glu Val Val Asn His Val Asp Lys Leu
                165                 170                 175

Tyr Gln Lys Leu Asn Phe Arg Val Val Leu Val Gly Leu Glu Ile Trp
            180                 185                 190

Asn Ser Gln Asp Arg Phe His Val Ser Pro Asp Pro Ser Val Thr Leu
        195                 200                 205

Glu Asn Leu Leu Thr Trp Gln Ala Arg Gln Arg Thr Arg Arg His Leu
    210                 215                 220

His Asp Asn Val Gln Leu Ile Thr Gly Val Asp Phe Thr Gly Thr Thr
225                 230                 235                 240

Val Gly Phe Ala Arg Val Ser Ala Met Cys Ser His Ser Ser Gly Ala
                245                 250                 255

Val Asn Gln Asp His Ser Lys Asn Pro Val Gly Val Ala Cys Thr Met
            260                 265                 270

Ala His Glu Met Gly His Asn Leu Gly Met Asp His Asp Glu Asn Val
        275                 280                 285

Gln Gly Cys Arg Cys Gln Glu Arg Phe Glu Ala Gly Arg Cys Ile Met
    290                 295                 300

Ala Gly Ser Ile Gly Ser Ser Phe Pro Arg Met Phe Ser Asp Cys Ser
305                 310                 315                 320

Gln Ala Tyr Leu Glu Ser Phe Leu Glu Arg Pro Gln Ser Val Cys Leu
                325                 330                 335

Ala Asn Ala Pro Asp Leu Ser His Leu Val Gly Gly Pro Val Cys Gly
            340                 345                 350

Asn Leu Phe Val Glu Arg Gly Glu Gln Cys Asp Cys Gly Pro Pro Glu
```

```
        355                 360                 365

Asp Cys Arg Asn Arg Cys Cys Asn Ser Thr Thr Cys Gln Leu Ala Glu
    370                 375                 380

Gly Ala Gln Cys Ala His Gly Thr Cys Cys Gln Glu Cys Lys Val Lys
385                 390                 395                 400

Pro Ala Gly Glu Leu Cys Arg Pro Lys Lys Asp Met Cys Asp Leu Glu
                405                 410                 415

Glu Phe Cys Asp Gly Arg His Pro Glu Cys Pro Glu Asp Ala Phe Gln
            420                 425                 430

Glu Asn Gly Thr Pro Cys Ser Gly Gly Tyr Cys Tyr Asn Gly Ala Cys
        435                 440                 445

Pro Thr Leu Ala Gln Gln Cys Gln Ala Phe Trp Gly Pro Gly Gly Gln
    450                 455                 460

Ala Ala Glu Glu Ser Cys Phe Ser Tyr Asp Ile Leu Pro Gly Cys Lys
465                 470                 475                 480

Ala Ser Arg Tyr Arg Ala Asp Met Cys Gly Val Leu Gln Cys Lys Gly
                485                 490                 495

Gly Gln Gln Pro Leu Gly Arg Ala Ile Cys Ile Val Asp Val Cys His
            500                 505                 510

Ala Leu Thr Thr Glu Asp Gly Thr Ala Tyr Glu Pro Val Pro Glu Gly
        515                 520                 525

Thr Arg Cys Gly Pro Glu Lys Val Cys Trp Lys Gly Arg Cys Gln Asp
    530                 535                 540

Leu His Val Tyr Arg Ser Ser Asn Cys Ser Ala Gln Cys His Asn His
545                 550                 555                 560

Gly Val Cys Asn His Lys Gln Glu Cys His Cys His Ala Gly Trp Ala
                565                 570                 575
```

```
Pro Pro His Cys Ala Lys Leu Leu Thr Glu Val His Ala Ala Ser Gly
            580                 585                 590

Ser Leu Pro Val Phe Val Val Val Val Leu Val Leu Leu Ala Val Val
        595                 600                 605

Leu Val Thr Leu Ala Gly Ile Ile Val Tyr Arg Lys Ala Arg Ser Arg
    610                 615                 620

Ile Leu Ser Arg Asn Val Ala Pro Lys Thr Thr Met Gly Arg Ser Asn
625                 630                 635                 640

Pro Leu Phe His Gln Ala Ala Ser Arg Val Pro Ala Lys Gly Gly Ala
                645                 650                 655

Pro Ala Pro Ser Arg Gly Pro Gln Glu Leu Val Pro Thr Thr His Pro
            660                 665                 670

Gly Gln Pro Ala Arg His Pro Ala Ser Ser Val Ala Leu Lys Arg Pro
        675                 680                 685

Pro Pro Ala Pro Pro Val Thr Val Ser Ser Pro Pro Phe Pro Val Pro
    690                 695                 700

Val Tyr Thr Arg Gln Ala Pro Lys Gln Val Ile Lys Pro Thr Phe Ala
705                 710                 715                 720

Pro Pro Val Pro Pro Val Lys Pro Gly Ala Gly Ala Ala Asn Pro Gly
                725                 730                 735

Pro Ala Glu Gly Ala Val Gly Pro Lys Val Ala Leu Lys Pro Pro Ile
            740                 745                 750

Gln Arg Lys Gln Gly Ala Gly Ala Pro Thr Ala Pro
        755                 760
```

<210> 152
<211> 819
<212> PRT
<213> Homo sapiens

<400> 152

```
Met Gly Ser Gly Ala Arg Phe Pro Ser Gly Thr Leu Arg Val Arg Trp
1               5                  10                  15

Leu Leu Leu Leu Gly Leu Val Gly Pro Val Leu Gly Ala Ala Arg Pro
            20                  25                  30

Gly Phe Gln Gln Thr Ser His Leu Ser Ser Tyr Glu Ile Ile Thr Pro
        35                  40                  45

Trp Arg Leu Thr Arg Glu Arg Arg Glu Ala Pro Arg Pro Tyr Ser Lys
    50                  55                  60

Gln Val Ser Tyr Val Ile Gln Ala Glu Gly Lys Glu His Ile Ile His
65                  70                  75                  80

Leu Glu Arg Asn Lys Asp Leu Leu Pro Glu Asp Phe Val Val Tyr Thr
                85                  90                  95

Tyr Asn Lys Glu Gly Thr Leu Ile Thr Asp His Pro Asn Ile Gln Asn
            100                 105                 110

His Cys His Tyr Arg Gly Tyr Val Glu Gly Val His Asn Ser Ser Ile
        115                 120                 125

Ala Leu Ser Asp Cys Phe Gly Leu Arg Gly Leu Leu His Leu Glu Asn
    130                 135                 140

Ala Ser Tyr Gly Ile Glu Pro Leu Gln Asn Ser Ser His Phe Glu His
145                 150                 155                 160

Ile Ile Tyr Arg Met Asp Asp Val Tyr Lys Glu Pro Leu Lys Cys Gly
                165                 170                 175

Val Ser Asn Lys Asp Ile Glu Lys Glu Thr Ala Lys Asp Glu Glu Glu
            180                 185                 190

Glu Pro Pro Ser Met Thr Gln Leu Leu Arg Arg Arg Arg Ala Val Leu
        195                 200                 205
```

```
Pro Gln Thr Arg Tyr Val Glu Leu Phe Ile Val Val Asp Lys Glu Arg
    210                 215                 220

Tyr Asp Met Met Gly Arg Asn Gln Thr Ala Val Arg Glu Glu Met Ile
225                 230                 235                 240

Leu Leu Ala Asn Tyr Leu Asp Ser Met Tyr Ile Met Leu Asn Ile Arg
                245                 250                 255

Ile Val Leu Val Gly Leu Glu Ile Trp Thr Asn Gly Asn Leu Ile Asn
            260                 265                 270

Ile Val Gly Gly Ala Gly Asp Val Leu Gly Asn Phe Val Gln Trp Arg
        275                 280                 285

Glu Lys Phe Leu Ile Thr Arg Arg Arg His Asp Ser Ala Gln Leu Val
    290                 295                 300

Leu Lys Lys Gly Phe Gly Gly Thr Ala Gly Met Ala Phe Val Gly Thr
305                 310                 315                 320

Val Cys Ser Arg Ser His Ala Gly Gly Ile Asn Val Phe Gly Gln Ile
                325                 330                 335

Thr Val Glu Thr Phe Ala Ser Ile Val Ala His Glu Leu Gly His Asn
            340                 345                 350

Leu Gly Met Asn His Asp Asp Gly Arg Asp Cys Ser Cys Gly Ala Lys
        355                 360                 365

Ser Cys Ile Met Asn Ser Gly Ala Ser Gly Ser Arg Asn Phe Ser Ser
    370                 375                 380

Cys Ser Ala Glu Asp Phe Glu Lys Leu Thr Leu Asn Lys Gly Gly Asn
385                 390                 395                 400

Cys Leu Leu Asn Ile Pro Lys Pro Asp Glu Ala Tyr Ser Ala Pro Ser
                405                 410                 415

Cys Gly Asn Lys Leu Val Asp Ala Gly Glu Glu Cys Asp Cys Gly Thr
            420                 425                 430
```

```
Pro Lys Glu Cys Glu Leu Asp Pro Cys Cys Glu Gly Ser Thr Cys Lys
        435                 440                 445

Leu Lys Ser Phe Ala Glu Cys Ala Tyr Gly Asp Cys Cys Lys Asp Cys
    450                 455                 460

Arg Phe Leu Pro Gly Gly Thr Leu Cys Arg Gly Lys Thr Ser Glu Cys
465                 470                 475                 480

Asp Val Pro Glu Tyr Cys Asn Gly Ser Ser Gln Phe Cys Gln Pro Asp
                485                 490                 495

Val Phe Ile Gln Asn Gly Tyr Pro Cys Gln Asn Asn Lys Ala Tyr Cys
            500                 505                 510

Tyr Asn Gly Met Cys Gln Tyr Tyr Asp Ala Gln Cys Gln Val Ile Phe
        515                 520                 525

Gly Ser Lys Ala Lys Ala Ala Pro Lys Asp Cys Phe Ile Glu Val Asn
    530                 535                 540

Ser Lys Gly Asp Arg Phe Gly Asn Cys Gly Phe Ser Gly Asn Glu Tyr
545                 550                 555                 560

Lys Lys Cys Ala Thr Gly Asn Ala Leu Cys Gly Lys Leu Gln Cys Glu
                565                 570                 575

Asn Val Gln Glu Ile Pro Val Phe Gly Ile Val Pro Ala Ile Ile Gln
            580                 585                 590

Thr Pro Ser Arg Gly Thr Lys Cys Trp Gly Val Asp Phe Gln Leu Gly
        595                 600                 605

Ser Asp Val Pro Asp Pro Gly Met Val Asn Glu Gly Thr Lys Cys Gly
    610                 615                 620

Ala Gly Lys Ile Cys Arg Asn Phe Gln Cys Val Asp Ala Ser Val Leu
625                 630                 635                 640
```

```
Asn Tyr Asp Cys Asp Val Gln Lys Lys Cys His Gly His Gly Val Cys
                645                 650                 655

Asn Ser Asn Lys Asn Cys His Cys Glu Asn Gly Trp Ala Pro Pro Asn
            660                 665                 670

Cys Glu Thr Lys Gly Tyr Gly Gly Ser Val Asp Ser Gly Pro Thr Tyr
        675                 680                 685

Asn Glu Met Asn Thr Ala Leu Arg Asp Gly Leu Leu Val Phe Phe Phe
    690                 695                 700

Leu Ile Val Pro Leu Ile Val Cys Ala Ile Phe Ile Phe Ile Lys Arg
705                 710                 715                 720

Asp Gln Leu Trp Arg Ser Tyr Phe Arg Lys Lys Arg Ser Gln Thr Tyr
                725                 730                 735

Glu Ser Asp Gly Lys Asn Gln Ala Asn Pro Ser Arg Gln Pro Gly Ser
            740                 745                 750

Val Pro Arg His Val Ser Pro Val Thr Pro Pro Arg Glu Val Pro Ile
        755                 760                 765

Tyr Ala Asn Arg Phe Ala Val Pro Thr Tyr Ala Ala Lys Gln Pro Gln
    770                 775                 780

Gln Phe Pro Ser Arg Pro Pro Pro Pro Gln Pro Lys Val Ser Ser Gln
785                 790                 795                 800

Gly Asn Leu Ile Pro Ala Arg Pro Ala Pro Ala Pro Pro Leu Tyr Ser
                805                 810                 815

Ser Leu Thr
```

<210> 153
<211> 710
<212> PRT
<213> Homo sapiens

<400> 153

```
Met Gly Gly Lys Gln Arg Asp Glu Asp Asp Glu Ala Tyr Gly Lys Pro
1               5                  10                  15

Val Lys Tyr Asp Pro Ser Phe Arg Gly Pro Ile Lys Asn Arg Ser Cys
            20                  25                  30

Thr Asp Val Ile Cys Cys Val Leu Phe Leu Leu Phe Ile Leu Gly Tyr
        35                  40                  45

Ile Val Val Gly Ile Val Ala Trp Leu Tyr Gly Asp Pro Arg Gln Val
    50                  55                  60

Leu Tyr Pro Arg Asn Ser Thr Gly Ala Tyr Cys Gly Met Gly Glu Asn
65                  70                  75                  80

Lys Asp Lys Pro Tyr Leu Leu Tyr Phe Asn Ile Phe Ser Cys Ile Leu
                85                  90                  95

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

Pro Gln Val Cys Val Ser Ser Cys Pro Glu Asp Pro Trp Thr Val Gly
        115                 120                 125

Lys Asn Glu Phe Ser Gln Thr Val Gly Glu Val Phe Tyr Thr Lys Asn
    130                 135                 140

Arg Asn Phe Cys Leu Pro Gly Val Pro Trp Asn Met Thr Val Ile Thr
145                 150                 155                 160

Ser Leu Gln Gln Glu Leu Cys Pro Ser Phe Leu Leu Pro Ser Ala Pro
                165                 170                 175

Ala Leu Gly Arg Cys Phe Pro Trp Thr Asn Val Thr Pro Pro Ala Leu
            180                 185                 190

Pro Gly Ile Thr Asn Asp Thr Thr Ile Gln Gln Gly Ile Ser Gly Leu
        195                 200                 205

Ile Asp Ser Leu Asn Ala Arg Asp Ile Ser Val Lys Ile Phe Glu Asp
```

```
    210                 215                 220

Phe Ala Gln Ser Trp Tyr Trp Ile Leu Val Ala Leu Gly Val Ala Leu
225                 230                 235                 240

Val Leu Ser Leu Leu Phe Ile Leu Leu Leu Arg Leu Val Ala Gly Pro
                245                 250                 255

Leu Val Leu Val Leu Ile Leu Gly Val Leu Gly Val Leu Ala Tyr Gly
            260                 265                 270

Ile Tyr Tyr Cys Trp Glu Glu Tyr Arg Val Leu Arg Asp Lys Gly Ala
        275                 280                 285

Ser Ile Ser Gln Leu Gly Phe Thr Thr Asn Leu Ser Ala Tyr Gln Ser
    290                 295                 300

Val Gln Glu Thr Trp Leu Ala Ala Leu Ile Val Leu Ala Val Leu Glu
305                 310                 315                 320

Ala Ile Leu Leu Leu Met Leu Ile Phe Leu Arg Gln Arg Ile Arg Ile
                325                 330                 335

Ala Ile Ala Leu Leu Lys Glu Ala Ser Lys Ala Val Gly Gln Met Met
            340                 345                 350

Ser Thr Met Phe Tyr Pro Leu Val Thr Phe Val Leu Leu Leu Ile Cys
        355                 360                 365

Ile Ala Tyr Trp Ala Met Thr Ala Leu Tyr Leu Ala Thr Ser Gly Gln
    370                 375                 380

Pro Gln Tyr Val Leu Trp Ala Ser Asn Ile Ser Ser Pro Gly Cys Glu
385                 390                 395                 400

Lys Val Pro Ile Asn Thr Ser Cys Asn Pro Thr Ala His Leu Val Asn
                405                 410                 415

Ser Ser Cys Pro Gly Leu Met Cys Val Phe Gln Gly Tyr Ser Ser Lys
            420                 425                 430
```

```
Gly Leu Ile Gln Arg Ser Val Phe Asn Leu Gln Ile Tyr Gly Val Leu
        435                 440                 445

Gly Leu Phe Trp Thr Leu Asn Trp Val Leu Ala Leu Gly Gln Cys Val
    450                 455                 460

Leu Ala Gly Ala Phe Ala Ser Phe Tyr Trp Ala Phe His Lys Pro Gln
465                 470                 475                 480

Asp Ile Pro Thr Phe Pro Leu Ile Ser Ala Phe Ile Arg Thr Leu Arg
                485                 490                 495

Tyr His Thr Gly Ser Leu Ala Phe Gly Ala Leu Ile Leu Thr Leu Val
            500                 505                 510

Gln Ile Ala Arg Val Ile Leu Glu Tyr Ile Asp His Lys Leu Arg Gly
        515                 520                 525

Val Gln Asn Pro Val Ala Arg Cys Ile Met Cys Cys Phe Lys Cys Cys
    530                 535                 540

Leu Trp Cys Leu Glu Lys Phe Ile Lys Phe Leu Asn Arg Asn Ala Tyr
545                 550                 555                 560

Ile Met Ile Ala Ile Tyr Gly Lys Asn Phe Cys Val Ser Ala Lys Asn
                565                 570                 575

Ala Phe Met Leu Leu Met Arg Asn Ile Val Arg Val Val Val Leu Asp
            580                 585                 590

Lys Val Thr Asp Leu Leu Leu Phe Phe Gly Lys Leu Leu Val Val Gly
        595                 600                 605

Gly Val Gly Val Leu Ser Phe Phe Phe Phe Ser Gly Arg Ile Pro Gly
    610                 615                 620

Leu Gly Lys Asp Phe Lys Ser Pro His Leu Asn Tyr Tyr Trp Leu Pro
625                 630                 635                 640

Ile Met Thr Ser Ile Leu Gly Ala Tyr Val Ile Ala Ser Gly Phe Phe
```

645 650 655

Ser Val Phe Gly Met Cys Val Asp Thr Leu Phe Leu Cys Phe Leu Glu
660 665 670

Asp Leu Glu Arg Asn Asn Gly Ser Leu Asp Arg Pro Tyr Tyr Met Ser
675 680 685

Lys Ser Leu Leu Lys Ile Leu Gly Lys Lys Asn Glu Ala Pro Pro Asp
690 695 700

Asn Lys Lys Arg Lys Lys
705 710

<210> 154
<211> 333
<212> PRT
<213> Homo sapiens

<400> 154

Met Ala Cys Ser Arg Pro Pro Ser Gln Cys Glu Pro Thr Ser Leu Pro
1 5 10 15

Pro Gly Pro Pro Ala Gly Arg Arg His Leu Pro Leu Ser Arg Arg Arg
20 25 30

Arg Glu Met Ser Ser Asn Lys Glu Gln Arg Ser Ala Val Phe Val Ile
35 40 45

Leu Phe Ala Leu Ile Thr Ile Leu Ile Leu Tyr Ser Ser Asn Ser Ala
50 55 60

Asn Glu Val Phe His Tyr Gly Ser Leu Arg Gly Arg Ser Arg Arg Pro
65 70 75 80

Val Asn Leu Lys Lys Trp Ser Ile Thr Asp Gly Tyr Val Pro Ile Leu
85 90 95

Gly Asn Lys Thr Leu Pro Ser Arg Cys His Gln Cys Val Ile Val Ser
100 105 110

```
Ser Ser Ser His Leu Leu Gly Thr Lys Leu Gly Pro Glu Ile Glu Arg
        115                 120                 125

Ala Glu Cys Thr Ile Arg Met Asn Asp Ala Pro Thr Thr Gly Tyr Ser
    130                 135                 140

Ala Asp Val Gly Asn Lys Thr Thr Tyr Arg Val Val Ala His Ser Ser
145                 150                 155                 160

Val Phe Arg Val Leu Arg Arg Pro Gln Glu Phe Val Asn Arg Thr Pro
                165                 170                 175

Glu Thr Val Phe Ile Phe Trp Gly Pro Pro Ser Lys Met Gln Lys Pro
            180                 185                 190

Gln Gly Ser Leu Val Arg Val Ile Gln Arg Ala Gly Leu Val Phe Pro
        195                 200                 205

Asn Met Glu Ala Tyr Ala Val Ser Pro Gly Arg Met Arg Gln Phe Asp
    210                 215                 220

Asp Leu Phe Arg Gly Glu Thr Gly Lys Asp Arg Glu Lys Ser His Ser
225                 230                 235                 240

Trp Leu Ser Thr Gly Trp Phe Thr Met Val Ile Ala Val Glu Leu Cys
                245                 250                 255

Asp His Val His Val Tyr Gly Met Val Pro Pro Asn Tyr Cys Ser Gln
            260                 265                 270

Arg Pro Arg Leu Gln Arg Met Pro Tyr His Tyr Tyr Glu Pro Lys Gly
        275                 280                 285

Pro Asp Glu Cys Val Thr Tyr Ile Gln Asn Glu His Ser Arg Lys Gly
    290                 295                 300

Asn His His Arg Phe Ile Thr Glu Lys Arg Val Phe Ser Ser Trp Ala
305                 310                 315                 320

Gln Leu Tyr Gly Ile Thr Phe Ser His Pro Ser Trp Thr
                325                 330
```

<210> 155
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 155

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

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

Trp Met Gln Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Asp Trp Ile
35 40 45

Gly Ala Ile Tyr Pro Gly Asp Gly Asn Thr Arg Tyr Thr His Lys Phe
50 55 60

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

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

Ala Arg Gly Glu Gly Asn Tyr Ala Trp Phe Ala Tyr Trp Gly Gln Gly
100 105 110

Thr Thr Val Thr Val Ser Ser Ala
115 120

<210> 156
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 156

Gly Tyr Thr Phe Thr Asn Tyr
1 5

<210> 157
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 157

Tyr Pro Gly Asp Gly Asn
1 5

<210> 158
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 158

Gly Glu Gly Asn Tyr Ala Trp Phe Ala Tyr
1 5 10

<210> 159
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 159

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

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

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

Tyr Asn Ala Lys Thr Leu Ala Gly Gly Val Ser Ser Arg Phe Ser Gly
50 55 60

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

Glu Asp Phe Gly Ile Tyr Tyr Cys Gln His His Tyr Gly Ile Leu Pro
85 90 95

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

<210> 160
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 160

Glu Asn Ile Tyr Ser Tyr Leu Ala
1 5

<210> 161
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 161

Asn Ala Lys Thr Leu Ala Gly
1 5

<210> 162
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 162

Gln His His Tyr Gly Ile Leu Pro Thr
1 5

<210> 163
<211> 117
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 163

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

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

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

Val Gly Tyr Ile Ser Tyr Ser Gly Tyr Thr Thr Tyr Asn Pro Ser Leu
50 55 60

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

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

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

Thr Val Ser Ser Ala
115

<210> 164
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 164

Gly Tyr Ser Ile Thr Asn Asp Tyr
1 5

<210> 165
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 165

Ser Tyr Ser Gly Tyr
1 5

<210> 166
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 166

Trp Thr Ser Gly Leu Asp Tyr
1 5

<210> 167
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 167

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

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Asp Leu Ile His Asn Trp
20 25 30

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

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

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

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

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

<210> 168
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 168

Asp Leu Ile His Asn Trp Leu Ala
1 5

<210> 169
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 169

Gly Ala Thr Ser Leu Glu Thr
1 5

<210> 170
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 170

Gln Gln Tyr Trp Thr Thr Pro Phe Thr
1 5

<210> 171
<211> 121
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 171

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

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Asp Phe
20 25 30

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

Ala Thr Ile Gly Arg Val Ala Phe His Thr Tyr Tyr Pro Asp Ser Met
50 55 60

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

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

Ala Arg His Arg Gly Phe Asp Val Gly His Phe Asp Phe Trp Gly Gln
100 105 110

Gly Thr Leu Val Thr Val Ser Ser Ala
115 120

<210> 172
<211> 7
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 172

Gly Phe Ser Phe Ser Asp Phe
1 5

<210> 173
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 173

Gly Arg Val Ala Phe His
1 5

<210> 174
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 174

His Arg Gly Phe Asp Val Gly His Phe Asp Phe
1 5 10

<210> 175
<211> 113
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 175

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

Asp Arg Val Thr Ile Thr Cys Arg Ser Ser Glu Thr Leu Val His Ser
20 25 30

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

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

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

Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly
85 90 95

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

Arg

<210> 176
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 176

Glu Thr Leu Val His Ser Ser Gly Asn Thr Tyr Leu Glu
1 5 10

<210> 177
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 177

Arg Val Ser Asn Arg Phe Ser
1 5

<210> 178
<211> 9

<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 178

Phe Gln Gly Ser Phe Asn Pro Leu Thr
1 5

<210> 179
<211> 118
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 179

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

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

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

Ser Tyr Ile Ser Ser Ser Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Arg Ala Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser Ala
115

<210> 180
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 180

Gly Phe Thr Phe Ser Ser Tyr
1 5

<210> 181
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 181

Ser Ser Ser Ser Ser Thr
1 5

<210> 182
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 182

Ala Tyr Tyr Tyr Gly Met Asp Val
1 5

<210> 183
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 183

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

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

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

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

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

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

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

<210> 184
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 184

Gln Gly Ile Ser Gly Trp Leu Ala
1 5

<210> 185
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 185

Ala Ala Ser Thr Leu Gln Ser
1 5

<210> 186
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 186

Gln Gln Ala Asn Ser Phe Pro Pro Thr
1 5

<210> 187
<211> 122
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 187

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

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

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

Ser Tyr Ile Ser Arg Ser Gly Arg Asp Ile Tyr Tyr Ala Asp Ser Val
50 55 60

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

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

Ala Gly Thr Val Thr Thr Tyr Tyr Tyr Asp Phe Gly Met Asp Val Trp
100 105 110

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

<210> 188
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 188

Gly Phe Thr Phe Ser Arg Tyr
1 5

<210> 189
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 189

Ser Arg Ser Gly Arg Asp
1 5

<210> 190
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 190

Thr Val Thr Thr Tyr Tyr Tyr Asp Phe Gly Met Asp Val
1 5 10

<210> 191
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 191

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

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

Leu Ala Trp Tyr Gln Gln Lys Pro Glu Lys Ala Pro Lys Ser Leu Ile
        35                  40                  45

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

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

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

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


<210>  192
<211>  8
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic peptide

<400>  192

Gln Gly Ile Ser Ser Trp Leu Ala
1               5


<210>  193
<211>  7
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic peptide

<400>  193

Ala Ala Ser Ser Leu Gln Ser
1               5
```

<210> 194
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 194

Gln Gln Tyr Asn Ser Tyr Pro Pro Thr
1 5

<210> 195
<211> 125
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 195

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

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

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

Ala Val Met Ser Tyr Asp Gly Ser Lys Lys Phe Tyr Thr Asp Ser Val
50 55 60

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

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

Ala Arg Asp Gly Gly Asp Tyr Val Arg Tyr His Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala
115 120 125

<210> 196
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 196

Gly Phe Thr Phe Ser Ser Tyr
1 5

<210> 197
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 197

Ser Tyr Asp Gly Ser Lys
1 5

<210> 198
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 198

Asp Gly Gly Asp Tyr Val Arg Tyr His Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> 199
<211> 108
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 199

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

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

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

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

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

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

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

<210> 200
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 200

Gln Gly Ile Ser Tyr Tyr Leu Ala
1 5

<210> 201
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 201

Asp Thr Ser Ser Leu Gln Ser
1 5

<210> 202
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 202

Gln Arg Tyr Asp Ser Ala Pro Leu Thr
1 5

<210> 203
<211> 706
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 203

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

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

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

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
50 55 60

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

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
85 90 95

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
100 105 110

```
Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

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

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

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

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320
```

```
Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Arg Val Tyr
            340                 345                 350

Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

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

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

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

Gly Ser Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Met Thr Gln Ser
    450                 455                 460

Pro Ser Ser Val Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys
465                 470                 475                 480

Arg Ala Ser Gln Gly Ile Ser Ser Trp Leu Ala Trp Tyr Gln Gln Lys
                485                 490                 495

Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Ala Ala Ser Ser Leu Gln
            500                 505                 510

Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe
        515                 520                 525

Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr
    530                 535                 540
```

```
Cys Gln Gln Gly Val Ser Phe Pro Arg Thr Phe Gly Cys Gly Thr Lys
545                 550                 555                 560

Val Glu Ile Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
                565                 570                 575

Gly Gly Ser Gly Gly Gly Gly Ser Glu Val Gln Leu Val Glu Ser Gly
            580                 585                 590

Gly Gly Leu Val Lys Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala
        595                 600                 605

Ser Gly Phe Thr Phe Ser Ser Tyr Ser Met Asn Trp Val Arg Gln Ala
    610                 615                 620

Pro Gly Lys Cys Leu Glu Trp Val Ser Ser Ile Ser Ser Ser Ser Ser
625                 630                 635                 640

Tyr Ile Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg
                645                 650                 655

Asp Asn Ala Lys Asn Ser Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala
            660                 665                 670

Glu Asp Thr Ala Val Tyr Tyr Cys Ala Arg Gly Ala Pro Met Gly Ala
        675                 680                 685

Ala Ala Gly Trp Phe Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val
    690                 695                 700

Ser Ser
705
```

<210> 204
<211> 449
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 204

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

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

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

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
    50                  55                  60

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

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
                85                  90                  95

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

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

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205
```

```
Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

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

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Cys
            340                 345                 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Glu Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Trp Leu Thr Val Asp
                405                 410                 415

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

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

Gly

<210> 205
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 205

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

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

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

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

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

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

Thr Phe Gly Cys Gly Thr Lys Val Glu Ile Lys Gly Gly Gly Gly Ser
100 105 110

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu
115 120 125

Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly Ser
130 135 140

```
Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr Ser
145                 150                 155                 160

Met Asn Trp Val Arg Gln Ala Pro Gly Lys Cys Leu Glu Trp Val Ser
                165                 170                 175

Ser Ile Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val Lys
            180                 185                 190

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr Leu
        195                 200                 205

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
    210                 215                 220

Arg Gly Ala Pro Met Gly Ala Ala Ala Gly Trp Phe Asp Pro Trp Gly
225                 230                 235                 240

Gln Gly Thr Leu Val Thr Val Ser Ser
                245
```

<210> 206
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic peptide

<400> 206

```
Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1               5                   10                  15

Gly Gly Gly Ser
            20
```

<210> 207
<211> 8
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic peptide

<400> 207

Ser Gly Ser Gly Gly Gly Gly Ser
1 5

<210> 208
<211> 253
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 208

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
20 25 30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn
85 90 95

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

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
115 120 125

Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu
130 135 140

```
Leu Val Arg Pro Gly Thr Ser Val Lys Ile Ser Cys Lys Ala Ser Gly
145                 150                 155                 160

Tyr Ala Phe Thr Asn Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly
                165                 170                 175

His Cys Leu Glu Trp Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile
            180                 185                 190

His Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys
        195                 200                 205

Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp
    210                 215                 220

Ser Ala Val Tyr Phe Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met
225                 230                 235                 240

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
                245                 250


<210>  209
<211>  253
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Description of Artificial Sequence: Synthetic polypeptide

<400>  209

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

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

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Cys Leu Glu Trp
        35                  40                  45

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
    50                  55                  60
```

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

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
                85                  90                  95

Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met
    130                 135                 140

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

Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys
                165                 170                 175

Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
            180                 185                 190

Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe
        195                 200                 205

Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val
    210                 215                 220

Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn Asp Tyr Ser Tyr
225                 230                 235                 240

Pro Leu Thr Phe Gly Cys Gly Thr Lys Leu Glu Ile Lys
                245                 250
```

<210> 210
<211> 482
<212> PRT
<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 210

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn
                85                  90                  95

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

Lys Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
        115                 120                 125

Gly Gly Gly Gly Ser Glu Val Gln Leu Leu Glu Gln Ser Gly Ala Glu
    130                 135                 140

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

Tyr Ala Phe Thr Asn Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly
                165                 170                 175

His Cys Leu Glu Trp Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile
            180                 185                 190

His Tyr Asn Glu Lys Phe Lys Gly Lys Ala Thr Leu Thr Ala Asp Lys
        195                 200                 205
```

```
Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp
    210                 215                 220

Ser Ala Val Tyr Phe Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met
225                 230                 235                 240

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Gly Ala Ser
                245                 250                 255

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
            260                 265                 270

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

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
    290                 295                 300

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
305                 310                 315                 320

His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
                325                 330                 335

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
            340                 345                 350

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
        355                 360                 365

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Arg Val
    370                 375                 380

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
385                 390                 395                 400

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
                405                 410                 415
```

```
Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
            420                 425                 430

Val Leu Val Ser Asp Gly Ser Phe Thr Leu Tyr Ser Lys Leu Thr Val
        435                 440                 445

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
    450                 455                 460

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
465                 470                 475                 480

Pro Gly
```

<210> 211
<211> 482
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 211

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

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

Tyr Trp Leu Gly Trp Val Lys Gln Arg Pro Gly His Cys Leu Glu Trp
        35                  40                  45

Ile Gly Asp Ile Phe Pro Gly Ser Gly Asn Ile His Tyr Asn Glu Lys
    50                  55                  60

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

Tyr Met Gln Leu Ser Ser Leu Thr Phe Glu Asp Ser Ala Val Tyr Phe
                85                  90                  95
```

```
Cys Ala Arg Leu Arg Asn Trp Asp Glu Pro Met Asp Tyr Trp Gly Gln
            100                 105                 110

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

Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Leu Val Met
    130                 135                 140

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

Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser Gly Asn Gln Lys
                165                 170                 175

Asn Tyr Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro Lys Leu
            180                 185                 190

Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val Pro Asp Arg Phe
        195                 200                 205

Thr Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Val
    210                 215                 220

Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn Asp Tyr Ser Tyr
225                 230                 235                 240

Pro Leu Thr Phe Gly Cys Gly Thr Lys Leu Glu Ile Lys Gly Ala Ser
                245                 250                 255

Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly
            260                 265                 270

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

Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His
    290                 295                 300

Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val
305                 310                 315                 320
```

```
His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr
                325                 330                 335

Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly
            340                 345                 350

Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile
        355                 360                 365

Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Arg Val
    370                 375                 380

Tyr Thr Leu Pro Pro Cys Arg Asp Glu Leu Thr Lys Asn Gln Val Ser
385                 390                 395                 400

Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu
                405                 410                 415

Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro
            420                 425                 430

Val Leu Val Ser Asp Gly Ser Phe Thr Leu Tyr Ser Lys Leu Thr Val
        435                 440                 445

Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met
    450                 455                 460

His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser
465                 470                 475                 480

Pro Gly
```

<210> 212
<211> 451
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 212

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

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

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

Ser Ser Ile Ser Ser Ser Ser Ser Ser Tyr Ile Tyr Tyr Ala Asp Ser Val
    50                  55                  60

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

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

Ala Arg Gly Ala Pro Met Gly Ala Ala Ala Gly Trp Phe Asp Pro Trp
            100                 105                 110

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

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

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

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

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205
```

```
His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser
    210                 215                 220

Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Cys Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Glu Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

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

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

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

Ser Pro Gly
450

<210> 213
<211> 210
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 213

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

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

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

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

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

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

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

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

Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
130 135 140

```
Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
145                 150                 155                 160

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

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

Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
        195                 200                 205

Glu Cys
    210
```

<210> 214
<211> 221
<212> PRT
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: Synthetic polypeptide

<400> 214

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

Glu Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Ser
            20                  25                  30

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

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

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

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Val Tyr Tyr Cys Gln Asn
                85                  90                  95
```

```
Asp Tyr Ser Tyr Pro Leu Thr Phe Gly Ala Gly Thr Lys Leu Glu Ile
            100                 105                 110

Lys Gly Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser
        115                 120                 125

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

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

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

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

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

Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215                 220
```