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(54) Title: RADIOLABELED ANTI-LAG3 ANTIBODIES FOR IMMUNO-PET IMAGING

(57) Abstract: Radiolabeled anti-LAG3 antibodies and their use in immuno-PET imaging are provided herein. Included are methods of detecting the presence of LAG3 proteins in a patient or sample.



**RADIOLABELED ANTI-LAG3 ANTIBODIES FOR IMMUNO-PET IMAGING****FIELD**

**[001]** This disclosure relates to radiolabeled anti-LAG3 antibodies and their use in immuno-PET imaging.

**SEQUENCE LISTING**

**[002]** An official copy of the sequence listing is submitted concurrently with the specification electronically via EFS-Web as an ASCII formatted sequence listing with a file name of "10329WO01\_SEQ\_LIST\_ST25.txt", a creation date of February 09, 2018, and a size of about 254KB. The sequence listing contained in this ASCII formatted document is part of the specification and is herein incorporated by reference in its entirety.

**BACKGROUND**

**[003]** T cell co-stimulatory and co-inhibitory molecules (collectively named co-signaling molecules) play a crucial role in regulating T cell activation, subset differentiation, effector function and survival (Chen et al 2013, Nature Rev. Immunol. 13: 227-242). Following recognition of cognate peptide-MHC complexes on antigen-presenting cells by the T cell receptor (TCR), co-signaling receptors co-localize with T cell receptors at the immune synapse, where they synergize with TCR signaling to promote or inhibit T cell activation and function (Flies et al 2011, Yale J. Biol. Med. 84: 409-421). The ultimate immune response is regulated by a balance between co-stimulatory and co-inhibitory signals ("immune checkpoints") (Pardoll 2012, Nature Reviews Cancer 12: 252-264). Lymphocyte activation gene-3 (LAG3) functions as one such 'immune checkpoint' in mediating peripheral T cell tolerance.

**[004]** LAG3 (also called CD223) is a 503 amino acid transmembrane protein receptor expressed on activated CD4 and CD8 T cells,  $\gamma\delta$  T cells, natural killer T cells, B-cells, natural killer cells, plasmacytoid dendritic cells and regulatory T cells. LAG3 is a member of the immunoglobulin (Ig) superfamily. The primary function of LAG3 is to attenuate the immune response. LAG3 binding to MHC class II molecules results in delivery of a negative signal to LAG3-expressing cells and down-regulates antigen-dependent CD4 and CD8 T cell responses. LAG3 negatively regulates the ability of T cells to proliferate, produce cytokines and lyse target cells, termed as 'exhaustion' of T cells. LAG3 is also reported to play a role in enhancing T regulatory (Treg) cell function (Pardoll 2012, Nature Reviews Cancer 12: 252-264).

**[005]** Immuno-positron emission tomography (PET) is a diagnostic imaging tool that utilizes monoclonal antibodies labeled with positron emitters, combining the targeting properties of

an antibody with the sensitivity of positron emission tomography cameras. See, e.g., *The Oncologist*, 12: 1379 (2007); *Journal of Nuclear Medicine*, 52(8): 1171 (2011). Immuno-PET enables the visualization and quantification of antigen and antibody accumulation *in vivo* and, as such, can serve as an important tool for diagnostics and complementing therapy. For example, immuno-PET can aid in the selection of potential patient candidates for a particular therapy, as well as in the monitoring of treatment.

**[006]** As LAG3 has emerged as a target for tumor immunotherapy and infectious immunotherapy, there is need for diagnostic tools for anti-LAG3 therapy, including, *inter alia*, diagnostic tools that enable the detection of suitable patient candidates for said therapy. It is an object of the present invention to go at least some way to meeting the abovementioned need, and/or to at least provide the public with a useful choice.

### BRIEF SUMMARY

**[006a]** In a first aspect, the invention provides a radiolabeled antibody conjugate comprising an antibody or antigen binding fragment thereof that binds lymphocyte activation gene-3 (LAG3), a chelating moiety, and a positron emitter, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (HCDRs) (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO:418 and three light chain complementarity determining regions (LCDRs) (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO:426, and wherein the positron emitter is <sup>89</sup>Zr.

**[006b]** In a second aspect, the invention relates to a method of imaging a tissue that expresses LAG3 comprising administering the radiolabeled antibody conjugate according to the first aspect of the invention to the tissue; and visualizing LAG3 expression by positron emission tomography (PET) imaging.

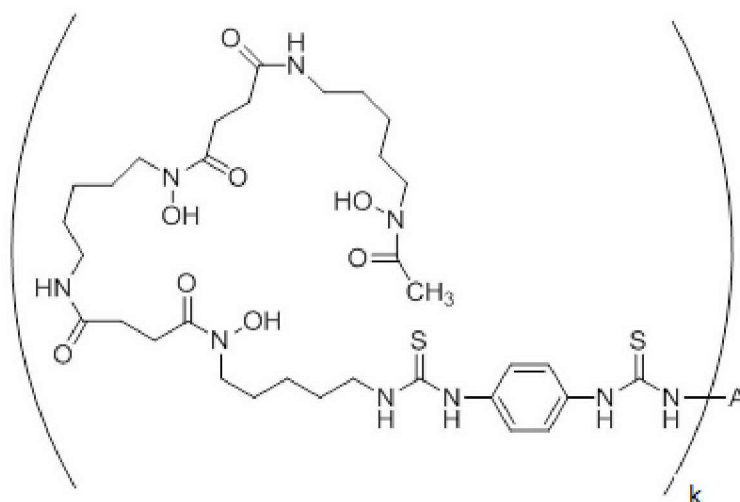
**[006c]** In a third aspect, the invention relates to a method for determining that a solid tumor comprises LAG3-positive cells, comprising (i) administering the radiolabeled antibody conjugate according to the first aspect of the invention to a subject in need thereof; and (ii) imaging localization of the radiolabeled antibody conjugate in the tumor in the subject by positron emission tomography (PET) imaging, wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor comprises LAG3-positive cells.

**[006d]** In a fourth aspect, the invention relates to use of the conjugate according to the first aspect of the invention in the manufacture of a medicament for determining that a solid



tumor comprises LAG3-positive cells, the determining comprising imaging localization of the radiolabeled antibody conjugate in the tumor in the subject by positron emission tomography (PET) imaging, wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor comprises LAG3-positive cells.

**[006e]** In a fifth aspect, the invention provides a compound of Formula (III):



Wherein A is an antibody or antigen-binding fragment thereof that binds LAG3, k is an integer from 1-30; wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (HCDRs) within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 418 and three light chain complementarity determining regions (LCDRs) within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 426.

**[006f]** In a sixth aspect, the invention relates to a method for identifying T-cell exhaustion in a subject comprising administering the radiolabeled conjugate according to the first aspect of the invention to the subject.

**[006g]** In a seventh aspect, the invention relates to use of the conjugate according to the first aspect the invention in the manufacture of a medicament for identifying T-cell exhaustion in a subject.

**[006h]** In an eighth aspect, the invention provides a composition comprising:

(i) a radiolabeled antibody conjugate comprising an antibody or antigen binding fragment thereof that binds lymphocyte activation gene-3 (LAG3), desferrioxamine, and a  $^{89}\text{Zr}$  positron emitter, wherein the antibody or antigen-binding fragment thereof comprises three

heavy chain complementarity determining regions (HCDRs) within a heavy chain variable region (HCVR) amino acid sequence as set forth in SEQ ID NO: 418 and three light chain complementarity determining regions (LCDRs) within a light chain variable region (LCVR) amino acid sequence as set forth in SEQ ID NO: 426; and

(ii) LAG3 expressing T cells.

**[006i]** The invention is defined in the claims. However, the disclosure preceding the claims may refer to additional methods and other subject matter outside the scope of the present claims. This disclosure is retained for technical purposes.

**[007]** Included in this disclosure are radiolabeled anti-LAG3 antibody conjugates for use in immuno-PET imaging.

**[008]** In one aspect, the conjugate comprises an anti-LAG3 antibody or antigen-binding fragment thereof, a chelating moiety, and a positron emitter.

**[009]** Provided herein are also processes for synthesizing said conjugates and synthetic intermediates useful for the same.

**[010]** Provided herein are also methods of imaging a tissue that expresses LAG3, the methods comprising administering a radiolabeled anti-LAG3 antibody conjugate described herein to the tissue; and visualizing the LAG3 expression by positron emission tomography (PET) imaging.

**[011]** Provided herein are also methods of imaging a tissue comprising LAG3-expressing cells, for example, LAG3-expressing intratumoral lymphocytes, the methods comprising administering a radiolabeled anti-LAG3 antibody conjugate described herein to the tissue, and visualizing the LAG3 expression by PET imaging.

**[012]** Provided herein are also methods for detecting LAG3 in a tissue, the methods comprising administering a radiolabeled anti-LAG3 antibody conjugate described herein to the tissue; and visualizing the LAG3 expression by PET imaging. In one embodiment, the tissue is present in a human subject. In certain embodiments, the subject is a non-human mammal. In certain embodiments, the subject has a disease or disorder such as cancer, an inflammatory disease, or an infection.

**[013]** Provided herein are also methods for identifying a patient to be suitable for anti-tumor therapy comprising an inhibitor of LAG3, the methods comprising selecting a patient with a solid tumor, administering a radiolabeled antibody conjugate described herein, and

visualizing the administered radiolabeled antibody conjugate in the tumor by PET imaging wherein presence of the radiolabeled antibody conjugate in the tumor identifies the patient as suitable for anti-tumor therapy comprising an inhibitor of LAG3.

**[014]** Provided herein are also methods of treating a tumor, the methods comprising selecting a subject with a solid tumor; determining that the solid tumor is LAG3-positive; and administering an anti-tumor therapy to the subject in need thereof. In certain embodiments, the anti-tumor therapy comprises an inhibitor of LAG3. In certain embodiments, the anti-tumor therapy comprises an inhibitor of the PD-1/PD-L1 signaling axis (*e.g.*, an anti-PD-1 antibody or an anti-PD-L1 antibody). In certain embodiments, the anti-tumor therapy comprises an inhibitor of LAG3 and/or an inhibitor of the PD-1/PD-L1 signaling axis. In certain embodiments, the subject is administered a radiolabeled anti-LAG3 antibody conjugate described herein, and localization of the radiolabeled antibody conjugate is imaged via positron emission tomography (PET) imaging to determine if the tumor is LAG3-positive. In certain embodiments, the subject is further administered a radiolabeled anti-PD-1 antibody conjugate, and localization of the radiolabeled antibody conjugate is imaged via positron emission tomography (PET) imaging to determine if the tumor is PD-1-positive.

**[015]** Provided herein are also methods for monitoring the efficacy of an anti-tumor therapy in a subject, wherein the methods comprise selecting a subject with a solid tumor wherein the subject is being treated with an anti-tumor therapy; administering a radiolabeled anti-LAG3 conjugate described herein to the subject; imaging the localization of the administered radiolabeled conjugate in the tumor by PET imaging; and determining tumor growth, wherein a decrease from the baseline in uptake of the conjugate or radiolabeled signal indicates efficacy of the anti-tumor therapy. In certain embodiments, the anti-tumor therapy comprises an inhibitor of LAG3 (*e.g.*, an anti-LAG3 antibody). In certain embodiments, the anti-tumor therapy comprises an inhibitor of LAG3 and an inhibitor of the PD-1/PD-L1 signaling axis. In certain embodiments, the anti-tumor therapy comprises a PD-1 inhibitor (*e.g.*, REGN2810, BGB-A317, nivolumab, pidilizumab, and pembrolizumab), a PD-L1 inhibitor (*e.g.*, atezolizumab, avelumab, durvalumab, MDX-1105, and REGN3504, as well as those disclosed in Patent Publication No. US 2015-0203580), CTLA-4 inhibitor (*e.g.*, ipilimumab), a TIM3 inhibitor, a BTLA inhibitor, a TIGIT inhibitor, a CD47 inhibitor, a GITR inhibitor, an antagonist of another T cell co-inhibitor or ligand (*e.g.*, an antibody to CD-28, 2B4, LY108, LAIR1, ICOS, CD160 or VISTA), an indoleamine-2,3-dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist [*e.g.*, a “VEGF-Trap” such as aflibercept or other VEGF-inhibiting fusion protein as set forth in US 7,087,411, or an anti-VEGF antibody or antigen binding fragment thereof (*e.g.*, bevacizumab, or ranibizumab) or a small molecule kinase inhibitor of VEGF receptor (*e.g.*, sunitinib,

sorafenib, or pazopanib)], an Ang2 inhibitor (e.g., nesvacumab), a transforming growth factor beta (TGF $\beta$ ) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor (e.g., erlotinib, cetuximab), a CD20 inhibitor (e.g., an anti-CD20 antibody such as rituximab), an antibody to a tumor-specific antigen [e.g., CA9, CA125, melanoma-associated antigen 3 (MAGE3), carcinoembryonic antigen (CEA), vimentin, tumor-M2-PK, prostate-specific antigen (PSA), mucin-1, MART-1, and CA19-9], a vaccine (e.g., Bacillus Calmette-Guerin, a cancer vaccine), an adjuvant to increase antigen presentation (e.g., granulocyte-macrophage colony-stimulating factor), a bispecific antibody (e.g., CD3xCD20 bispecific antibody, or PSMAxCD3 bispecific antibody), a cytotoxin, a chemotherapeutic agent (e.g., dacarbazine, temozolomide, cyclophosphamide, docetaxel, doxorubicin, daunorubicin, cisplatin, carboplatin, gemcitabine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, and vincristine), cyclophosphamide, radiotherapy, an IL-6R inhibitor (e.g., sarilumab), an IL-4R inhibitor (e.g., dupilumab), an IL-10 inhibitor, a cytokine such as IL-2, IL-7, IL-21, and IL-15, and an antibody-drug conjugate (ADC) (e.g., anti-CD19-DM4 ADC, and anti-DS6-DM4 ADC).

**[016]** Provided herein are also methods for predicting response of a patient to an anti-tumor therapy, the methods comprising selecting a patient with a solid tumor; and determining if the tumor is LAG3-positive, wherein if the tumor is LAG3-positive it predicts a positive response of the patient to an anti-tumor therapy. In certain embodiments, the tumor is determined positive by administering a radiolabeled anti-LAG3 antibody conjugate of the present disclosure and localizing the radiolabeled antibody conjugate in the tumor by PET imaging wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor is LAG3-positive. In some embodiments, the anti-tumor therapy is selected from a PD-1 inhibitor (e.g., REGN2810, BGB-A317, nivolumab, pidilizumab, and pembrolizumab), a PD-L1 inhibitor (e.g., atezolizumab, avelumab, durvalumab, MDX-1105, and REGN3504), CTLA-4 inhibitor (e.g., ipilimumab), a TIM3 inhibitor, a BTLA inhibitor, a TIGIT inhibitor, a CD47 inhibitor, a GITR inhibitor, an antagonist of another T cell co-inhibitor or ligand (e.g., an antibody to CD-28, 2B4, LY108, LAIR1, ICOS, CD160 or VISTA), an indoleamine-2,3-dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist [e.g., a “VEGF-Trap” such as aflibercept or other VEGF-inhibiting fusion protein as set forth in US 7,087,411, or an anti-VEGF antibody or antigen binding fragment thereof (e.g., bevacizumab, or ranibizumab) or a small molecule kinase inhibitor of VEGF receptor (e.g., sunitinib, sorafenib, or pazopanib)], an Ang2 inhibitor (e.g., nesvacumab), a transforming growth factor beta (TGF $\beta$ ) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor (e.g., erlotinib, cetuximab), a CD20 inhibitor (e.g., an anti-CD20 antibody such as rituximab), an antibody to a tumor-specific antigen [e.g., CA9, CA125, melanoma-associated antigen 3



(MAGE3), carcinoembryonic antigen (CEA), vimentin, tumor-M2-PK, prostate-specific antigen (PSA), mucin-1, MART-1, and CA19-9], a vaccine (e.g., Bacillus Calmette-Guerin, a cancer vaccine), an adjuvant to increase antigen presentation (e.g., granulocyte-macrophage colony-stimulating factor), a bispecific antibody (e.g., CD3xCD20 bispecific antibody, or PSMAxCD3 bispecific antibody), a cytotoxin, a chemotherapeutic agent (e.g., dacarbazine, temozolomide, cyclophosphamide, docetaxel, doxorubicin, daunorubicin, cisplatin, carboplatin, gemcitabine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, and vincristine), cyclophosphamide, radiotherapy, an IL-6R inhibitor (e.g., sarilumab), an IL-4R inhibitor (e.g., dupilumab), an IL-10 inhibitor, a cytokine such as IL-2, IL-7, IL-21, and IL-15, and an antibody-drug conjugate (ADC) (e.g., anti-CD19-DM4 ADC, and anti-DS6-DM4 ADC).

**[017]** Provided herein are also methods for predicting response of a patient to an anti-tumor therapy comprising an inhibitor LAG3, the methods comprising selecting a patient with a solid tumor; and determining if the tumor is LAG3-positive, wherein if the tumor is LAG3-positive it indicates a positive response of the patient to an anti-tumor therapy comprising an inhibitor of LAG3. In certain embodiments, the tumor is determined positive by administering a radiolabeled anti-LAG3 antibody conjugate of the present disclosure and localizing the radiolabeled antibody conjugate in the tumor by PET imaging wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor is LAG3-positive.

### BRIEF DESCRIPTION OF THE FIGURES

**[018] Figure 1** depicts UV/VIS spectrum of DFO modified anti-LAG3 antibody (mAb1-DFO).

**[019] Figure 2** depicts HPLC-SEC of DFO modified anti-LAG3 antibody.

**[020] Figure 3** depicts radio-SEC-HPLC of isotype-DFO-conjugate after <sup>89</sup>Zr radiolabeling for Study 1.

**[021] Figure 4** depicts radio-SEC-HPLC of anti-LAG3-DFO-conjugate after <sup>89</sup>Zr radiolabeling for Study 1.

**[022] Figure 5** depicts radio-SEC-HPLC of anti-LAG3-DFO-conjugate after <sup>89</sup>Zr radiolabeling for Study 2.

**[023] Figure 6** depicts UV280-SEC-HPLC chromatogram and radio-iTLC trace of isotype-DFO-conjugate after <sup>89</sup>Zr radiolabeling for Study 1.

**[024] Figure 7** depicts UV280-SEC-HPLC chromatogram and radio-iTLC trace of anti-

LAG3-DFO-conjugate after  $^{89}\text{Zr}$  radiolabeling for Study 1.

**[025] Figure 8** depicts UV280-SEC-HPLC chromatogram and radio-iTLC trace of anti-LAG3-DFO-conjugate after  $^{89}\text{Zr}$  radiolabeling for Study 2.

**[026] Figure 9** provides representative images of  $^{89}\text{Zr}$ -DFO-mAb1 injected at a protein dose of 5 mg/kg (Ms01) or 0.03 mg/kg (Ms14) demonstrating specific targeting of  $^{89}\text{Zr}$ -DFO-mAb1 to Raji/hPBMC tumors using 0.03 mg/kg of  $^{89}\text{Zr}$ -DFO-mAb1 and blocking at 5 mg/kg of  $^{89}\text{Zr}$ -DFO-mAb1. Specific uptake in the spleen and lymph nodes is seen at the lower dose of 0.03 mg/kg  $^{89}\text{Zr}$ -DFO-mAb1.

**[027] Figure 10** shows LAG3 expression in tissue samples from PBMC/Raji xenografts (obtained at 27 days and 15 days after tumor implantation) and in melanoma clinical samples.

**[028] Figure 11** provides data demonstrating REGN2810 anti-human PD-1 Ab and mAb1 anti-human LAG-3 respectively increase LAG-3+ T cells and PD-1+ T cells in tumor microenvironment.

**[029] Figure 12** provides characteristics of the melanoma samples studied in Example 7.

## DETAILED DESCRIPTION

### I. Definitions

**[030]** Unless defined otherwise herein, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the disclosed subject matter belongs.

**[031]** The term “LAG3” refers to the lymphocyte activation gene-3 protein, an immune checkpoint receptor or T cell co-inhibitor, also known as CD223. The amino acid sequence of full-length LAG3 is provided in GenBank as accession number NP\_002277.4 and is also referred to herein as SEQ ID NO: 582. The term “LAG3” also includes protein variants of LAG3 having the amino acid sequence of SEQ ID NOs: 574, 575 or 576. The term “LAG3” includes recombinant LAG3 or a fragment thereof. The term also encompasses LAG3 or a fragment thereof coupled to, for example, histidine tag, mouse or human Fc, or a signal sequence such as the signal sequence of ROR1. For example, the term includes sequences exemplified by SEQ ID NO: 575, comprising a mouse Fc (mIgG2a) at the C-terminal, coupled to amino acid residues 29 – 450 of full-length ectodomain LAG3. Protein variants as exemplified by SEQ ID NO: 574 comprise a histidine tag at the C-terminal,

coupled to amino acid residues 29 – 450 of full length ectodomain LAG3. Unless specified as being from a non-human species, the term “LAG3” means human LAG3.

**[032]** LAG3 is a member of the immunoglobulin (Ig) superfamily. LAG3 is a type-1 transmembrane protein with four extracellular Ig-like domains D1 to D4 and is expressed on intratumoral lymphocytes including activated T cells, natural killer cells, B cells, plasmacytoid dendritic cells, and regulatory T cells. The LAG3 receptor binds to MHC class II molecules present on antigen presenting cells (APCs).

**[033]** The term “B7-1” refers to the T-lymphocyte activation antigen, also known as costimulatory factor CD80. B7-1 is a 288 amino acid membrane receptor with an extracellular N-terminal domain which comprises IgV-like (aa 37 – 138) and IgC-like (aa 154 – 232) regions, a transmembrane domain (aa 243 – 263) and a C-terminal intracellular region (aa 263 – 288). The amino acid sequence of full-length B7-1 is provided in GenBank as accession number NP\_005182.1.

**[034]** As used herein, the term “T-cell co-inhibitor” refers to a ligand and/or receptor which modulates the immune response via T-cell activation or suppression. The term “T-cell co-inhibitor”, also known as T-cell co-signaling molecule, includes, but is not limited to, lymphocyte activation gene 3 protein (LAG-3, also known as CD223), programmed death-1 (PD-1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), B and T lymphocyte attenuator (BTLA), CD-28, 2B4, LY108, T-cell immunoglobulin and mucin-3 (TIM3), T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT; also known as VSIG9), leucocyte associated immunoglobulin-like receptor 1 (LAIR1; also known as CD305), inducible T-cell costimulator (ICOS; also known as CD278), B7-1 (CD80), and CD160.

**[035]** The term “antibody”, as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains interconnected by disulfide bonds (*i.e.*, “full antibody molecules”), as well as multimers thereof (*e.g.* IgM) or antigen-binding fragments thereof. Each heavy chain is comprised of a heavy chain variable region (“HCVR” or “V<sub>H</sub>”) and a heavy chain constant region (comprised of domains C<sub>H1</sub>, C<sub>H2</sub> and C<sub>H3</sub>). Each light chain is comprised of a light chain variable region (“LCVR or “V<sub>L</sub>”) and a light chain constant region (C<sub>L</sub>). The V<sub>H</sub> and V<sub>L</sub> regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V<sub>H</sub> and V<sub>L</sub> is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In certain embodiments, the FRs of the antibody (or antigen binding fragment thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or

more CDRs.

**[036]** Substitution of one or more CDR residues or omission of one or more CDRs is also possible. Antibodies have been described in the scientific literature in which one or two CDRs can be dispensed with for binding. Padlan *et al.* (1995 FASEB J. 9:133-139) analyzed the contact regions between antibodies and their antigens, based on published crystal structures, and concluded that only about one fifth to one third of CDR residues actually contact the antigen. Padlan also found many antibodies in which one or two CDRs had no amino acids in contact with an antigen (see also, Vajdos *et al.* 2002 J Mol Biol 320:415-428).

**[037]** CDR residues not contacting antigen can be identified based on previous studies (for example residues H60-H65 in CDRH2 are often not required), from regions of Kabat CDRs lying outside Chothia CDRs, by molecular modeling and/or empirically. If a CDR or residue(s) thereof is omitted, it is usually substituted with an amino acid occupying the corresponding position in another human antibody sequence or a consensus of such sequences. Positions for substitution within CDRs and amino acids to substitute can also be selected empirically. Empirical substitutions can be conservative or non-conservative substitutions.

**[038]** The anti-LAG3 monoclonal antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present disclosure includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V<sub>H</sub> and/or V<sub>L</sub> domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other embodiments, only certain residues are mutated back to the original germline sequence, e.g., only the mutated



residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (*i.e.*, a germline sequence that is different from the germline sequence from which the antibody was originally derived). Furthermore, the antibodies of the present disclosure may contain any combination of two or more germline mutations within the framework and/or CDR regions, *e.g.*, wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present disclosure.

**[039]** The present disclosure also includes anti-LAG3 monoclonal antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present disclosure includes anti-LAG3 antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, *e.g.*, 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

**[040]** The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human mAbs of the disclosure may include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (*e.g.*, mouse), have been grafted onto human FR sequences.

**[041]** The term "multi-specific antigen-binding molecules", as used herein refers to bispecific, tri-specific or multi-specific antigen-binding molecules, and antigen-binding fragments thereof. Multi-specific antigen-binding molecules may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for epitopes of more than one target polypeptide. A multi-specific antigen-binding molecule can be a single multifunctional polypeptide, or it can be a multimeric complex of two or more

polypeptides that are covalently or non-covalently associated with one another. The term "multi-specific antigen-binding molecules" includes antibodies of the present disclosure that may be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, non-covalent association or otherwise) to one or more other molecular entities, such as a protein or fragment thereof to produce a bi-specific or a multi-specific antigen-binding molecule with a second binding specificity. According to the present disclosure, the term "multi-specific antigen-binding molecules" also includes bi-specific, tri-specific or multi-specific antibodies or antigen-binding fragments thereof. In certain embodiments, an antibody of the present disclosure is functionally linked to another antibody or antigen-binding fragment thereof to produce a bispecific antibody with a second binding specificity. Bispecific and multi-specific antibodies of the present disclosure are described elsewhere herein.

**[042]** The term "specifically binds," or "binds specifically to", or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about  $1 \times 10^{-8}$  M or less (e.g., a smaller  $K_D$  denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. As described herein, antibodies have been identified by surface plasmon resonance, e.g., BIACORE™, which bind specifically to LAG3. Moreover, multi-specific antibodies that bind to one domain in LAG3 and one or more additional antigens or a bi-specific that binds to two different regions of LAG3 are nonetheless considered antibodies that "specifically bind", as used herein.

**[043]** The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding fragment" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to bind to LAG3.

**[044]** An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies (Abs) having different antigenic specificities (e.g., an isolated antibody that specifically binds LAG3, or a fragment thereof, is substantially free of Abs that specifically bind antigens other than LAG3).

**[045]** The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection

of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.).

**[046]** The term " $K_D$ ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

**[047]** The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term "epitope" also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

**[048]** The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or GAP.

**[049]** As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 90% sequence identity, even more preferably at least 95%, 98% or 99% sequence identity. Preferably, residue positions, which are not identical, differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. See, e.g., Pearson (1994) *Methods Mol. Biol.* 24: 307-331, which is herein incorporated by reference.

Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992) Science 256: 1443-45, herein incorporated by reference. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix. Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) *supra*). Another preferred algorithm when comparing a sequence of the disclosure to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. See, e.g., Altschul *et al.* (1990) J. Mol. Biol. 215: 403-410 and (1997) Nucleic Acids Res. 25:3389-3402, each of which is herein incorporated by reference.

**[050]** By the phrase "therapeutically effective amount" is meant an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

**[051]** As used herein, the term "subject" refers to an animal, preferably a mammal, in need of amelioration, prevention and/or treatment of a disease or disorder such as chronic viral infection, cancer or autoimmune disease.

**[051a]** The term "comprising" as used in this specification and claims means "consisting at

least in part of". When interpreting statements in this specification and claims which include the term "comprising", other features besides the features prefaced by this term in each statement can also be present. Related terms such as "comprise" and "comprised" are to be interpreted in similar manner.

## II. Radiolabeled Immunoconjugates of LAG3 Antibodies for Immuno-PET Imaging

**[052]** Provided herein are radiolabeled antigen-binding proteins that bind LAG3. In some embodiments, the radiolabeled antigen-binding proteins comprise an antigen-binding protein covalently linked to a positron emitter. In some embodiments, the radiolabeled antigen-binding proteins comprise an antigen-binding protein covalently linked to one or more chelating moieties, which are chemical moieties that are capable of chelating a positron emitter.

**[053]** In some embodiments, antigen-binding proteins that bind LAG3, *e.g.*, antibodies, are provided, wherein said antigen-binding proteins that bind LAG3 are covalently bonded to one or more moieties having the following structure:



wherein L is a chelating moiety; M is a positron emitter; and z, independently at each occurrence, is 0 or 1; and wherein at least one of z is 1.

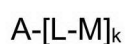
**[054]** In some embodiments, the radiolabeled antigen-binding protein is a compound of Formula (I):



(I)

A is a protein that binds LAG3; L is a chelating moiety; M is a positron emitter; z is 0 or 1; and k is an integer from 0-30. In some embodiments, k is 1.

**[055]** In certain embodiments, the radiolabeled antigen-binding protein is a compound of Formula (II):



(II)

wherein A is a protein that binds LAG3; L is a chelating moiety; M is a positron emitter; and k is an integer from 1-30.

**[056]** In some embodiments, provided herein are compositions comprising a conjugate

having the following structure:



wherein A is a protein that binds LAG3; L is a chelating moiety; and k is an integer from 1-30; wherein the conjugate is chelated with a positron emitter in an amount sufficient to provide a specific activity suitable for clinical PET imaging.

**[057]** Suitable binding proteins, chelating moieties, and positron emitters are provided below.

### A. LAG3 Binding Proteins

**[058]** Suitable LAG3 binding protein are proteins that specifically bind to LAG3, including those described in PCT/US16/56156, incorporated herein by reference in its entirety.

Exemplary anti-LAG3 antibodies of the present disclosure are listed in Table 1 of PCT/US16/56156, also presented below.

**Table 1: Amino Acid Sequence Identifiers**

| Antibody Designation | SEQ ID NOs: |       |        |       |      |       |       |       |
|----------------------|-------------|-------|--------|-------|------|-------|-------|-------|
|                      | HCVR        | HCDR1 | HCDR 2 | HCDR3 | LCVR | LCDR1 | LCDR2 | LCDR3 |
| H1M14985N            | 2           | 4     | 6      | 8     | 10   | 12    | 14    | 16    |
| H1M14987N            | 18          | 20    | 22     | 24    | 26   | 28    | 30    | 32    |
| H2M14811N            | 34          | 36    | 38     | 40    | 42   | 44    | 46    | 48    |
| H2M14885N            | 50          | 52    | 54     | 56    | 58   | 60    | 62    | 64    |
| H2M14926N            | 66          | 68    | 70     | 72    | 74   | 76    | 78    | 80    |
| H2M14927N            | 82          | 84    | 86     | 88    | 90   | 92    | 94    | 96    |
| H2M14931N            | 98          | 100   | 102    | 104   | 106  | 108   | 110   | 112   |
| H2M18336N            | 114         | 116   | 118    | 120   | 122  | 124   | 126   | 128   |
| H2M18337N            | 130         | 132   | 134    | 136   | 138  | 140   | 142   | 144   |
| H4H15477P            | 146         | 148   | 150    | 152   | 154  | 156   | 158   | 160   |
| H4H15483P            | 162         | 164   | 166    | 168   | 170  | 172   | 174   | 176   |
| H4H15484P            | 178         | 180   | 182    | 184   | 186  | 188   | 190   | 192   |
| H4H15491P            | 194         | 196   | 198    | 200   | 202  | 204   | 206   | 208   |
| H4H17823P            | 210         | 212   | 214    | 216   | 218  | 220   | 222   | 224   |
| H4H17826P2           | 226         | 228   | 230    | 232   | 234  | 236   | 238   | 240   |
| H4H17828P2           | 242         | 244   | 246    | 248   | 250  | 252   | 254   | 256   |
| H4sH15460P           | 258         | 260   | 262    | 264   | 266  | 268   | 270   | 272   |

|                 |     |     |     |     |     |     |     |     |
|-----------------|-----|-----|-----|-----|-----|-----|-----|-----|
| H4sH15462P      | 274 | 276 | 278 | 280 | 282 | 284 | 286 | 288 |
| H4sH15463P      | 290 | 292 | 294 | 296 | 298 | 300 | 302 | 304 |
| H4sH15464P      | 306 | 308 | 310 | 312 | 314 | 316 | 318 | 320 |
| H4sH15466P      | 322 | 324 | 326 | 328 | 330 | 332 | 334 | 336 |
| H4sH15467P      | 338 | 340 | 342 | 344 | 346 | 348 | 350 | 352 |
| H4sH15470P      | 354 | 356 | 358 | 360 | 362 | 364 | 366 | 368 |
| H4sH15475P      | 370 | 372 | 374 | 376 | 378 | 380 | 382 | 384 |
| H4sH15479P      | 386 | 388 | 390 | 392 | 394 | 396 | 398 | 400 |
| H4sH15480P      | 402 | 404 | 406 | 408 | 410 | 412 | 414 | 416 |
| H4sH15482P      | 418 | 420 | 422 | 424 | 426 | 428 | 430 | 432 |
| H4sH15488P      | 434 | 436 | 438 | 440 | 442 | 444 | 446 | 448 |
| H4sH15496P<br>2 | 450 | 452 | 454 | 456 | 522 | 524 | 526 | 528 |
| H4sH15498P<br>2 | 458 | 460 | 462 | 464 | 522 | 524 | 526 | 528 |
| H4sH15505P<br>2 | 466 | 468 | 470 | 472 | 522 | 524 | 526 | 528 |
| H4sH15518P<br>2 | 474 | 476 | 478 | 480 | 522 | 524 | 526 | 528 |
| H4sH15523P<br>2 | 482 | 484 | 486 | 488 | 522 | 524 | 526 | 528 |
| H4sH15530P<br>2 | 490 | 492 | 494 | 496 | 522 | 524 | 526 | 528 |
| H4sH15555P<br>2 | 498 | 500 | 502 | 504 | 530 | 532 | 534 | 536 |
| H4sH15558P<br>2 | 506 | 508 | 510 | 512 | 530 | 532 | 534 | 536 |
| H4sH15567P<br>2 | 514 | 516 | 518 | 520 | 530 | 532 | 534 | 536 |
| H4H14813N       | 538 | 540 | 542 | 544 | 546 | 548 | 550 | 552 |
| H4H17819P       | 554 | 556 | 558 | 560 | 562 | 564 | 566 | 568 |

Table 1 sets forth the amino acid sequence identifiers of the heavy chain variable regions (HCVRs), light chain variable regions (LCVRs), heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3), and light chain complementarity determining

regions (LCDR1, LCDR2 and LCDR3) of the exemplary anti-LAG3 antibodies.

**[059]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising an HCVR comprising an amino acid sequence selected from any of the HCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

**[060]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising an LCVR comprising an amino acid sequence selected from any of the LCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

**[061]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising an HCVR and an LCVR amino acid sequence pair (HCVR/LCVR) comprising any of the HCVR amino acid sequences listed in Table 1 paired with any of the LCVR amino acid sequences listed in Table 1. According to certain embodiments, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCVR/LCVR amino acid sequence pair contained within any of the exemplary anti-LAG3 antibodies listed in Table 1. In certain embodiments, the HCVR/LCVR amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 370/378, 386/394, 402/410, 418/426, 434/442, 450/522, 458/522, 466/522, 474/522, 482/522, 490/522, 498/530, 506/530, 514/530, 538/546, and 554/562. In certain embodiments, the HCVR/LCVR amino acid sequence pair is selected from one of SEQ ID NOs: 386/394 (*e.g.*, H4sH15479P), 418/426 (*e.g.*, H4sH15482P) or 538/546 (*e.g.*, H4sH14813N). In certain other embodiments, the HCVR/LCVR amino acid sequence pair is selected from one of SEQ ID NOs: 458/464 (*e.g.*, H4sH15498P2), 162/170 (*e.g.*, H4H15483P), and 579/578 (*e.g.*, H4H15482P).

**[062]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising a heavy chain CDR1 (HCDR1) comprising an amino acid sequence selected from any of the HCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

**[063]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising a heavy chain CDR2 (HCDR2) comprising an amino acid sequence selected from any of the HCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.



**[064]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising a heavy chain CDR3 (HCDR3) comprising an amino acid sequence selected from any of the HCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

**[065]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising a light chain CDR1 (LCDR1) comprising an amino acid sequence selected from any of the LCDR1 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

**[066]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising a light chain CDR2 (LCDR2) comprising an amino acid sequence selected from any of the LCDR2 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

**[067]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising a light chain CDR3 (LCDR3) comprising an amino acid sequence selected from any of the LCDR3 amino acid sequences listed in Table 1 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

**[068]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising an HCDR3 and an LCDR3 amino acid sequence pair (HCDR3/LCDR3) comprising any of the HCDR3 amino acid sequences listed in Table 1 paired with any of the LCDR3 amino acid sequences listed in Table 1. According to certain embodiments, the present disclosure provides antibodies, or antigen-binding fragments thereof, comprising an HCDR3/LCDR3 amino acid sequence pair contained within any of the exemplary anti-LAG3 antibodies listed in Table 1. In certain embodiments, the HCDR3/LCDR3 amino acid sequence pair is selected from the group consisting of SEQ ID NOs: 392/400 (e.g., H4sH15479P), 424/432 (e.g., H4sH15482P), and 544/552 (e.g., H4sH14813N).

**[069]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising a set of six CDRs (i.e., HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within any of the exemplary anti-LAG3 antibodies listed in Table 1. In certain embodiments, the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequence set is selected from the group consisting of SEQ ID NOs: 388-390-392-396-398-400 (e.g., H4sH15479P), 420-422-424-428-430-432 (e.g., H4sH15482P), and 540-542-544-548-550-552 (e.g., H4sH14813N).

**[070]** In some embodiments, the binding protein is an antibody or antigen binding fragment comprising a set of six CDRs (*i.e.*, HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3) contained within an HCVR/LCVR amino acid sequence pair as defined by any of the exemplary anti-LAG3 antibodies listed in Table 1. For example, in some embodiments, the binding protein is an antibody or antigen binding fragment comprising the HCDR1-HCDR2-HCDR3-LCDR1-LCDR2-LCDR3 amino acid sequences set contained within an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 386/394 (*e.g.*, H4sH15479P), 418/426 (*e.g.*, H4sH15482P) and 538/546 (*e.g.*, H4sH14813N). Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, *e.g.*, the Kabat definition, the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. See, *e.g.*, Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani *et al.*, *J. Mol. Biol.* 273:927-948 (1997); and Martin *et al.*, *Proc. Natl. Acad. Sci. USA* 86:9268-9272 (1989). Public databases are also available for identifying CDR sequences within an antibody.

**[071]** In some embodiments, binding proteins are antibodies and antigen-binding fragments thereof that compete for specific binding to LAG3 with an antibody or antigen-binding fragment thereof comprising the CDRs of a HCVR and the CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.

**[072]** Additional exemplary anti-LAG3 antibodies useful herein include LAG525 (and other LAG3 antibodies disclosed in U.S. 20100233183), relatlimab (and other LAG3 antibodies disclosed in U.S. 20110150892), GSK2831781 (and other LAG3 antibodies disclosed in U.S. 20140286935), MGD013 (and other LAG3 antibodies disclosed in WO2015200119) and LAG3 antibodies disclosed in U.S. 20160222116, U.S. 20170022273, U.S. 20170097333, U.S. 20170137517, U.S. 20170267759, U.S. 20170290914, U.S. 20170334995, WO2016126858, WO2016200782, WO2017087589, WO2017087901, WO2017106129, WO2017149143, WO2017198741, WO2017219995, and WO2017220569.

**[073]** Also provided herein are isolated antibodies and antigen-binding fragments thereof that block LAG3 binding to MHC class II. In some embodiments, the antibody or antigen-binding fragment thereof that blocks LAG3 binding may bind to the same epitope on LAG3

as MHC class II or may bind to a different epitope on LAG3 as MHC class II. In certain embodiments, the antibodies of the disclosure that block LAG3 binding to MHC class II comprise the CDRs of an HCVR having an amino acid sequence selected from the group consisting of HCVR sequences listed in Table 1; and the CDRs of a LCVR having an amino acid sequence selected from the group consisting of LCVR sequences listed in Table 1.

**[074]** In alternate embodiments, the present disclosure provides antibodies and antigen-binding fragments thereof that do not block LAG3 binding to MHC class II.

**[075]** In some embodiments, the binding proteins are antibodies and antigen-binding fragments thereof that bind specifically to LAG3 from human or other species. In certain embodiments, the antibodies may bind to human LAG3 and/or to cynomolgus LAG3.

**[076]** In some embodiments, the binding proteins are antibodies and antigen-binding fragments thereof that cross-compete for binding to LAG3 with a reference antibody or antigen-binding fragment thereof comprising the CDRs of a HCVR and the CDRs of a LCVR, wherein the HCVR and LCVR each has an amino acid sequence selected from the HCVR and LCVR sequences listed in Table 1.

**[077]** In one embodiment, the binding protein is an isolated antibody or antigen-binding fragment that has one or more of the following characteristics: (a) blocks the binding of LAG3 or to MHC class II; (b) binds specifically to human LAG3 and/or cynomolgus LAG3; (c) blocks LAG3-induced impairment of T cell activation and rescues T cell signaling; and (d) suppresses tumor growth and increases survival in a subject with cancer.

**[078]** In some embodiments, the antibody or antigen binding fragment thereof may bind specifically to LAG3 in an agonist manner, i.e., it may enhance or stimulate LAG3 binding and/or activity; in other embodiments, the antibody may bind specifically to LAG3 in an antagonist manner, i.e., it may block LAG3 from binding to its ligand.

**[079]** In some embodiments, the antibody or antigen binding fragment thereof may bind specifically to LAG3 in a neutral manner, i.e., it binds but does not block or enhance or stimulate LAG3 binding and/or activity.

**[080]** In certain embodiments, the antibodies or antigen-binding fragments are bispecific comprising a first binding specificity to LAG3 and a second binding specificity for a second target epitope. The second target epitope may be another epitope on LAG3 or on a different protein. In certain embodiments, the second target epitope may be on a different cell including a different T cell, a B-cell, a tumor cell or a virally infected cell.

**[081]** In certain embodiments, an isolated antibody or antigen-binding fragment thereof is provided that binds specifically to human lymphocyte activation gene 3 (LAG3) protein, wherein the antibody or antigen-binding fragment thereof has a property selected from the group consisting of: (a) binds monomeric human LAG3 with a binding dissociation

equilibrium constant ( $K_D$ ) of less than about 10nM as measured in a surface plasmon resonance assay at 25°C (using the assay format as defined in Example 3 of PCT/US16/56156, or a substantially similar assay); (b) binds monomeric human LAG3 with a  $K_D$  less than about 8nM as measured in a surface plasmon resonance assay at 37°C; (c) binds dimeric human LAG3 with a  $K_D$  less than about 1.1nM as measured in a surface plasmon resonance assay at 25°C; (d) binds dimeric human LAG3 with a  $K_D$  less than about 1nM as measured in a surface plasmon resonance assay at 37°C; (e) binds to a hLAG3-expressing cell with an  $EC_{50}$  less than about 8nM as measured in a flow cytometry assay; (f) binds to a mLAG3-expressing cell with a  $EC_{50}$  less than about 2.3nM as measured in a flow cytometry assay; (g) blocks binding of hLAG3 to human MHC class II with  $IC_{50}$  less than about 32nM as determined by a cell adherence assay; (h) blocks binding of hLAG3 to mouse MHC class II with  $IC_{50}$  less than about 30nM as determined by a cell adherence assay; (i) blocks binding of hLAG3 to MHC class II by more than 90% as determined by a cell adherence assay; (j) rescues LAG3-mediated inhibition of T cell activity with  $EC_{50}$  less than about 9nM as determined in a luciferase reporter assay; and (k) binds to activated CD4+ and CD8+ T cells with  $EC_{50}$  less than about 1.2nM, as determined in a fluorescence assay.

**[082]** In some embodiments, the antibodies and antigen-binding fragments thereof bind LAG3 with a dissociative half-life ( $t_{1/2}$ ) of greater than about 1.6 minutes as measured by surface plasmon resonance at 25°C or 37°C, *e.g.*, using an assay format as defined in Example 3 of PCT/US16/56156, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments bind LAG3 with a  $t_{1/2}$  of greater than about 5 minutes, greater than about 10 minutes, greater than about 30 minutes, greater than about 50 minutes, greater than about 60 minutes, greater than about 70 minutes, greater than about 80 minutes, greater than about 90 minutes, greater than about 100 minutes, greater than about 200 minutes, greater than about 300 minutes, greater than about 400 minutes, greater than about 500 minutes, greater than about 600 minutes, greater than about 700 minutes, greater than about 800 minutes, greater than about 900 minutes, greater than about 1000 minutes, or greater than about 1100 minutes, as measured by surface plasmon resonance at 25°C or 37°C, *e.g.*, using an assay format as defined in Example 3 of PCT/US16/56156 (*e.g.*, mAb-capture or antigen-capture format), or a substantially similar assay.

**[083]** In some embodiments, antibodies or antigen-binding fragments thereof bind to a human LAG3-expressing cell with an  $EC_{50}$  less than about 8nM as measured by a flow cytometry assay as defined in Example 5 of PCT/US16/56156, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments thereof bind to

a hLAG3-expressing cell with an  $EC_{50}$  less than about 5nM, less than about 2nM, less than about 1nM, or less than about 0.5nM, as measured by a flow cytometry assay, *e.g.*, using the assay format in Example 5 of PCT/US16/56156, or a substantially similar assay.

**[084]** In some embodiments, antibodies or antigen-binding fragments thereof bind to a cynomolgus monkey LAG3-expressing cell with an  $EC_{50}$  less than about 2.5nM as measured by a flow cytometry assay as defined in Example 5 of PCT/US16/56156, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments thereof bind to a mLAG3-expressing cell with an  $EC_{50}$  less than about 2nM, or less than about 1nM, as measured by a flow cytometry assay, *e.g.*, using the assay format as defined in Example 5 of PCT/US16/56156, or a substantially similar assay.

**[085]** In some embodiments, antibodies or antigen-binding fragments thereof block LAG3 binding to MHC class II (*e.g.*, human HLA-DR2) with an  $IC_{50}$  of less than about 32 nM as determined using a cell adherence assay, *e.g.*, as shown in Example 7 of PCT/US16/56156, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments thereof block LAG3 binding to human MHC class II with an  $IC_{50}$  less than about 25nM, less than about 20nM, less than about 10nM, or less than about 5nM, as measured by a cell adherence assay, *e.g.*, using the assay format as defined in Example 7 of PCT/US16/56156, or a substantially similar assay.

**[086]** In some embodiments, the antibodies or antigen-binding fragments thereof block LAG3 binding to MHC class II with an  $IC_{50}$  of less than about 30 nM as determined using a cell adherence assay, *e.g.*, as shown in Example 7 of PCT/US16/56156, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments thereof block mouse LAG3 binding to human MHC class II with an  $IC_{50}$  less than about 25nM, less than about 20nM, less than about 10nM, or less than about 5nM, as measured by a cell adherence assay, *e.g.*, using the assay format as defined in Example 7 of PCT/US16/56156, or a substantially similar assay.

**[087]** In some embodiments, the antibodies or antigen-binding fragments thereof block binding of LAG3 to human or mouse MHC class II by more than 90% as measured by a cell adherence assay as defined in Example 7 of PCT/US16/56156, or a substantially similar assay.

**[088]** In some embodiments, the antibodies or antigen-binding fragments thereof block LAG-induced T cell down-regulation with an  $EC_{50}$  less than 9nM as measured by a T cell/APC luciferase reporter assay as defined in Example 8 of PCT/US16/56156, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments thereof block LAG3-induced T cell down-regulation with an  $EC_{50}$  less than about 5nM, less than about 1nM, less than about 0.5nM, or less than about 0.1nM, as measured by a T cell/APC

luciferase reporter assay, e.g., using the assay format as defined in Example 8 of PCT/US16/56156, or a substantially similar assay.

**[089]** In some embodiments, the antibodies or antigen-binding fragments thereof bind to cynomolgus activated CD4<sup>+</sup> and CD8<sup>+</sup> T cells with an EC<sub>50</sub> less than about 1.2nM as measured by a fluorescence assay as defined in Example 9 of PCT/US16/56156, or a substantially similar assay. In certain embodiments, the antibodies or antigen-binding fragments thereof bind to cynomolgus activated CD4<sup>+</sup> and CD8<sup>+</sup> T cells with an EC<sub>50</sub> less than about 1.1nM, less than about 1nM, less than about 0.5nM, less than about 0.2nM, or less than about 0.1nM, as measured by a fluorescence assay, e.g., using the assay format as defined in Example 9 of PCT/US16/56156, or a substantially similar assay.

**[090]** In one embodiment, the antibody or fragment thereof is a monoclonal antibody or antigen-binding fragment thereof that binds to LAG3, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 370, 386, 402, 418, 434, 450, 458, 466, 474, 482, 490, 498, 506, 514, 538, and 554, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 522, 530, 546, and 562, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, 376, 392, 408, 424, 440, 456, 464, 472, 480, 488, 496, 504, 512, 520, 544, and 560, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 528, 536, 552, and 568, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 372, 388, 404, 420, 436, 452, 460, 468, 476, 484, 492, 500, 508, 516, 540, and 556, or a substantially similar sequence thereof having at least 90%, at least

95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 374, 390, 406, 422, 438, 454, 462, 470, 478, 486, 494, 502, 510, 518, 542, and 558, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 380, 396, 412, 428, 444, 524, 532, 548, and 564, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 398, 414, 430, 446, 526, 534, 550, and 566, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) binds monomeric human LAG3 with a binding dissociation equilibrium constant ( $K_D$ ) of less than about 10nM as measured in a surface plasmon resonance assay at 25°C; (vi) binds monomeric human LAG3 with a  $K_D$  less than about 8nM as measured in a surface plasmon resonance assay at 37°C; (vii) binds dimeric human LAG3 with a  $K_D$  less than about 1.1nM as measured in a surface plasmon resonance assay at 25°C; (viii) binds dimeric human LAG3 with a  $K_D$  less than about 1nM as measured in a surface plasmon resonance assay at 37°C; (ix) binds to a hLAG3-expressing cell with an  $EC_{50}$  less than about 8nM as measured in a flow cytometry assay; (x) binds to a mfLAG3-expressing cell with a  $EC_{50}$  less than about 2.3nM as measured in a flow cytometry assay; (xi) blocks binding of hLAG3 to human MHC class II with  $IC_{50}$  less than about 32nM as determined by a cell adherence assay; (xii) blocks binding of hLAG3 to mouse MHC class II with  $IC_{50}$  less than about 30nM as determined by a cell adherence assay; (xiii) blocks binding of hLAG3 to MHC class II by more than 90% as determined by a cell adherence assay; (xiv) rescues LAG3-mediated inhibition of T cell activity with  $EC_{50}$  less than about 9nM as determined in a luciferase reporter assay; (xv) binds to activated CD4+ and CD8+ T cells with  $EC_{50}$  less than about 1.2nM, as determined in a fluorescence assay; and (xvi) suppresses tumor growth and increases survival in a subject with cancer.

**[091]** In one embodiment, the antibody or fragment thereof is a monoclonal antibody or antigen-binding fragment thereof that blocks LAG3 binding to MHC class II, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258,

274, 290, 306, 322, 338, 354, 370, 386, 402, 418, 434, 450, 458, 466, 474, 482, 490, 498, 506, 514, 538, and 554, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 522, 530, 546, and 562, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, 376, 392, 408, 424, 440, 456, 464, 472, 480, 488, 496, 504, 512, 520, 544, and 560, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 528, 536, 552, and 568, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 372, 388, 404, 420, 436, 452, 460, 468, 476, 484, 492, 500, 508, 516, 540, and 556, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 374, 390, 406, 422, 438, 454, 462, 470, 478, 486, 494, 502, 510, 518, 542, and 558, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 380, 396, 412, 428, 444, 524, 532, 548, and 564, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 398, 414, 430, 446, 526, 534, 550, and 566, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) binds monomeric human LAG3 with a binding dissociation equilibrium constant ( $K_D$ ) of less than about 10nM as measured in a surface plasmon resonance assay



at 25°C; (vi) binds monomeric human LAG3 with a  $K_D$  less than about 8nM as measured in a surface plasmon resonance assay at 37°C; (vii) binds dimeric human LAG3 with a  $K_D$  less than about 1.1nM as measured in a surface plasmon resonance assay at 25°C; (viii) binds dimeric human LAG3 with a  $K_D$  less than about 1nM as measured in a surface plasmon resonance assay at 37°C; (ix) binds to a hLAG3-expressing cell with an  $EC_{50}$  less than about 8nM as measured in a flow cytometry assay; (x) binds to a mfLAG3-expressing cell with a  $EC_{50}$  less than about 2.3nM as measured in a flow cytometry assay; (xi) blocks binding of hLAG3 to human MHC class II with  $IC_{50}$  less than about 32nM as determined by a cell adherence assay; (xii) blocks binding of hLAG3 to mouse MHC class II with  $IC_{50}$  less than about 30nM as determined by a cell adherence assay; (xiii) blocks binding of hLAG3 to MHC class II by more than 90% as determined by a cell adherence assay; (xiv) rescues LAG3-mediated inhibition of T cell activity with  $EC_{50}$  less than about 9nM as determined in a luciferase reporter assay; (xv) binds to activated CD4+ and CD8+ T cells with  $EC_{50}$  less than about 1.2nM, as determined in a fluorescence assay; and (xvi) suppresses tumor growth and increases survival in a subject with cancer.

**[092]** In certain embodiments, the antibodies may function by blocking or inhibiting the MHC class II-binding activity associated with LAG3 by binding to any other region or fragment of the full length protein, the amino acid sequence of which is shown in SEQ ID NO: 582.

**[093]** In certain embodiments, the antibodies are bi-specific antibodies. The bi-specific antibodies can bind one epitope in one domain and can also bind a second epitope in a different domain of LAG3. In certain embodiments, the bi-specific antibodies bind two different epitopes in the same domain. In one embodiment, the multi-specific antigen-binding molecule comprises a first antigen-binding specificity wherein the first binding specificity comprises the extracellular domain or fragment thereof of LAG3; and a second antigen-binding specificity to another epitope of LAG3.

**[094]** In certain embodiments, the anti-LAG3 antibodies or antigen-binding fragments thereof bind an epitope within any one or more of the regions exemplified in LAG3, either in natural form, as exemplified in SEQ ID NO: 582, or recombinantly produced, as exemplified in SEQ ID NOS: 574 – 576, or to a fragment thereof. In some embodiments, the antibodies bind to an extracellular region comprising one or more amino acids selected from the group consisting of amino acid residues 29 – 450 of LAG3. In some embodiments, the antibodies bind to an extracellular region comprising one or more amino acids selected from the group consisting of amino acid residues 1 – 533 of cynomolgus LAG3, as exemplified by SEQ ID NO: 576.

**[095]** In certain embodiments, anti-LAG3 antibodies and antigen-binding fragments thereof interact with one or more epitopes found within the extracellular region of LAG3 (SEQ ID

NO: 588). The epitope(s) may consist of one or more contiguous sequences of 3 or more (e.g., 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more) amino acids located within the extracellular region of LAG3. Alternatively, the epitope may consist of a plurality of non-contiguous amino acids (or amino acid sequences) located within the extracellular region of LAG3. The epitope of LAG3 with which the exemplary antibody H4sH15482P interacts is defined by the amino acid sequence

LRRAGVTWQHQPDSGPPAAAPGHPLAPGPHPAAPSSWGPRPRRY (SEQ ID NO: 589), which corresponds to amino acids 28 to 71 of SEQ ID NO: 588. Accordingly, also included are anti-LAG3 antibodies that interact with one or more amino acids contained within the region consisting of amino acids 28 to 71 of SEQ ID NO: 588 (*i.e.*, the sequence LRRAGVTWQHQPDSGPPAAAPGHPLAPGPHPAAPSSWGPRPRRY [SEQ ID NO: 589]).

**[096]** The present disclosure includes anti-LAG3 antibodies that bind to the same epitope, or a portion of the epitope, as any of the specific exemplary antibodies described herein in Table 1, or an antibody having the CDR sequences of any of the exemplary antibodies described in Table 1. Likewise, also included are anti-LAG3 antibodies that compete for binding to LAG3 or a LAG3 fragment with any of the specific exemplary antibodies described herein in Table 1, or an antibody having the CDR sequences of any of the exemplary antibodies described in Table 1. For example, the present disclosure includes anti-LAG3 antibodies that cross-compete for binding to LAG3 with one or more antibodies provided herein (e.g., H4sH15482P, H4sH15479P, H4sH14813N, H4H14813N, H4H15479P, H4H15482P, H4H15483P, H4sH15498P, H4H15498P, H4H17828P2, H4H17819P, and H4H17823P).

**[097]** The antibodies and antigen-binding fragments described herein specifically bind to LAG3 and modulate the interaction of LAG3 with MHC class II. The anti-LAG3 antibodies may bind to LAG3 with high affinity or with low affinity. In certain embodiments, the antibodies are blocking antibodies wherein the antibodies bind to LAG3 and block the interaction of LAG3 with MHC class II. In some embodiments, the blocking antibodies of the disclosure block the binding of LAG3 to MHC class II and/or stimulate or enhance T-cell activation. In some embodiments, the blocking antibodies are useful for stimulating or enhancing the immune response and/or for treating a subject suffering from cancer, or a chronic viral infection. The antibodies when administered to a subject in need thereof may reduce the chronic infection by a virus such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), human papilloma virus (HPV), lymphocytic choriomeningitis virus (LCMV), and simian immunodeficiency virus (SIV) in the subject. They may be used to inhibit the growth of tumor cells in a subject. They may be used alone or as adjunct therapy with other therapeutic moieties or modalities known in the art for

treating cancer, or viral infection. In certain embodiments, the anti-LAG3 antibodies that bind to LAG3 with a low affinity are used as multi-specific antigen-binding molecules wherein the first binding specificity binds to LAG3 with a low affinity and the second binding specificity binds to an antigen selected from the group consisting of a different epitope of LAG3 and another T-cell co-inhibitor.

**[098]** In some embodiments, the antibodies bind to LAG3 and reverse the anergic state of exhausted T cells. In certain embodiments, the antibodies bind to LAG3 and inhibit regulatory T cell activity. In some embodiments, the antibodies may be useful for stimulating or enhancing the immune response and/or for treating a subject suffering from cancer, a viral infection, a bacterial infection, a fungal infection, or a parasitic infection. The antibodies when administered to a subject in need thereof may reduce chronic infection by a virus such as HIV, LCMV or HBV in the subject. They may be used to inhibit the growth of tumor cells in a subject. They may be used alone or as adjunct therapy with other therapeutic moieties or modalities known in the art for treating cancer, or viral infection.

**[099]** In certain embodiments, the antibodies of the present disclosure are agonist antibodies, wherein the antibodies bind to LAG3 and enhance the interaction of LAG3 and MHC class II. In some embodiments, the activating antibodies enhance binding of LAG3 to MHC class II and/or inhibit or suppress T-cell activation. The activating antibodies of the present disclosure may be useful for inhibiting the immune response in a subject and/or for treating autoimmune disease.

**[0100]** Certain anti-LAG3 antibodies are able to bind to and neutralize the activity of LAG3, as determined by *in vitro* or *in vivo* assays. The ability of the antibodies to bind to and neutralize the activity of LAG3 may be measured using any standard method known to those skilled in the art, including binding assays, or activity assays, as described herein.

**[0101]** Non-limiting, exemplary *in vitro* assays for measuring binding activity are illustrated in Examples provided in PCT/US16/56156: in Example 3, the binding affinities and kinetic constants of human anti-LAG3 antibodies for human LAG3 were determined by surface plasmon resonance and the measurements were conducted on a Biacore 4000 or T200 instrument; in Example 4, blocking assays were used to determine cross-competition between anti-LAG3 antibodies; Examples 5 and 6 describe the binding of the antibodies to cells overexpressing LAG3; in Example 7, binding assays were used to determine the ability of the anti-LAG3 antibodies to block MHC class II-binding ability of LAG3 *in vitro*; in Example 8, a luciferase assay was used to determine the ability of anti-LAG3 antibodies to antagonize LAG3 signaling in T cells; and in Example 9, a fluorescence assay was used to determine the ability of anti-LAG3 antibodies to bind to activated monkey CD4+ and CD8+ T cells.

**[0102]** Unless specifically indicated otherwise, the term "antibody," as used herein, shall be understood to encompass antibody molecules comprising two immunoglobulin heavy chains and two immunoglobulin light chains (*i.e.*, "full antibody molecules") as well as antigen-binding fragments thereof. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding fragment" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to LAG3. An antibody fragment may include a Fab fragment, a F(ab')<sub>2</sub> fragment, a Fv fragment, a dAb fragment, a fragment containing a CDR, or an isolated CDR. In certain embodiments, the term "antigen-binding fragment" refers to a polypeptide or fragment thereof of a multi-specific antigen-binding molecule. In such embodiments, the term "antigen-binding fragment" includes, *e.g.*, MHC class II molecule which binds specifically to LAG3. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and (optionally) constant domains. Such DNA is known and/or is readily available from, *e.g.*, commercial sources, DNA libraries (including, *e.g.*, phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

**[0103]** Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')<sub>2</sub> fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.* monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

**[0104]** An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and

will generally comprise at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a  $V_H$  domain associated with a  $V_L$  domain, the  $V_H$  and  $V_L$  domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain  $V_H - V_H$ ,  $V_H - V_L$  or  $V_L - V_L$  dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric  $V_H$  or  $V_L$  domain.

**[0105]** In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present disclosure include: (i)  $V_H - C_H1$ ; (ii)  $V_H - C_H2$ ; (iii)  $V_H - C_H3$ ; (iv)  $V_H - C_H1 - C_H2$ ; (v)  $V_H - C_H1 - C_H2 - C_H3$ ; (vi)  $V_H - C_H2 - C_H3$ ; (vii)  $V_H - C_L$ ; (viii)  $V_L - C_H1$ ; (ix)  $V_L - C_H2$ ; (x)  $V_L - C_H3$ ; (xi)  $V_L - C_H1 - C_H2$ ; (xii)  $V_L - C_H1 - C_H2 - C_H3$ ; (xiii)  $V_L - C_H2 - C_H3$ ; and (xiv)  $V_L - C_L$ . In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present disclosure may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric  $V_H$  or  $V_L$  domain (e.g., by disulfide bond(s)).

**[0106]** As with full antibody molecules, antigen-binding fragments may be mono-specific or multi-specific (e.g., bi-specific). A multi-specific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multi-specific antibody format, including the exemplary bi-specific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present disclosure using routine techniques available in the art.

**[0107]** The anti-LAG3 antibodies and antibody fragments of the present disclosure encompass proteins having amino acid sequences that vary from those of the described antibodies, but that retain the ability to bind LAG3. Such variant antibodies and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the antibody-encoding DNA sequences of the

present disclosure encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an antibody or antibody fragment that is essentially bioequivalent to an antibody or antibody fragment of the disclosure.

**[0108]** Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single dose or multiple doses. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

**[0109]** In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, or potency.

**[0110]** In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

**[0111]** In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

**[0112]** Bioequivalence may be demonstrated by *in vivo* and/or *in vitro* methods.

Bioequivalence measures include, e.g., (a) an *in vivo* test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an *in vitro* test that has been correlated with and is reasonably predictive of human *in vivo* bioavailability data; (c) an *in vivo* test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

**[0113]** Bioequivalent variants of the antibodies of the disclosure may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine

residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include antibody variants comprising amino acid changes, which modify the glycosylation characteristics of the antibodies, e.g., mutations that eliminate or remove glycosylation.

**[0114]** According to certain embodiments of the present disclosure, anti-LAG3 antibodies comprise an Fc domain comprising one or more mutations which enhance or diminish antibody binding to the FcRn receptor, e.g., at acidic pH as compared to neutral pH. For example, the present disclosure includes anti-LAG3 antibodies comprising a mutation in the C<sub>H</sub>2 or a C<sub>H</sub>3 region of the Fc domain, wherein the mutation(s) increases the affinity of the Fc domain to FcRn in an acidic environment (e.g., in an endosome where pH ranges from about 5.5 to about 6.0). Such mutations may result in an increase in serum half-life of the antibody when administered to an animal. Non-limiting examples of such Fc modifications include, e.g., a modification at position 250 (e.g., E or Q); 250 and 428 (e.g., L or F); 252 (e.g., L/Y/F/W or T), 254 (e.g., S or T), and 256 (e.g., S/R/Q/E/D or T); or a modification at position 428 and/or 433 (e.g., H/L/R/S/P/Q or K) and/or 434 (e.g., A, W, H, F or Y [N434A, N434W, N434H, N434F or N434Y]); or a modification at position 250 and/or 428; or a modification at position 307 or 308 (e.g., 308F, V308F), and 434. In one embodiment, the modification comprises a 428L (e.g., M428L) and 434S (e.g., N434S) modification; a 428L, 259I (e.g., V259I), and 308F (e.g., V308F) modification; a 433K (e.g., H433K) and a 434 (e.g., 434Y) modification; a 252, 254, and 256 (e.g., 252Y, 254T, and 256E) modification; a 250Q and 428L modification (e.g., T250Q and M428L); and a 307 and/or 308 modification (e.g., 308F or 308P). In yet another embodiment, the modification comprises a 265A (e.g., D265A) and/or a 297A (e.g., N297A) modification.

**[0115]** For example, the present disclosure includes anti-LAG3 antibodies comprising an Fc domain comprising one or more pairs or groups of mutations selected from the group consisting of: 250Q and 248L (e.g., T250Q and M248L); 252Y, 254T and 256E (e.g., M252Y, S254T and T256E); 428L and 434S (e.g., M428L and N434S); 257I and 311I (e.g., P257I and Q311I); 257I and 434H (e.g., P257I and N434H); 376V and 434H (e.g., D376V and N434H); 307A, 380A and 434A (e.g., T307A, E380A and N434A); and 433K and 434F (e.g., H433K and N434F). In one embodiment, the present disclosure includes anti-LAG3 antibodies comprising an Fc domain comprising a S108P mutation in the hinge region of IgG4 to promote dimer stabilization. All possible combinations of the foregoing Fc domain mutations, and other mutations within the antibody variable domains disclosed herein, are contemplated within the scope of the present disclosure.

**[0116]** The present disclosure also includes anti-LAG3 antibodies comprising a chimeric

heavy chain constant ( $C_H$ ) region, wherein the chimeric  $C_H$  region comprises segments derived from the  $C_H$  regions of more than one immunoglobulin isotype. For example, the antibodies of the disclosure may comprise a chimeric  $C_H$  region comprising part or all of a  $C_{H2}$  domain derived from a human IgG1, human IgG2 or human IgG4 molecule, combined with part or all of a  $C_{H3}$  domain derived from a human IgG1, human IgG2 or human IgG4 molecule. According to certain embodiments, the antibodies of the disclosure comprise a chimeric  $C_H$  region having a chimeric hinge region. For example, a chimeric hinge may comprise an "upper hinge" amino acid sequence (amino acid residues from positions 216 to 227 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region, combined with a "lower hinge" sequence (amino acid residues from positions 228 to 236 according to EU numbering) derived from a human IgG1, a human IgG2 or a human IgG4 hinge region. According to certain embodiments, the chimeric hinge region comprises amino acid residues derived from a human IgG1 or a human IgG4 upper hinge and amino acid residues derived from a human IgG2 lower hinge. An antibody comprising a chimeric  $C_H$  region as described herein may, in certain embodiments, exhibit modified Fc effector functions without adversely affecting the therapeutic or pharmacokinetic properties of the antibody. (See, e.g., US Patent Publication No. 20140243504, the disclosure of which is hereby incorporated by reference in its entirety). In certain embodiments, the Fc region comprises a sequence selected from the group consisting of SEQ ID NOs: 569, 570, 571, 572 and 573.

## **B. Positron Emitters and Chelating Moieties**

**[0117]** Suitable positron emitters include, but are not limited to, those that form stable complexes with the chelating moiety and have physical half-lives suitable for immuno-PET imaging purposes. Illustrative positron emitters include, but are not limited to,  $^{89}\text{Zr}$ ,  $^{68}\text{Ga}$ ,  $^{64}\text{Cu}$ ,  $^{44}\text{Sc}$ , and  $^{86}\text{Y}$ . Suitable positron emitters also include those that directly bond with the LAG3 binding protein, including, but not limited to,  $^{76}\text{Br}$  and  $^{124}\text{I}$ , and those that are introduced via prosthetic group, e.g.,  $^{18}\text{F}$ .

**[0118]** The chelating moieties described herein are chemical moieties that are covalently linked to the LAG3 binding protein, e.g., anti-LAG3 antibody and comprise a portion capable of chelating a positron emitter, i.e., capable of reacting with a positron emitter to form a coordinated chelate complex. Suitable moieties include those that allow efficient loading of the particular metal and form metal-chelator complexes that are sufficiently stable *in vivo* for diagnostic uses, e.g., immuno-PET imaging. Illustrative chelating moieties include those that minimize dissociation of the positron emitter and accumulation in mineral bone, plasma



proteins, and/or bone marrow depositing to an extent suitable for diagnostic uses.

**[0119]** Examples of chelating moieties include, but are not limited to, those that form stable complexes with positron emitters  $^{89}\text{Zr}$ ,  $^{68}\text{Ga}$ ,  $^{64}\text{Cu}$ ,  $^{44}\text{Sc}$ , and/or  $^{86}\text{Y}$ . Illustrative chelating moieties include, but are not limited to, those described in *Nature Protocols*, 5(4): 739, 2010; *Bioconjugate Chem.*, 26(12): 2579 (2015); *Chem Commun (Camb)*, 51(12): 2301 (2015); *Mol. Pharmaceutics*, 12: 2142 (2015); *Mol. Imaging Biol.*, 18: 344 (2015); *Eur. J. Nucl. Med. Mol. Imaging*, 37:250 (2010); *Eur. J. Nucl. Med. Mol. Imaging* (2016). doi:10.1007/s00259-016-3499-x; *Bioconjugate Chem.*, 26(12): 2579 (2015); WO 2015/140212A1; and US 5,639,879, incorporated by reference in their entireties.

**[0120]** Illustrative chelating moieties also include, but are not limited to, those that comprise desferrioxamine (DFO), 1,4,7,10-tetraacetic acid (DOTA), diethylenetriaminepentaacetic acid (DTPA), ethylenediaminetetraacetic acid (EDTA), (1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetra(methylene phosphonic) acid (DOTP), 1R, 4R, 7R, 10R)- $\alpha'$ -Tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTMA), 1,4,8,11-Tetraazacyclotetradecane-1,4,8, 11-tetraacetic acid (TETA),  $\text{H}_4\text{octapa}$ ,  $\text{H}_6\text{phospa}$ ,  $\text{H}_2\text{dedpa}$ ,  $\text{H}_5\text{decapa}$ ,  $\text{H}_2\text{azapa}$ , HOPO, DO2A, 1,4,7,10-Tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane (DOTAM), 1,4,7-triazacyclononane-N,N',N''-triacetic acid (NOTA), 1,4,7,10-Tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane (DOTAM), 1,4,8,11-tetraazabicyclo[6.6.2]hexadecane-4, 11-dicetic acid (CB-TE2A), 1,4,7,10-Tetraazacyclododecane (Cyclen), 1,4,8,11-Tetraazacyclotetradecane (Cyclam), octadentate chelators, e.g., DFO\*, which can be conjugated to the antibody via DFO\*-pPhe-NCS (See Vugt et al., *Eur J Nucl Med Mol Imaging* (2017) 44: 286–295), hexadentate chelators, phosphonate-based chelators, macrocyclic chelators, chelators comprising macrocyclic terephthalamide ligands, bifunctional chelators, fusarinine C and fusarinine C derivative chelators, triacetyl-fusarinine C (TAFC), ferrioxamine E (FOX E), ferrioxamine B (FOX B), ferrichrome A (FCHA), and the like.

**[0121]** In some embodiments, the chelating moieties are covalently bonded to the LAG3 binding protein, e.g., antibody or antigen binding fragment thereof, via a linker moiety, which covalently attaches the chelating portion of the chelating moiety to the binding protein. In some embodiments, these linker moieties are formed from a reaction between a reactive moiety of the LAG3 binding protein, e.g., cysteine or lysine of an antibody, and reactive moiety that is attached to a chelator, including, for example, a p-isothiocyanatobenzyl group and the reactive moieties provided in the conjugation methods below. In addition, such linker moieties optionally comprise chemical groups used for purposes of adjusting polarity, solubility, steric interactions, rigidity, and/or the length between the chelating portion and the

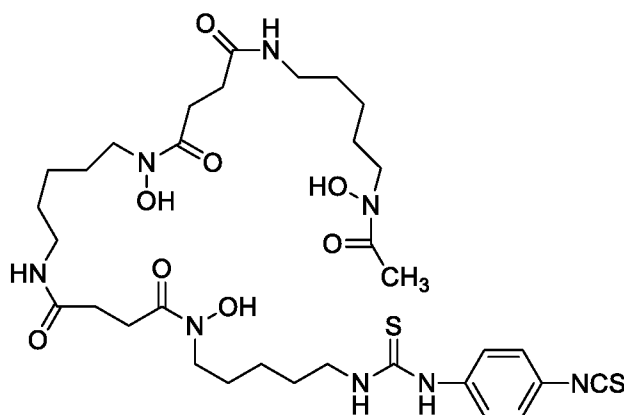
LAG3 binding protein.

### C. Preparation of Radiolabeled Anti-LAG3 Conjugates

**[0122]** The radiolabeled anti-LAG3 protein conjugates can be prepared by (1) reacting a LAG3 binding protein, *e.g.*, antibody, with a molecule comprising a positron emitter chelator and a moiety reactive to the desirable conjugation site of the LAG3 binding protein and (2) loading the desirable positron emitter.

**[0123]** Suitable conjugation sites include, but are not limited to, lysine and cysteine, both of which can be, for example, native or engineered, and can be, for example, present on the heavy or light chain of an antibody. Cysteine conjugation sites include, but are not limited to, those obtained from mutation, insertion, or reduction of antibody disulfide bonds. Methods for making cysteine engineered antibodies include, but are not limited to, those disclosed in WO2011/056983. Site-specific conjugation methods can also be used to direct the conjugation reaction to specific sites of an antibody, achieve desirable stoichiometry, and/or achieve desirable chelator-to-antibody ratios. Such conjugation methods are known to those of ordinary skill in the art and include, but are not limited to cysteine engineering and enzymatic and chemo-enzymatic methods, including, but not limited to, glutamine conjugation, Q295 conjugation, and transglutaminase-mediated conjugation, as well as those described in *J.Clin.Immunol.*, 36: 100 (2016), incorporated herein by reference in its entirety. Suitable moieties reactive to the desirable conjugation site generally enable efficient and facile coupling of the LAG3 binding protein, *e.g.*, antibody and positron emitter chelator. Moieties reactive to lysine and cysteine sites include electrophilic groups, which are known to those of ordinary skill. In certain aspects, when the desired conjugation site is lysine, the reactive moiety is an isothiocyanate, *e.g.*, p-isothiocyanatobenzyl group or reactive ester. In certain aspects, when the desired conjugation site is cysteine, the reactive moiety is a maleimide.

**[0124]** When the chelator is desferrioxamine (DFO), suitable reactive moieties include, but are not limited to, an isothiocyanatobenzyl group, an n-hydroxysuccinimide ester, 2,3,5,6 tetrafluorophenol ester, n-succinimidyl-S-acetylthioacetate, and those described in *BioMed Research International*, Vol 2014, Article ID 203601, incorporated herein by reference in its entirety. In certain embodiments, the LAG3 binding protein is an antibody and the molecule comprising a positron emitter chelator and moiety reactive to the conjugation site is p-isothiocyanatobenzyl-desferrioxamine (p-SCN-Bn-DFO):



**[0125]** Positron emitter loading is accomplished by incubating the LAG3 binding protein chelator conjugate with the positron emitter for a time sufficient to allow coordination of said positron emitter to the chelator, *e.g.*, by performing the methods described in the examples provided herein, or substantially similar method.

#### D. Illustrative Embodiments of Conjugates

**[0126]** Included in the instant disclosure are radiolabeled antibody conjugates comprising an antibody or antigen binding fragment thereof that binds human LAG3 and a positron emitter. Also included in the instant disclosure are radiolabeled antibody conjugates comprising an antibody or antigen binding fragment thereof that binds human LAG3, a chelating moiety, and a positron emitter.

**[0127]** In some embodiments, the chelating moiety comprises a chelator capable of forming a complex with  $^{89}\text{Zr}$ . In certain embodiments, the chelating moiety comprises desferrioxamine. In certain embodiments, the chelating moiety is p-isothiocyanatobenzyl-desferrioxamine.

**[0128]** In some embodiments, the positron emitter is  $^{89}\text{Zr}$ . In some embodiments, less than 1.0% of the anti-LAG3 antibody is conjugated with the positron emitter, less than 0.9% of the anti-LAG3 antibody is conjugated with the positron emitter, less than 0.8% of the anti-LAG3 antibody is conjugated with the positron emitter, less than 0.7% of the anti-LAG3 antibody is conjugated with the positron emitter, less than 0.6% of the anti-LAG3 antibody is conjugated with the positron emitter, less than 0.5% of the anti-LAG3 antibody is conjugated with the positron emitter, less than 0.4% of the anti-LAG3 antibody is conjugated with the positron emitter, less than 0.3% of the anti-LAG3 antibody is conjugated with the positron emitter, less than 0.2% of the anti-LAG3 antibody is conjugated with the positron emitter, or less than 0.1% of the anti-LAG3 antibody is conjugated with the positron emitter.

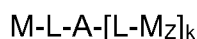
**[0129]** In some embodiments, the chelating moiety-to-antibody ratio of the conjugate is from 1 to 2.

**[0130]** In a particular embodiment, chelating moiety is p-isothiocyanatobenzyl-desferrioxamine and the positron emitter is  $^{89}\text{Zr}$ . In another particular embodiment, the chelating moiety is p-isothiocyanatobenzyl-desferrioxamine and the positron emitter is  $^{89}\text{Zr}$ , and the chelating moiety-to-antibody ratio of the conjugate is from 1 to 2.

**[0131]** In some embodiments, provided herein are antigen-binding proteins that bind LAG3, wherein said antigen-binding proteins that bind LAG3 are covalently bonded to one or more moieties having the following structure:



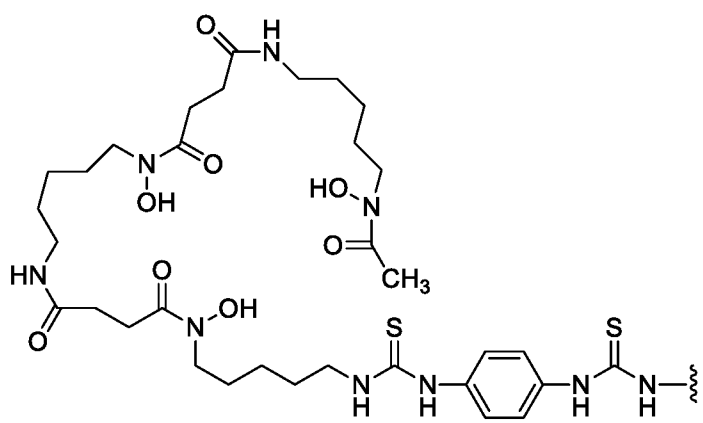
wherein L is a chelating moiety; M is a positron emitter; and z, independently at each occurrence, is 0 or 1; and wherein at least one of z is 1. In certain embodiments, the radiolabeled antigen-binding protein is a compound of Formula (I):



(I)

A is a protein that binds LAG3; L is a chelating moiety; M is a positron emitter; z is 0 or 1; and k is an integer from 0-30. In some embodiments, k is 1.

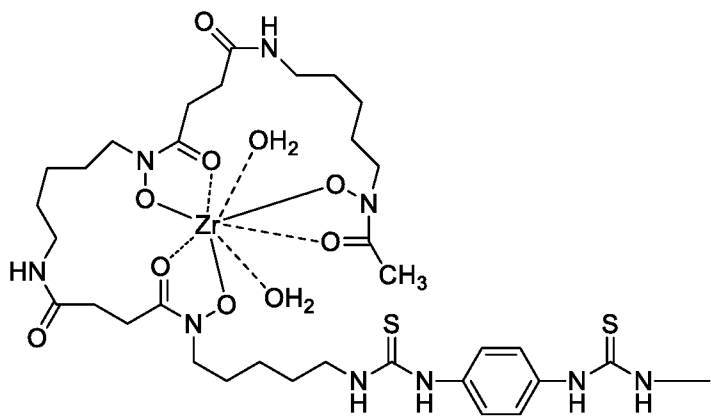
**[0132]** In some embodiments, L is:



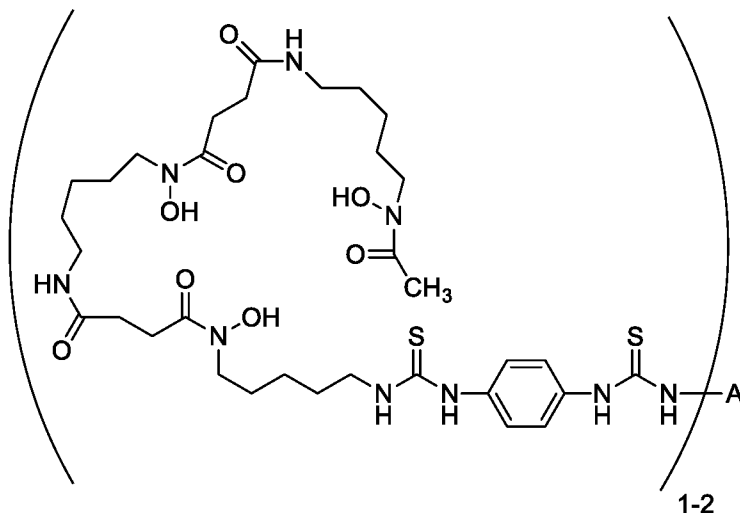
**[0133]** In some embodiments, M is  $^{89}\text{Zr}$ .

**[0134]** In some embodiments, k is an integer from 1 to 2. In some embodiments, k is 1.

**[0135]** In some embodiments, -L-M is



**[0136]** Included in the instant disclosure are also methods of synthesizing a radiolabeled antibody conjugates comprising contacting a compound of Formula (III):

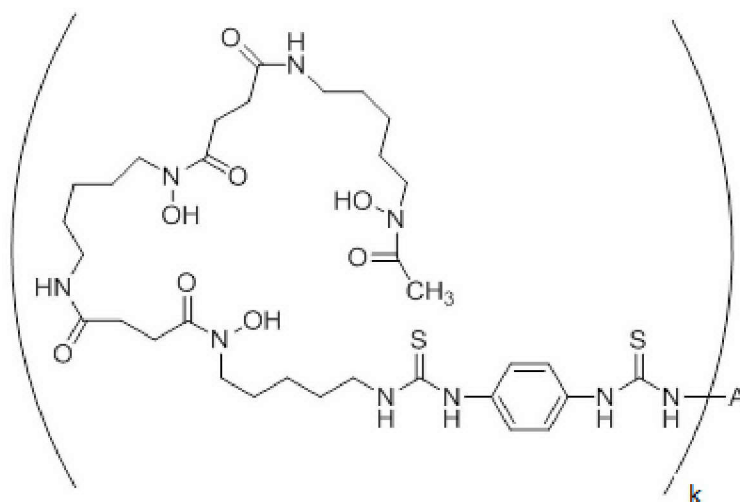


(III)

with  $^{89}\text{Zr}$ , wherein A is an antibody or antigen-binding fragment thereof that binds LAG3. In certain embodiments, the compound of Formula (III) is synthesized by contacting an antibody, or antigen binding fragment thereof, that binds LAG3, with p-SCN-Bn-DFO.

**[0137]** Provided herein is also the product of the reaction between a compound of Formula (III) with  $^{89}\text{Zr}$ .

**[0138]** Provided herein are compounds of Formula (III):



wherein A is an antibody or antigen binding fragment thereof that binds LAG3 and k is an integer from 1-30. In some embodiments, k is 1 or 2.

**[0139]** In some embodiments, provided herein are compositions comprising a conjugate having the following structure:



wherein A is a protein that binds LAG3; L is a chelating moiety; and k is an integer from 1-30; wherein the conjugate is chelated with a positron emitter in an amount sufficient to provide a specific activity suitable for clinical PET imaging. In some embodiments, the amount of chelated positron emitter is an amount sufficient to provide a specific activity of about 1 to about 20 mCi per 1-50 mg of the protein that binds LAG3. In some embodiments, the amount of chelated positron emitter is an amount sufficient to provide a specific activity of up to 20 mCi, up to 15 mCi, or up to 10 mCi per 1-50 mg of the protein that binds LAG3, for example, in a range of about 3 to about 20 mCi, about 5 to about 20 mCi, about 1 to about 15 mCi, about 3 to about 15 mCi, about 5 to about 15 mCi, about 1 to about 10 mCi, or about 3 to about 10 mCi.

**[0140]** In some embodiments, the antibody or antigen-binding fragment thereof binds monomeric human LAG3 with a binding dissociation equilibrium constant ( $K_D$ ) of less than about 2 nM as measured in a surface plasmon resonance assay at 37°C.

**[0141]** In some embodiments, the antibody or antigen-binding fragment thereof binds monomeric human LAG3 with a  $K_D$  less than about 1.5 nM in a surface plasmon resonance assay at 25°C.

**[0142]** In some embodiments, the antibody or antigen-binding fragment thereof binds dimeric human LAG3 with a  $K_D$  of less than about 90 pM as measured in a surface plasmon resonance assay at 37°C.

**[0143]** In some embodiments, the antibody or antigen-binding fragment thereof that binds dimeric human LAG3 with a  $K_D$  less than about 20 pM in a surface plasmon resonance assay at 25°C.

**[0144]** In some embodiments, the antibody or antigen-binding fragment thereof competes for binding to human LAG3 with a reference antibody comprising the complementarity determining regions (CDRs) of a HCVR, wherein the HCVR has an amino acid sequence selected from the group consisting of HCVR sequences listed in Table 1; and the CDRs of a LCVR, wherein the LCVR has an amino acid sequence selected from the group consisting of LCVR sequences listed in Table 1. In some embodiments, the reference antibody or antigen-binding fragment thereof comprises an HCVR/LCVR amino acid sequence pair as set forth in Table 1. In some embodiments, the reference antibody comprises an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 370/378, 386/394, 402/410, 418/426, 434/442, 450/522, 458/522, 466/522, 474/522, 482/522, 490/522, 498/530, 506/530, 514/530, 538/546, and 554/562.

**[0145]** In some embodiments, the antibody or antigen-binding fragment thereof enhances LAG3 binding to MHC class II. In some embodiments, the antibody or antigen binding fragment thereof blocks LAG3 binding to MHC class II. In some embodiments, the antibody or antigen binding fragment thereof do not increase or decrease LAG3 binding to its ligands.

**[0146]** In some embodiments, the antibody or antigen-binding fragment thereof comprises the complementarity determining regions (CDRs) of a HCVR, wherein the HCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322, 338, 354, 370, 386, 402, 418, 434, 450, 458, 466, 474, 482, 490, 498, 506, 514, 538, and 554; and the CDRs of a LCVR, wherein the LCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 522, 530, 546, and 562. In certain embodiments, the isolated antibody comprises an HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 370/378, 386/394, 402/410, 418/426, 434/442, 450/522, 458/522, 466/522, 474/522, 482/522, 490/522, 498/530, 506/530, 514/530, 538/546, and 554/562. In certain embodiments, the isolated antibody comprises an HCVR/LCVR amino acid sequence pair

selected from the group consisting of SEQ ID NOs: 386/394, 418/426, 538/546, 577/578, 579/578, and 580/581.

**[0147]** In some embodiments, the antibody is a human monoclonal antibody or antigen-binding fragment thereof that binds specifically to human LAG3, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of HCVR sequences listed in Table 1.

**[0148]** In some embodiments, the antibody is a human monoclonal antibody or antigen-binding fragment thereof that binds specifically to human LAG3, wherein the antibody or antigen-binding fragment thereof comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of LCVR sequences listed in Table 1.

**[0149]** In some embodiments, the antibody a human monoclonal antibody or antigen-binding fragment thereof that binds specifically to human LAG3, wherein the antibody or antigen-binding fragment thereof comprises (a) a HCVR having an amino acid sequence selected from the group consisting of HCVR sequences listed in Table 1; and (b) a LCVR having an amino acid sequence selected from the group consisting of LCVR sequences listed in Table 1.

**[0150]** In some embodiments, the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) sequences listed in Table 1; and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) sequences listed in Table 1.

**[0151]** In some embodiments, the antibody or antigen-binding fragment thereof comprises:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324, 340, 356, 372, 388, 404, 420, 436, 452, 460, 468, 476, 484, 492, 500, 508, 516, 540, and 556;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326, 342, 358, 374, 390, 406, 422, 438, 454, 462, 470, 478, 486, 494, 502, 510, 518, 542, and 558;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, 344, 360, 376, 392, 408, 424, 440, 456, 464, 472, 480, 488, 496, 504, 512, 520, 544, and 560;



(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332, 348, 364, 380, 396, 412, 428, 444, 524, 532, 548, and 564;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334, 350, 366, 382, 398, 414, 430, 446, 526, 534, 550, and 566; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336, 352, 368, 384, 400, 416, 432, 448, 528, 536, 552, and 568.

**[0152]** In some embodiments, the antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346, 354/362, 370/378, 386/394, 402/410, 418/426, 434/442, 450/522, 458/522, 466/522, 474/522, 482/522, 490/522, 498/530, 506/530, 514/530, 538/546, and 554/562. In some embodiments, the antibody or antigen-binding fragment comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 386/394, 418/426, and 538/546.

## **E. Scaled Manufacturing for Production of Anti-LAG3 Antibody-Chelator Conjugates**

**[0153]** Included in the present disclosure are scaled-up manufacturing processes for producing anti-LAG3 antibodies conjugated to a chelator. The anti-LAG3 antibody-chelator conjugates are in a form suitable for radiolabeling.

**[0154]** Good manufacturing processes are adhered to in all aspects of production, including maintaining a sterile environment, practicing aseptic procedures, keeping records of all processes, and documenting product quality, purity, strength, and identity, and any deviations therefrom.

**[0155]** The scaled-up manufacturing process is, in some embodiments, much faster than the manufacturing process for research and development. In some embodiments, the scaled-up manufacturing process can take less than 12 hours, or less than 10 hours, or less than 8 hours, or less than 6 hours, or less than 4 hours, or less than or about 2 hours.

**[0156]** In some embodiments, a first step comprises ultrafiltration and diafiltration (UFDF), using a 30-50kDa membrane, of the anti-LAG3 antibody to remove excipients, conjugation interfering species, and salts that inhibit the conjugation process. Exemplary membrane polymers include polyethersulfone (PES), cellulose acetate (CA), and regenerated cellulose (RC). In this step, the antibody is buffer exchanged in a low ionic strength and non-interfering buffer solution. The buffer pH can be between about 4.5 to about 6, or about 5 to about 6, or about 5.3 to about 5.7, or about 5.5. Buffer systems contemplated herein include any buffer system lacking a primary amine. Exemplary buffers include acetate, phosphate, or citrate buffers. The buffer provides protein stability during pre-conjugation processing. The process volume can be further reduced to concentrate the antibody, then sterile filtered.

**[0157]** Following the pre-conjugation UFDF, the concentrated and filtered antibody can be transferred into an amine free carbonate buffer system. The carbonate buffer system can have a pH in a range from about 8.5 to about 9.6, or from about 9.0 to about 9.6, or from about 9.2 to about 9.4, or from about 9.4 to about 9.6, or a pH of about 9.4.

**[0158]** A chelator, for example, DFO, in solvent is added to a target concentration into the buffer system containing the antibody, and additional solvent can be added to the solution to a desired percentage. The chelator can be added in molar excess of the antibody, for example, 3.5-5:1 chelator to antibody. The total reaction volume can be up to 5 L.

**[0159]** The reaction temperature and the reaction time are inversely related. For example, if the reaction temperature is higher, the reaction time is lower. If the reaction temperature is lower, the reaction time is higher. Illustratively, at a temperature above about 18°C, the reaction may take less than 2 hours; at a temperature below 18°C, the reaction may take more than 2 hours.

**[0160]** The conjugation reaction can be terminated by quenching, for example, by the addition of acetic acid.

**[0161]** In some embodiments, conjugation of the antibody with deferoxamine is performed to produce DFO-mAb conjugates. In some embodiments, conjugation of the antibody with p-SCN-Bn-deferoxamine is performed to produce DFO-mAb conjugates.

**[0162]** Exemplary solvents for the chelator include DMSO and DMA. Subsequent UFDF steps utilize membranes, and the membrane is chosen based on the solvent system used in the conjugation step. For example, DMA dissolves PES membranes, so the two could not be used in the same system.

**[0163]** Carbonate buffers are not preferred for stability of the conjugate during long term storage. Thus, once the antibody-chelator conjugates have been formed, they can be buffer exchanged into a buffer chosen specifically for long term storage and stability. Exemplary buffers include citrate, acetate, phosphate, arginine, and histidine buffers. A further UFDF

step can be performed to remove residual salts and to provide a suitable concentration, excipient level, and pH of the conjugated monoclonal antibody. The resulting antibody-chelator conjugates can be sterile filtered and stored for subsequent formulation.

### **III. Methods of Using Radiolabeled Immunoconjugates**

**[0164]** In certain aspects, the present disclosure provides diagnostic and therapeutic methods of use of the radiolabeled antibody conjugates of the present disclosure.

**[0165]** According to one aspect, the present disclosure provides methods of detecting LAG3 in a tissue, the methods comprising administering a radiolabeled anti-LAG3 antibody conjugate of the provided herein to the tissue; and visualizing the LAG3 expression by positron emission tomography (PET) imaging. In certain embodiments, the tissue comprises cells or cell lines. In certain embodiments, the tissue is present in a subject, wherein the subject is a mammal. In certain embodiments, the subject is a human subject. In certain embodiments, the subject has a disease or disorder selected from the group consisting of cancer, infectious disease and inflammatory disease. In one embodiment, the subject has cancer. In certain embodiments, the infectious disease is a bacterial infection caused by, for example, rickettsial bacteria, bacilli, klebsiella, meningococci and gonococci, proteus, pneumonococci, pseudomonas, streptococci, staphylococci, serratia, Borriella, Bacillus anthracis, Chlamydia, Clostridium, Corynebacterium diphtheriae, Legionella, Mycobacterium leprae, Mycobacterium lepromatosis, Salmonella, Vibrio cholerae, and Yersinia pestis. In certain embodiments, the infectious disease is a viral infection caused by, for example, human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), herpes virus (e.g., VZV, HSV-I, HAV-6, HSV-II, CMV, and Epstein Barr virus), human papilloma virus (HPV), lymphocytic choriomeningitis virus (LCMV), and simian immunodeficiency virus (SIV). In certain embodiments, the infectious disease is a parasitic infection caused by, for example, Entamoeba spp., Enterobius vermicularis, Leishmania spp., Toxocara spp., Plasmodium spp., Schistosoma spp., Taenia solium, Toxoplasma gondii, and Trypanosoma cruzi. In certain embodiments, the infectious disease is a fungal infection caused by, for example, Aspergillus (fumigatus, niger, etc.), Blastomyces dermatitidis, Candida (albicans, krusei, glabrata, tropicalis, etc.), Coccidioides immitis, Cryptococcus neoformans, Genus Mucorales (mucor, absidia, rhizopus, etc.), Histoplasma capsulatum, Paracoccidioides brasiliensis, and Sporothrix schenkii.

**[0166]** According to one aspect, the present disclosure provides methods of imaging a tissue that expresses LAG3 comprising administering a radiolabeled anti-LAG3 antibody conjugate of the present disclosure to the tissue; and visualizing the LAG3 expression by positron emission tomography (PET) imaging. In one embodiment, the tissue is comprised

in a tumor. In one embodiment, the tissue is comprised in a tumor cell culture or tumor cell line. In one embodiment, the tissue is comprised in a tumor lesion in a subject. In one embodiment, the tissue is intratumoral lymphocytes in a tissue. In one embodiment, the tissue comprises LAG3-expressing cells.

**[0167]** According to one aspect, the present disclosure provides methods for measuring response to a therapy, wherein the response to a therapy is measured by measuring inflammation. The methods, according to this aspect, comprise administering a radiolabeled antibody conjugate provided herein to a subject in need thereof and visualizing the LAG3 expression by positron emission tomography (PET) imaging. In certain embodiments, the inflammation is present in a tumor in the subject. In certain embodiments, an increase in LAG3 expression correlates to increase in inflammation in a tumor. In certain embodiments, the inflammation is present in an infected tissue in the subject. In certain embodiments, an decrease in LAG3 expression correlates to a decrease in inflammation in an infected tissue.

**[0168]** According to one aspect, the present disclosure provides methods for measuring response to a therapy, wherein the response to a therapy is measured by measuring inflammation. The methods, according to this aspect, comprise (i) administering a radiolabeled antibody conjugate provided herein to a subject in need thereof and visualizing the LAG3 expression by positron emission tomography (PET) imaging, and (ii) repeating step (i) one or more times after initiation of therapy. In certain embodiments, the inflammation is present in a tissue in the subject. In certain embodiments, an increase in LAG3 expression correlates to increase in inflammation in the tissue. In certain embodiments, a decrease in LAG3 expression correlates to a decrease in inflammation in the tissue. In certain embodiments, LAG3 expression visualized in step (i) is compared to LAG3 expression visualized in step (ii).

**[0169]** According to one aspect, the present disclosure provides methods for determining if a patient is suitable for anti-tumor therapy comprising an inhibitor of LAG3, the methods comprising selecting a patient with a solid tumor, administering a radiolabeled antibody conjugate of the present disclosure, and localizing the administered radiolabeled antibody conjugate in the tumor by PET imaging wherein presence of the radiolabeled antibody conjugate in the tumor identifies the patient as suitable for anti-tumor therapy comprising an inhibitor of LAG3.

**[0170]** According to one aspect, the present disclosure provides methods for identifying a candidate for anti-tumor therapy comprising an inhibitor of LAG3 and an inhibitor of the PD-1/PD-L1 signaling axis, the methods comprising selecting a patient with a solid tumor, administering a radiolabeled antibody conjugate of the present disclosure, and localizing the administered radiolabeled antibody conjugate in the tumor by PET imaging wherein

presence of the radiolabeled antibody conjugate in the tumor identifies the patient as suitable for anti-tumor therapy comprising an inhibitor of LAG3. In some embodiments, the patient is further administered a radiolabeled anti-PD-1 conjugate and the administered radiolabeled anti-PD-1 conjugate is localized in the tumor by PET imaging, wherein presence of the radiolabeled antibody conjugate in the tumor identifies the patient as suitable for anti-tumor therapy comprising an inhibitor of the PD-1/PD-L1 signaling axis.

**[0171]** Provided herein are also methods for predicting response of a patient to an anti-tumor therapy, the methods comprising selecting a patient with a solid tumor; and determining if the tumor is LAG3-positive, wherein if the tumor is LAG3-positive it predicts a positive response of the patient to an anti-tumor therapy. In certain embodiments, the tumor is determined positive by administering a radiolabeled anti-LAG3 antibody conjugate of the present disclosure and localizing the radiolabeled antibody conjugate in the tumor by PET imaging wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor is LAG3-positive.

**[0172]** In some embodiments, the anti-tumor therapy is selected from a PD-1 inhibitor (e.g., REGN2810, BGB-A317, nivolumab, pidilizumab, and pembrolizumab), a PD-L1 inhibitor (e.g., atezolizumab, avelumab, durvalumab, MDX-1105, and REGN3504, as well as those disclosed in Patent Publication No. US 2015-0203580), CTLA-4 inhibitor (e.g., ipilimumab), a TIM3 inhibitor, a BTLA inhibitor, a TIGIT inhibitor, a CD47 inhibitor, a GITR inhibitor, an antagonist of another T cell co-inhibitor or ligand (e.g., an antibody to CD-28, 2B4, LY108, LAIR1, ICOS, CD160 or VISTA), an indoleamine-2,3-dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist [e.g., a “VEGF-Trap” such as aflibercept or other VEGF-inhibiting fusion protein as set forth in US 7,087,411, or an anti-VEGF antibody or antigen binding fragment thereof (e.g., bevacizumab, or ranibizumab) or a small molecule kinase inhibitor of VEGF receptor (e.g., sunitinib, sorafenib, or pazopanib)], an Ang2 inhibitor (e.g., nesvacumab), a transforming growth factor beta (TGF $\beta$ ) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor (e.g., erlotinib, cetuximab), a CD20 inhibitor (e.g., an anti-CD20 antibody such as rituximab), an antibody to a tumor-specific antigen [e.g., CA9, CA125, melanoma-associated antigen 3 (MAGE3), carcinoembryonic antigen (CEA), vimentin, tumor-M2-PK, prostate-specific antigen (PSA), mucin-1, MART-1, and CA19-9], a vaccine (e.g., Bacillus Calmette-Guerin, a cancer vaccine), an adjuvant to increase antigen presentation (e.g., granulocyte-macrophage colony-stimulating factor), a bispecific antibody (e.g., CD3xCD20 bispecific antibody, or PSMAxCD3 bispecific antibody), a cytotoxin, a chemotherapeutic agent (e.g., dacarbazine, temozolomide, cyclophosphamide, docetaxel, doxorubicin, daunorubicin, cisplatin, carboplatin, gemcitabine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, and

vincristine), cyclophosphamide, radiotherapy, an IL-6R inhibitor (e.g., sarilumab), an IL-4R inhibitor (e.g., dupilumab), an IL-10 inhibitor, a cytokine such as IL-2, IL-7, IL-21, and IL-15, and an antibody-drug conjugate (ADC) (e.g., anti-CD19-DM4 ADC, and anti-DS6-DM4 ADC).

**[0173]** In some embodiments, the anti-tumor therapy is selected from the following: nivolumab, ipilimumab, pembrolizumab, and combinations thereof.

**[0174]** According to one aspect, the present disclosure provides methods for predicting response of a patient to an anti-tumor therapy comprising an inhibitor of LAG3, the methods comprising selecting a patient with a solid tumor, determining if the tumor is LAG3-positive, wherein a positive response of the patient is predicted if the tumor is LAG3-positive. In certain embodiments, the tumor is determined positive by administering a radiolabeled antibody conjugate of the present disclosure and localizing the radiolabeled antibody conjugate in the tumor by PET imaging wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor is LAG3-positive.

**[0175]** According to one aspect, the present disclosure provides methods for predicting response of a patient to an anti-tumor therapy comprising an inhibitor of LAG3 in combination with an inhibitor of the PD-1/PD-L1 signaling axis, the methods comprising selecting a patient with a solid tumor, determining if the tumor is LAG3 positive and PD-1-positive, wherein a positive response of the patient is predicted if the tumor is LAG3 positive and PD-1-positive. In certain embodiments, the tumor is determined LAG3 positive by administering a radiolabeled anti-LAG3 conjugate and localizing the radiolabeled antibody conjugate in the tumor by PET imaging wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor is LAG3-positive. In certain embodiments, the tumor is determined PD-1 positive by further administering a radiolabeled anti-PD-1 conjugate and localizing the radiolabeled anti-PD-1 conjugate in the tumor by PET imaging wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor is PD-1-positive.

**[0176]** According to one aspect, the present disclosure provides methods for detecting a LAG3-positive tumor in a subject. The methods, according to this aspect, comprise selecting a subject with a solid tumor; administering a radiolabeled antibody conjugate of the present disclosure to the subject; and determining localization of the radiolabeled antibody conjugate by PET imaging, wherein presence of the radiolabeled antibody conjugate in a tumor indicates that the tumor is LAG3-positive.

**[0177]** In some aspects, the subject in need thereof is administered a dose of about 20 mg or less, a dose of about 15 mg or less, a dose of about 10 mg or less, for example, a dose of 2 mg, or 5 mg, or 10 mg, of a radiolabeled anti-LAG3 antibody conjugate.

**[0178]** As used herein, the expression “a subject in need thereof” means a human or non-human mammal that exhibits one or more symptoms or indications of cancer, and/or who has been diagnosed with cancer, including a solid tumor and who needs treatment for the same. In many embodiments, the term “subject” may be interchangeably used with the term “patient”. For example, a human subject may be diagnosed with a primary or a metastatic tumor and/or with one or more symptoms or indications including, but not limited to, unexplained weight loss, general weakness, persistent fatigue, loss of appetite, fever, night sweats, bone pain, shortness of breath, swollen abdomen, chest pain/pressure, enlargement of spleen, and elevation in the level of a cancer-related biomarker (*e.g.*, CA125). The expression includes subjects with primary or established tumors. In specific embodiments, the expression includes human subjects that have and/or need treatment for a solid tumor, *e.g.*, colon cancer, breast cancer, lung cancer, prostate cancer, skin cancer, liver cancer, bone cancer, ovarian cancer, cervical cancer, pancreatic cancer, head and neck cancer, and brain cancer. The term includes subjects with primary or metastatic tumors (advanced malignancies). In certain embodiments, the expression “a subject in need thereof” includes patients with a solid tumor that is resistant to or refractory to or is inadequately controlled by prior therapy (*e.g.*, treatment with an anti-cancer agent). For example, the expression includes subjects who have been treated with one or more lines of prior therapy such as treatment with chemotherapy (*e.g.*, carboplatin or docetaxel). In certain embodiments, the expression “a subject in need thereof” includes patients with a solid tumor which has been treated with one or more lines of prior therapy but which has subsequently relapsed or metastasized. In certain embodiments, the term includes subjects having an inflammatory disease or disorder including, but not limited to, cancer, rheumatoid arthritis, atherosclerosis, periodontitis, hay fever, heart disease, coronary artery disease, infectious disease, bronchitis, dermatitis, meningitis, asthma, tuberculosis, ulcerative colitis, Crohn’s disease, inflammatory bowel disease, hepatitis, sinusitis, psoriasis, allergy, fibrosis, lupus, vasculitis, ankylosing spondylitis, Graves’ disease, Celiac disease, fibromyalgia, and transplant rejection.

**[0179]** In certain embodiments, the methods of the present disclosure are used in a subject with a solid tumor. The terms “tumor”, “cancer” and “malignancy” are interchangeably used herein. As used herein, the term “solid tumor” refers to an abnormal mass of tissue that usually does not contain cysts or liquid areas. Solid tumors may be benign (not cancer) or malignant (cancer). In some embodiments, the tumor is metastatic. For the purposes of the present disclosure, the term “solid tumor” means malignant solid tumors. The term includes different types of solid tumors named for the cell types that form them, *viz.* sarcomas, carcinomas and lymphomas. In certain embodiments, the term “solid



tumor” includes cancers including, but not limited to, colorectal cancer, ovarian cancer, prostate cancer, breast cancer, brain cancer, cervical cancer, bladder cancer, anal cancer, uterine cancer, colon cancer, liver cancer, melanoma, metastatic melanoma, pancreatic cancer, lung cancer, endometrial cancer, bone cancer, testicular cancer, skin cancer, kidney cancer, stomach cancer, esophageal cancer, head and neck cancer, salivary gland cancer, and myeloma.

**[0180]** In some embodiments, the methods disclosed herein can be used in a subject with cancer, for example, a subject having blood cancer, brain cancer, renal cell cancer, ovarian cancer, bladder cancer, prostate cancer, breast cancer, hepatic cell carcinoma, bone cancer, colon cancer, non-small-cell lung cancer, squamous cell carcinoma of head and neck, colorectal cancer, mesothelioma, B cell lymphoma, and melanoma. In some aspects, the cancer is metastatic, for example, metastatic melanoma.

**[0181]** According to one aspect, the present disclosure provides methods of treating a tumor in a subject. The methods, according to this aspect, comprise selecting a subject with a solid tumor; determining that the tumor is LAG3-positive; and administering one or more doses of an inhibitor of LAG3. In certain embodiments, the tumor is determined to be LAG3-positive by administering a radiolabeled antibody conjugate of the present disclosure to the subject; and visualizing the radiolabeled antibody conjugate in the tumor by PET imaging, wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor is LAG3-positive.

**[0182]** In a further aspect, the methods of treating comprise administering one or more doses of an inhibitor of LAG3 in combination with a CTLA-4 inhibitor (e.g., ipilimumab), a TIM3 inhibitor, a BTLA inhibitor, a TIGIT inhibitor, a CD47 inhibitor, a GITR inhibitor, an antagonist of another T cell co-inhibitor or ligand (e.g., an antibody to CD-28, 2B4, LY108, LAIR1, ICOS, CD160 or VISTA), an indoleamine-2,3-dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist [e.g., a “VEGF-Trap” such as aflibercept or other VEGF-inhibiting fusion protein as set forth in US 7,087,411, or an anti-VEGF antibody or antigen binding fragment thereof (e.g., bevacizumab, or ranibizumab) or a small molecule kinase inhibitor of VEGF receptor (e.g., sunitinib, sorafenib, or pazopanib)], an Ang2 inhibitor (e.g., nesvacumab), a transforming growth factor beta (TGF $\beta$ ) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor (e.g., erlotinib, cetuximab), a CD20 inhibitor (e.g., an anti-CD20 antibody such as rituximab), an antibody to a tumor-specific antigen [e.g., CA9, CA125, melanoma-associated antigen 3 (MAGE3), carcinoembryonic antigen (CEA), vimentin, tumor-M2-PK, prostate-specific antigen (PSA), mucin-1, MART-1, and CA19-9], a vaccine (e.g., Bacillus Calmette-Guerin, a cancer vaccine), an adjuvant to increase antigen presentation (e.g., granulocyte-macrophage colony-stimulating factor), a



bispecific antibody (e.g., CD3xCD20 bispecific antibody, or PSMAxCD3 bispecific antibody), a cytotoxin, a chemotherapeutic agent (e.g., dacarbazine, temozolomide, cyclophosphamide, docetaxel, doxorubicin, daunorubicin, cisplatin, carboplatin, gemcitabine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, and vincristine), cyclophosphamide, radiotherapy, an IL-6R inhibitor (e.g., sarilumab), an IL-4R inhibitor (e.g., dupilumab), an IL-10 inhibitor, a cytokine such as IL-2, IL-7, IL-21, and IL-15, an antibody-drug conjugate (ADC) (e.g., anti-CD19-DM4 ADC, and anti-DS6-DM4 ADC), an anti-inflammatory drug (e.g., corticosteroids, and non-steroidal anti-inflammatory drugs), a dietary supplement such as anti-oxidants or any other therapy care to treat cancer. In certain embodiments, an inhibitor of LAG3 may be used in combination with cancer vaccines including dendritic cell vaccines, oncolytic viruses, tumor cell vaccines, etc. to augment the anti-tumor response. Examples of cancer vaccines that can be used in combination with an inhibitor of LAG3 include MAGE3 vaccine for melanoma and bladder cancer, MUC1 vaccine for breast cancer, EGFRv3 (e.g., Rindopepimut) for brain cancer (including glioblastoma multiforme), or ALVAC-CEA (for CEA+ cancers).

**[0183]** In certain embodiments, an inhibitor of LAG3 may be used in combination with radiation therapy in methods to generate long-term durable anti-tumor responses and/or enhance survival of patients with cancer. In some embodiments, the inhibitor of LAG3, e.g. an anti-LAG3 antibody, may be administered prior to, concomitantly or after administering radiation therapy to a cancer patient. For example, radiation therapy may be administered in one or more doses to tumor lesions followed by administration of one or more doses of anti-LAG3 antibodies. In some embodiments, radiation therapy may be administered locally to a tumor lesion to enhance the local immunogenicity of a patient's tumor (adjuvating radiation) and/or to kill tumor cells (ablative radiation) followed by systemic administration of an anti-LAG3 antibody. For example, intracranial radiation may be administered to a patient with brain cancer (e.g., glioblastoma multiforme) in combination with systemic administration of an anti-LAG3 antibody. In certain embodiments, the anti-LAG3 antibodies may be administered in combination with radiation therapy and a chemotherapeutic agent (e.g., temozolomide) or a VEGF antagonist (e.g., aflibercept).

**[0184]** In certain embodiments, an inhibitor of LAG3 may be administered in combination with one or more anti-viral drugs to treat viral infection caused by, for example, LCMV, HIV, HPV, HBV or HCV. Examples of anti-viral drugs include, but are not limited to, zidovudine, lamivudine, abacavir, ribavirin, lopinavir, efavirenz, cobicistat, tenofovir, rilpivirine and corticosteroids.

**[0185]** In certain embodiments, an inhibitor of LAG3 may be administered in combination with one or more anti-bacterial drugs to treat bacterial infection caused by, for example,

rickettsial bacteria, bacilli, klebsiella, meningococci and gonococci, proteus, pneumonococci, pseudomonas, streptococci, staphylococci, serratia, Borriella, Bacillus anthracis, Chlamydia, Clostridium, Corynebacterium diphtheriae, Legionella, Mycobacterium leprae, Mycobacterium lepromatosis, Salmonella, Vibrio cholerae, and Yersinia pestis. Examples of anti-bacterial drugs include, but are not limited to, penicillins, tetracyclines, cephalosporins, quinolones, lincomycins, macrolides, ketolides, sulfonamides, glycopeptides, aminoglycosides, and carbapenems.

**[0186]** In certain embodiments, an inhibitor of LAG3 may be administered in combination with one or more anti-fungal drugs to treat fungal infection caused by, for example, *Aspergillus* (fumigatus, niger, etc.), *Blastomyces dermatitidis*, *Candida* (albicans, krusei, glabrata, tropicalis, etc.), *Coccidioides immitis*, *Cryptococcus neoformans*, Genus *Mucorales* (mucor, absidia, rhizopus, etc.), *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Sporothrix schenckii*. Examples of anti-fungal drugs include, but are not limited to, amphotericin B, fluconazole, voriconazole, posaconazole, itraconazole, voriconazole, anidulafungin, caspofungin, micafungin, and flucytosine.

**[0187]** In certain embodiments, an inhibitor of LAG3 may be administered in combination with one or more anti-parasitic drugs to treat parasitic infection caused by, for example, *Entamoeba* spp., *Enterobius vermicularis*, *Leishmania* spp., *Toxocara* spp., *Plasmodium* spp., *Schistosoma* spp., *Taenia solium*, *Toxoplasma gondii*, and *Trypanosoma cruzi*. Examples of anti-parasitic drugs include, but are not limited to, praziquantel, oxamniquine, metronidazole, tinidazole, nitazoxanide, dehydroemetine or chloroquine, diloxanide furoate, iodoquinoline, chloroquine, paromomycin, pyrantel pamoate, albendazole, nifurtimox, and benznidazole.

**[0188]** The additional therapeutically active agent(s)/component(s) may be administered prior to, concurrent with, or after the administration of the inhibitor of LAG3. For purposes of the present disclosure, such administration regimens are considered the administration of a LAG3 inhibitor “in combination with” a second therapeutically active component.

**[0189]** In some aspects, the methods of treating comprise selecting a subject with a bacterial infection, a viral infection, a fungal infection, or a parasitic infection; determining that an affected tissue in the subject is LAG3-positive; and administering one or more doses of a therapeutic agent appropriate to the infection. In certain embodiments, the affected tissue is determined to be LAG3-positive by administering a radiolabeled anti-LAG3 conjugate of the present disclosure to the subject; and visualizing the radiolabeled antibody conjugate in the subject by PET imaging, wherein presence of the radiolabeled antibody conjugate in a tissue indicates that the tissue is LAG3-positive. In certain embodiments, the steps of administering and visualizing are performed one or more times in order to monitor

the effectiveness of the therapeutic agent in treating the infection.

**[0190]** In some aspects, the methods of treating comprise selecting a subject with a solid tumor; determining that the tumor is LAG3-positive and PD-1-positive; and administering one or more doses of an inhibitor of LAG3 and/or one or more doses of an inhibitor of the PD-1/PD-L1 signaling axis (e.g., an anti-PD-1 antibody or an anti-PD-L1 antibody). In certain embodiments, the tumor is determined to be LAG3-positive by administering a radiolabeled anti-LAG3 conjugate of the present disclosure to the subject; and visualizing the radiolabeled antibody conjugate in the tumor by PET imaging, wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor is LAG3-positive. In certain embodiments, the tumor is determined to be PD-1-positive by administering a radiolabeled anti-PD-1 conjugate of the present disclosure to the subject; and visualizing the radiolabeled anti-PD-1 conjugate in the tumor by PET imaging, wherein presence of the radiolabeled anti-PD-1 conjugate in the tumor indicates that the tumor is PD-1-positive.

**[0191]** Exemplary anti-PD-1 antibodies include REGN2810, BGB-A317, nivolumab, pidilizumab, and pembrolizumab.

**[0192]** Exemplary anti-PD-L1 antibodies include atezolizumab, avelumab, durvalumab, MDX-1105, and REGN3504, as well as those disclosed in Patent Publication No. US 2015-0203580.

**[0193]** The inhibitor of the PD-1/PD-L1 signaling axis may be administered prior to, concurrent with, or after the administration of the inhibitor of LAG3. For purposes of the present disclosure, such administration regimens are considered the administration of a LAG3 inhibitor “in combination with” an inhibitor of the PD-1/PD-L1 signaling axis.

**[0194]** As used herein, the terms “treat”, “treating”, or the like, mean to alleviate symptoms, eliminate the causation of symptoms either on a temporary or permanent basis, to delay or inhibit tumor growth, to reduce tumor cell load or tumor burden, to promote tumor regression, to cause tumor shrinkage, necrosis and/or disappearance, to prevent tumor recurrence, to prevent or inhibit metastasis, to inhibit metastatic tumor growth, and/or to increase duration of survival of the subject.

**[0195]** According to one aspect, the present disclosure provides methods for monitoring the efficacy of an anti-tumor therapy in a subject, wherein the methods comprise selecting a subject with a solid tumor wherein the subject is being treated with an anti-tumor therapy; administering a radiolabeled anti-LAG3 conjugate of the present disclosure to the subject; imaging the localization of the administered radiolabeled conjugate in the tumor by PET imaging; and determining tumor growth, wherein a decrease from the baseline in radiolabeled signal indicates efficacy of the anti-tumor therapy. In certain embodiments, the anti-tumor therapy comprises an inhibitor of LAG3. In certain embodiments, the anti-tumor

therapy further comprises an inhibitor of the PD-1/PD-L1 signaling axis (e.g., an anti-PD-1 antibody or an anti-PD-L1 antibody).

**[0196]** In certain embodiments, the present disclosure provides methods to assess changes in the inflammatory state of a tumor, the methods comprising selecting a subject with a solid tumor wherein the subject is being treated with an anti-tumor therapy; administering a radiolabeled anti-LAG3 conjugate provided herein to the subject; and imaging the localization of the administered radiolabeled conjugate in the tumor by PET imaging, wherein an increase from the baseline in radiolabeled signal indicates increase in inflammation and efficacy of the anti-tumor therapy. In certain embodiments, the anti-tumor therapy comprises an inhibitor of LAG3 and/or an inhibitor of the PD-1/PD-L1 signaling axis (e.g., an anti-PD-1 antibody or an anti-PD-L1 antibody). In certain embodiments, the anti-tumor therapy comprises a PD-1 inhibitor (e.g., REGN2810, BGB-A317, nivolumab, pidilizumab, and pembrolizumab), a PD-L1 inhibitor (e.g., atezolizumab, avelumab, durvalumab, MDX-1105, and REGN3504), CTLA-4 inhibitor (e.g., ipilimumab), a TIM3 inhibitor, a BTLA inhibitor, a TIGIT inhibitor, a CD47 inhibitor, a GITR inhibitor, an antagonist of another T cell co-inhibitor or ligand (e.g., an antibody to CD-28, 2B4, LY108, LAIR1, ICOS, CD160 or VISTA), an indoleamine-2,3-dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist [e.g., a “VEGF-Trap” such as aflibercept or other VEGF-inhibiting fusion protein as set forth in US 7,087,411, or an anti-VEGF antibody or antigen binding fragment thereof (e.g., bevacizumab, or ranibizumab) or a small molecule kinase inhibitor of VEGF receptor (e.g., sunitinib, sorafenib, or pazopanib)], an Ang2 inhibitor (e.g., nesvacumab), a transforming growth factor beta (TGF $\beta$ ) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor (e.g., erlotinib, cetuximab), a CD20 inhibitor (e.g., an anti-CD20 antibody such as rituximab), an antibody to a tumor-specific antigen [e.g., CA9, CA125, melanoma-associated antigen 3 (MAGE3), carcinoembryonic antigen (CEA), vimentin, tumor-M2-PK, prostate-specific antigen (PSA), mucin-1, MART-1, and CA19-9], a vaccine (e.g., Bacillus Calmette-Guerin, a cancer vaccine), an adjuvant to increase antigen presentation (e.g., granulocyte-macrophage colony-stimulating factor), a bispecific antibody (e.g., CD3xCD20 bispecific antibody, or PSMAxCD3 bispecific antibody), a cytotoxin, a chemotherapeutic agent (e.g., dacarbazine, temozolomide, cyclophosphamide, docetaxel, doxorubicin, daunorubicin, cisplatin, carboplatin, gemcitabine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, and vincristine), cyclophosphamide, radiotherapy, an IL-6R inhibitor (e.g., sarilumab), an IL-4R inhibitor (e.g., dupilumab), an IL-10 inhibitor, a cytokine such as IL-2, IL-7, IL-21, and IL-15, and an antibody-drug conjugate (ADC) (e.g., anti-CD19-DM4 ADC, and anti-DS6-DM4 ADC).

**[0197]** As used herein, the term “baseline,” with respect to LAG3 expression in the tumor, means the numerical value of uptake of the radiolabeled conjugate for a subject prior to or at the time of administration of a dose of anti-tumor therapy. The uptake of the radiolabeled conjugate is determined using methods known in the art (see, for example, Oosting et al 2015, J. Nucl. Med. 56: 63-69). In certain embodiments, the anti-tumor therapy comprises an inhibitor of LAG3.

**[0198]** In some embodiments, sequential iPET scanning and tumor biopsies are performed before and after treatment with standard of care immunotherapies. Such immunotherapies can be selected from the following: nivolumab, ipilimumab, pembrolizumab, and combinations thereof.

**[0199]** To determine whether there is efficacy in anti-tumor therapy, the uptake of the radiolabeled conjugate is quantified at baseline and at one or more time points after administration of the LAG3 inhibitor. For example, the uptake of the administered radiolabeled antibody conjugate (e.g., radiolabeled anti-LAG3 antibody conjugate) may be measured at day 2, day 3, day 4, day 5, day 6, day 7, day 8, day 9, day 10, day 11, day 12, day 14, day 15, day 22, day 25, day 29, day 36, day 43, day 50, day 57, day 64, day 71, day 85; or at the end of week 1, week 2, week 3, week 4, week 5, week 6, week 7, week 8, week 9, week 10, week 11, week 12, week 13, week 14, week 15, week 16, week 17, week 18, week 19, week 20, week 21, week 22, week 23, week 24, or longer, after the initial treatment with the LAG3 inhibitor (e.g., an anti-LAG3 antibody). The difference between the value of the uptake at a particular time point following initiation of treatment and the value of the uptake at baseline is used to establish whether anti-tumor therapy is efficacious (tumor regression or progression).

**[0200]** In certain embodiments, the radiolabeled antibody conjugate is administered intravenously or subcutaneously to the subject. In certain embodiments, the radiolabeled antibody conjugate is administered intra-tumorally. Upon administration, the radiolabeled antibody conjugate is localized in the tumor. The localized radiolabeled antibody conjugate is imaged by PET imaging and the uptake of the radiolabeled antibody conjugate by the tumor is measured by methods known in the art. In certain embodiments, the imaging is carried out 1, 2, 3, 4, 5, 6 or 7 days after administration of the radiolabeled conjugate. In certain embodiments, the imaging is carried out on the same day upon administration of the radiolabeled antibody conjugate.

**[0201]** In certain embodiments, the antibody or antigen-binding fragment thereof that binds specifically to LAG3. In certain embodiments, the anti-LAG3 antibody comprises the CDRs of a HCVR, wherein the HCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226,

242, 258, 274, 290, 306, 322, 338, 354, 370, 386, 402, 418, 434, 450, 458, 466, 474, 482, 490, 498, 506, 514, 538, and 554; and the CDRs of a LCVR, wherein the LCVR has an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330, 346, 362, 378, 394, 410, 426, 442, 522, 530, 546, and 562.

**[0202]** In certain embodiments, the LAG3 inhibitor comprises an antibody or antigen-binding fragment thereof that binds specifically to LAG3. In certain embodiments, the anti-LAG3 antibody is BMS986016. In certain other embodiments, the LAG3 inhibitor comprises an antibody or antigen-binding fragment thereof that binds specifically to LAG3. In one embodiment, the anti-LAG3 antibody comprises an HCVR of SEQ ID NO: 418 and a LCVR of SEQ ID NO: 426.

**[0202a]** In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form part of the common general knowledge in the art.

#### **IV.Examples**

**[0203]** Certain embodiments of the disclosure are illustrated by the following non-limiting examples.

##### **Example 1: Generation of Human Antibodies to LAG3**

**[0204]** Human antibodies to LAG3 were generated using a fragment of LAG3 that ranges from about amino acids 29 – 450 of GenBank Accession NP\_002277.4 (SEQ ID NO: 582) genetically fused to a mouse Fc region. The immunogen was administered directly, with an adjuvant to stimulate the immune response, to a VELOCIMMUNE® mouse (*i.e.*, an engineered mouse comprising DNA encoding human Immunoglobulin heavy and kappa light chain variable regions), as described in US 8,502,018 B2, or to a humanized Universal Light Chain (ULC) VelocImmune® mouse, as described in WO 2013022782. The antibody immune response was monitored by a LAG3-specific immunoassay. When a desired immune response was achieved splenocytes were harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines were screened and selected to identify cell lines that produce LAG3-specific antibodies. Using this technique, and the immunogen described above, several anti-LAG3

chimeric antibodies (*i.e.*, antibodies possessing human variable domains and mouse constant domains) were obtained. Fully human versions of the antibodies can be made by replacing the mouse constant region with a human constant region. Exemplary antibodies generated in this manner from the VELOCIMMUNE® mice were designated as H1M14985N, H1M14987N, H2M14811N, H2M14885N, H2M14926N, H2M14927N, H2M14931N, H2M18336N, H2M18337N and H4H14813N.

**[0205]** Anti-LAG3 antibodies were also isolated directly from antigen-positive B cells (from either of the immunized mice) without fusion to myeloma cells, as described in U.S. Patent 7,582,298, herein specifically incorporated by reference in its entirety. Using this method, several anti-LAG3 antibodies (*i.e.*, antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H4H15477P, H4H15483P, H4H15484P, H4H15491P, H4H17823P, H4H17826P2, H4H17828P2, H4sH15460P, H4sH15462P, H4sH15463P, H4sH15464P, H4sH15466P, H4sH15467P, H4sH15470P, H4sH15475P, H4sH15479P, H4sH15480P, H4sH15482P, H4sH15488P, H4sH15496P2, H4sH15498P2, H4sH15505P2, H4sH15518P2, H4sH15523P2, H4sH15530P2, H4sH15555P2, H4sH15558P2, H4sH15567P2, and H4H17819P.

**[0206]** Exemplary antibodies H4sH15496P2, H4sH15498P2, H4sH15505P2, H4sH15518P2, H4sH15523P2, H4sH15530P2, H4sH15555P2, H4sH15558P2, and H4sH15567P2 were generated from B-cells from the ULC VELOCIMMUNE® mice.

**[0207]** The biological properties of the exemplary antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

## **Example 2: Conjugation of anti-LAG3 antibody H4sH15482P with p-SCN-Bn-DFO**

**[0208]** In order to modify the parental anti-LAG3 antibody, H4sH15482P (having an HCVR/LCVR sequence pair of SEQ ID NOs: 418/426; hereinafter referred to as mAb1), and an isotype control antibody to be suitable for ImmunoPET studies with radiolabeling, a chelator, p-SCN-bn-Deferoxamine (DFO; Macrocylics, Cat #: B-705), was attached to the antibodies.

**[0209]** For the modification, mAb1, was first buffer exchanged into PBS, pH 7.2 from histidine buffer by dialysis at 4°C overnight (Slide-A-Lyzer Dialysis Cassette G2 10k MWCO; ThermoScientific) then buffer exchanged again using a PD-10 column (GE Healthcare, Cat. #: 17-0851-01) into a buffer composed of 50 mM carbonate buffer, 150 mM NaCl, pH 9.0 (conjugation buffer). To determine the concentration following the buffer exchanges, the samples were measured on a Nanodrop 2000 UV/VIS spectrometer (Thermo Scientific)



using the MacVector sequence based extinction coefficient of 223400 M<sup>-1</sup> cm<sup>-1</sup> and molecular weight 145709 g/mol (see Table 2). In 15 a mL polypropylene tube, 1485.24 uL of mAb1 (70 mg) was added to 5374.8 uL of conjugation buffer. A 139 uL solution of DFO in DMSO was added in one-quarter increments to the mAb1 solution, each time gently being mixed by pipetting up-and-down. The final solution was 10 mg/mL mAb1 in conjugation buffer, 2% DMSO with 3-fold mole-to-mole excess of DFO. This solution was allowed to incubate in a 37°C water bath with no additional stirring.

**[0210]** After 30 minutes at 37°C, the solution was promptly passed through a PD-10 desalting column (GE Healthcare, Cat. #: 17-0851-01), pre-equilibrated with a buffer containing 250 mM NaAcO at pH 5.4 (formulation buffer). The volume of the solution was reduced by approximately 50% with a 10K MWCO concentrator (Amicon Ultra-15 Centrifugal Filter Unit, EMD Millipore, Cat #: UFC901024). The final solution was sterile-filtered via a syringe filter (Acrodisc 13 mm syringe filter, Pall Corporation, Cat #: 4602). The concentration and DFO-to-Antibody Ratio (DAR) was subsequently measured by UV/VIS spectroscopy. See Figure 1. For the absorbance measurement, the DFO-conjugated antibody was measured against the formulation buffer at 252 nm (A<sub>252</sub>), 280 nm (A<sub>280</sub>) and 600 nm (A<sub>600</sub>). For the calculation, the background was corrected at each absorbance value using the equation:

$$A'_{\lambda} = A_{\lambda} - A_{600}$$

**[0211]** The antibody conjugate was tested for aggregation using SEC chromatography, with 25 ug of the sample injected onto a Superdex 200 column (GE Healthcare, Cat. No. 17-5175-01) monitored at 280 nm with a PBS mobile phase (0.75 mL/min). See Figure 2. The antibody integrity was evaluated by SDS-PAGE 4-20% Tris/Gly pre-cast gel (Novex) with 2 ug of the sample loaded. The antibody concentration, conjugate concentration, and DAR were calculated using the equations below:

#### **Antibody concentration calculation**

$$\text{Conc mAb (mg/mL)} = \frac{A'_{280}}{\epsilon_{280}} * MW$$

#### **Conjugate concentration calculation**

$$\text{Conc conjugate (mg/mL)} = \frac{A'_{252} - 1.53A'_{280}}{\epsilon_{252} - 1.53\epsilon_{280}} * MW$$



**DAR calculation**

$$\text{DAR} = \frac{\epsilon_{252}A'_{280} - \epsilon_{280}A'_{252}}{18800A'_{252} - 28700A'_{280}}$$

**Table 2: Molar extinction coefficients and molecular weight**

| mAb  | MW (gmol <sup>-1</sup> ) | $\epsilon_{280}$ (M <sup>-1</sup> cm <sup>-1</sup> ) | $\epsilon_{252}$ (M <sup>-1</sup> cm <sup>-1</sup> ) |
|------|--------------------------|------------------------------------------------------|------------------------------------------------------|
| mAb1 | 145709                   | 223400                                               | 87077                                                |

**Table 3: UV DAR, percent aggregate and concentration post DFO-attachment**

| Antibody | UV DAR | Concentration (mg/mL) | % aggregate |
|----------|--------|-----------------------|-------------|
| mAb1     | 1.48   | 13.58                 | 1.4%        |

**Example 3: <sup>89</sup>Zr chelation of DFO conjugated monoclonal antibodies**

**[0212]** For usage in ImmunoPET in vivo studies, the DFO-conjugated anti-LAG3 antibody, mAb1, and a DFO-conjugated isotype control antibody were radiolabeled with <sup>89</sup>Zr.

**[0213]** DFO-conjugated antibody was first brought to 1.25 mg/mL in 1 M HEPES, pH 7.2. The composition of the DFO-Ab conjugate solutions for each study is listed in Table 4. Separately, <sup>89</sup>Zr solution was prepared using the compositions for each corresponding study shown in Table 5. Stock <sup>89</sup>Zr-oxalic acid solution was obtained from 3D Imaging. The final radioactivity of the solution was first confirmed using a Capintec CRC-25R dose calibrator (Capintec #520), then immediately combined with the DFO-Ab conjugate solution, gently mixed (pipetting up-and-down) and subsequently incubated for 45 minutes at room temperature.

**[0214]** After the incubation, the mixtures were transferred to desalting columns, either PD-10 (GE Healthcare, Cat. #: 17-0851-01) for study 1 or NAP-5 (GE Healthcare, Cat. # 17-0853-02) for study 2, pre-equilibrated with 250 mM sodium acetate at pH 5.4 for gravity-fed desalting. For study 1, the reaction mixture was added to a PD-10 column. After the contents of the reaction entered the column bed, the flow through was discarded. The product was eluted with 250 mM sodium acetate at pH 5.4 (formulation buffer) and eluate was collected as per manufacturer's instructions. For study 2, the mixture was transferred to

a NAP-5 column, and the flow through was discarded. The product was eluted with 250 mM sodium acetate at pH 5.4 (formulation buffer) and eluate was collected per the manufacturer's instructions. The Ab concentration was subsequently measured by UV/VIS spectroscopy, calculated using the appropriate extinction coefficient and the absorption at 280 nm using the equation:

Concentration in mg/mL = Absorption at 280 nm  $\div$  Extinction coefficient at 280 nm (found in Table 6)

**[0215]** The final mass measured in grams was recorded in Table 7. The radioactivity was then measured using the dose calibrator and reported in Table 7. The final material (5ug) was analyzed using a SEC-HPLC with UV 280 and radioisotope detector connected in series (Agilent 1260 with Lablogic Radio-TLC/HPLC Detector, SCAN-RAM) using a Superdex 200 Increase column with PBS mobile phase at a flow rate of 0.75 mL/min. The radiotrace was used for determining radiochemical purity (100% - percent of unlabeled  $^{89}\text{Zr}$ ) by comparing the integration of the total protein peak (~10 to 16 min) and unlabeled  $^{89}\text{Zr}$  peak (~ 25 min). The percent monomeric purity was determined by the UV 280 trace by comparing the integration of the high molecular weight (HMW) species peak (10 min to ~ 15 min) to the monomer (~16 min).

**[0216]** The specific activity and protein recovery (%) of each radiolabeled conjugate was determined using the following equations:

- a. Mass of conjugate in mg = concentration in mg/mL x mass of solution in grams
- b. Specific activity in mCi/mg = activity of vial in mCi  $\div$  mass of conjugate in mg
- c. Protein recovery = starting conjugate mass (mg)  $\div$  Mass of conjugate in mg

**[0217]** Finally the appearance was noted and recorded in Table 7. The results are consolidated in Table 7. The radio-SEC-HPLC chromatograms, shown in Figures 3-5, confirm at least 98% radiochemical purity. The UV280-HPLC SEC chromatograms shown in Figures 6-8 confirm the highly monomeric product (>90%).

**Table 4. DFO-antibody conjugate preparation for radiolabeling**

| Radio-labeling # | Study # | Radiolabeling Lots            | Concentration (mg/mL) | DAR* | Conjugate mass (mg) | Total volume (uL) | Final Concentration (mg/mL) |
|------------------|---------|-------------------------------|-----------------------|------|---------------------|-------------------|-----------------------------|
| 1                | 1       | Isotype-DFO- <sup>89</sup> Zr | 15.4                  | 1.53 | 250                 | 200               | 1.25                        |
| 2                | 1       | mAb1-DFO- <sup>89</sup> Zr    | 13.6                  | 1.48 | 500                 | 400               | 1.25                        |
| 3                | 2       | mAb1-DFO- <sup>89</sup> Zr    | 13.6                  | 1.48 | 100                 | 80                | 1.25                        |

\* DAR is defined as the DFO to Antibody Ratio

**Table 5. <sup>89</sup>Zr reaction solution preparation for radiolabeling**

| Radio-labeling | Study # | Radiolabeling Lots            | <sup>89</sup> Zr-oxalate (uL) | 1 M HEPES, pH 7.2 (uL) | Final Vol (uL) | Final Activity (uCi) | Specific Activity (uCi/uL) |
|----------------|---------|-------------------------------|-------------------------------|------------------------|----------------|----------------------|----------------------------|
| 1              | 1       | Isotype-DFO- <sup>89</sup> Zr | ~3                            | 500                    | 1000           | 995                  | 1.0                        |
| 2              | 1       | mAb1-DFO- <sup>89</sup> Zr    | ~5                            | 500                    | 2000           | 2060                 | 1.0                        |
| 3              | 2       | mAb1-DFO- <sup>89</sup> Zr    | ~6                            | 394                    | 400            | 2010                 | 5.0                        |

**Table 6: Extinction coefficients for conjugate lots**

| Radiolabeling Lot             | $\epsilon_{280}$ (AU ml mg <sup>-1</sup> cm <sup>-1</sup> ) |
|-------------------------------|-------------------------------------------------------------|
| Isotype-DFO- <sup>89</sup> Zr | 1.70                                                        |
| mAb1-DFO- <sup>89</sup> Zr    | 1.72                                                        |

**Table 7. Summary of <sup>89</sup>Zr labeled DFO-Ab conjugates for in vivo imaging and biodistribution studies**

| Radio-labeling | Study # | Conjugate Lots                | Appearance | Radiochemical Purity* (%) | Mono-meric Purity** (%) | Protein Recovery (%) | Conc. (mg/mL) | Specific Activity (mCi/mg) |
|----------------|---------|-------------------------------|------------|---------------------------|-------------------------|----------------------|---------------|----------------------------|
| 1              | 1       | Isotype-DFO- <sup>89</sup> Zr | Clear      | 99.7%                     | 98.6%                   | 70%                  | 0.108         | 3.41                       |
| 2              | 1       | mAb1-DFO- <sup>89</sup> Zr    | Clear      | >99.9%                    | 97.5%                   | 70%                  | 0.133         | 3.58                       |
| 3              | 2       | mAb1-DFO- <sup>89</sup> Zr    | Clear      | 98.2%                     | 93.8 %                  | 57%                  | 0.121         | 14.7                       |

\* by radio-SEC-HPLC, \*\* by UV-SEC-HPLC

#### Example 4: Immunoreactivity

**[0218]** The immunoreactivity (IR) of the radiolabeled anti-LAG3 antibody and isotype control antibody was measured as follows. In these assays, 20 ng of the respective  $^{89}\text{Zr}$  labeled antibodies were added to  $15 \times 10^6$  MC38-cOVA/eGFP-mLAG3<sup>-/-</sup>hLAG3<sup>Tg</sup> cells in a final volume of 1 mL. Samples were incubated for 45 minutes (at 37° C, 5% CO<sub>2</sub>) with continuous mixing before undergoing 2 washes with media to remove any unbound antibody. The radioactivity of the test cell pellets was then counted in an automatic gamma counter (2470 Wizard2, Perkin Elmer) against 2 reference standards containing the same 20 ng of  $^{89}\text{Zr}$  labeled antibody. The percentage immunoreactivity was determined for the samples using the average of the standards as a measure of total activity.

**[0219]** As seen in Table 8,  $^{89}\text{Zr}$  labeled anti-LAG3 antibody retained immunoreactivity following conjugation and radiolabeling, with 86%IR.

**Table 8: Immunoreactivity of  $^{89}\text{Zr}$  chelated DFO-conjugates**

| Samples              | Zr89 CPM |
|----------------------|----------|
| Standard 1           | 39643    |
| Standard 2           | 40134    |
| Average of Standards | 39889    |
| Cells                | 34261    |
| IR                   | 86%      |

#### Example 5: Selective localization of radiolabeled anti-LAG3 antibody to LAG3 positive tumors in mice

*Implantation of tumors and allocation of dosing groups:*

**[0220]** For in vivo imaging studies, a LAG3 positive tumor line was used. First, a murine colon carcinoma cell-line MC38-cOVA/eGFP-mLAG3<sup>-/-</sup>hLAG3<sup>Tg</sup> was used. Here, cells over-express human LAG3 and full-length chicken ovalbumin fused with eGFP that was introduced by lentiviral transduction (pLVX EF1a and pLKO SSFV, respectively). For MC38-cOVA/eGFP-mLAG3<sup>-/-</sup>hLAG3<sup>Tg</sup> tumor allografts,  $1 \times 10^6$  cells were implanted subcutaneously into the left flank of male NCr nude (Taconic, Hudson NY). Once tumors had reached an average volume of 100-150mm<sup>3</sup> (~Day 7 post implantation), mice were randomized into groups of 5 and dosed with test or control  $^{89}\text{Zr}$  radiolabeled antibodies.

*Dosing and biodistribution of  $^{89}\text{Zr}$ -DFO-mAb1:*

**[0221]** For the initial study in nude mice bearing MC38/ova/LAG3 tumors, mice received  $50 \pm 1$   $\mu\text{Ci}$  of  $^{89}\text{Zr}$  labeled antibody with a protein dose  $\sim 0.6$  mg/kg. For the biodistribution studies, mice were euthanized 6 days post-dosing and blood was collected via cardiac puncture. Tumors and normal tissues were then excised and placed in counting tubes. Count data for  $^{89}\text{Zr}$  in CPM was then collected by measuring samples on an automatic gamma counter (Wizard 2470, Perkin Elmer). All tissues were also weighed and the percent-injected dose per gram (%ID/g) was calculated for each sample using standards prepared from the injected material.

*Results, Summary, and Conclusion:*

**[0222]** In this example, the NCr mice bearing MC38/ova/hLAG3 tumors received  $^{89}\text{Zr}$  conjugated anti-LAG3 mAb1 or non-binding antibody at a final dose of  $50\mu\text{Ci}/\text{mouse}$ . Mice were subsequently left for 6 days until blood, tumor and tissues were taken and the %ID/g for the samples was calculated for all samples. The average %ID/g for each antibody is presented in Table 9. From this, the clear high uptake in MC38/ova/hLAG3 tumors is apparent over other normal tissues, with tumor uptake of 43.1% being significantly higher than the next highest uptake of 6.6 %ID/g observed in the thymus. The specificity of anti-LAG3 mAb1 uptake into tumor is apparent in the significantly reduced tumor uptake of 7.8% observed for the non-binding antibody.

**Table 9:**

| SAMPLE        | $^{89}\text{Zr}$ - mAb1 |             | $^{89}\text{Zr}$ -non-binding Ab |             |
|---------------|-------------------------|-------------|----------------------------------|-------------|
|               | AVERAGE %ID/G           | STDEV %ID/G | AVERAGE %ID/G                    | STDEV %ID/G |
| LIVER         | 0.5                     | 6.2         | 3.9                              | 0.3         |
| SPLEEN        | 4.2                     | 0.8         | 6.7                              | 0.8         |
| KIDNEY        | 5.1                     | 0.8         | 6.2                              | 1.2         |
| BONE          | 4.3                     | 2.1         | 4.9                              | 1.0         |
| LUNG          | 3.1                     | 2.3         | 9.3                              | 2.1         |
| HEART         | 2.6                     | 0.9         | 6.5                              | 2.4         |
| BLOOD         | 5.9                     | 3.1         | 15.7                             | 2.6         |
| THYMUS        | 6.7                     | 1.7         | 12.1                             | 1.8         |
| MC38/ova/LAG3 | 43.1                    | 9.5         | 7.8                              | 0.4         |
| S.BOWEL       | 1.7                     | 0.5         | 2.8                              | 0.5         |

**Example 6: Selective localization of radiolabeled anti-LAG3 antibody to Raji/PBMC tumors in mice**

**[0223]** This Example describes the in vivo imaging and ex vivo biodistribution of a Zirconium-89 labeled DFO-anti-LAG3 antibody conjugate in NSG mice co-implanted with Raji cells and human PBMC.

**[0224]** The exemplary antibody used in this Example was MAb1, comprising HCVR/LCVR of SEQ ID NOs: 418/426.

*Implantation of tumors and allocation of dosing groups:*

**[0225]** To demonstrate specificity of the radiolabeled antibody for LAG3 targeting,  $2 \times 10^6$  Raji cells and  $5 \times 10^5$  human PBMC (Lot 0151029, ReachBio Research Labs) were co-implanted into the right flank of female NSG mice (8 – 10 weeks old, Jackson Labs). 14 days post-tumor implantation, mice were randomized into groups of 4 and injected intravenously with varying protein doses of  $^{89}\text{Zr}$ -DFO-mAb1.

*Dosing and PET/CT imaging of  $^{89}\text{Zr}$ -DFO-mAb1:*

**[0226]** Mice bearing Raji/hPBMC tumors were injected with 5, 0.3, 0.1, or 0.03 mg/kg  $^{89}\text{Zr}$ -DFO-mAb1 at day 14 post-tumor implantation. Mice who received 0.1 and 0.03 mg/kg doses received ~30 or ~9  $\mu\text{Ci}$  of radiolabeled  $^{89}\text{Zr}$ -DFO-mAb1, respectively. The mice who received 5 or 0.3 mg/kg protein doses received ~30  $\mu\text{Ci}$  of radiolabeled  $^{89}\text{Zr}$ -DFO-mAb1 and additional non-DFO conjugated mAb1 (L5) as supplement to yield the final injected total protein dose.

**[0227]** PET imaging of antibody localization was assessed 6 days after administration of  $^{89}\text{Zr}$ -DFO-mAb1. A Sofie Biosciences G8 PET/CT was used to acquire PET/CT images (Sofie Biosciences and Perkin Elmer). The instrument was pre-calibrated for detection of  $^{89}\text{Zr}$  prior to image acquisition. The energy window ranged from 150 to 650 keV with a reconstructed resolution of 1.4 mm at the center of the field of view. Mice underwent induction anesthesia using isoflurane and were kept under continuous flow of isoflurane during imaging. Static 10-minute images were acquired using the G8 acquisition software and subsequently reconstructed using the pre-configured settings. Image data was corrected for decay and other parameters. CT images were acquired following PET acquisition and subsequently co-registered with the PET images. Images were prepared using VivoQuant post-processing software (inviCRO Imaging Services).

*Biodistribution of  $^{89}\text{Zr}$ -DFO-mAb1:*

**[0228]** For biodistribution studies, mice were euthanized at the final time-point (6 days post- $^{89}\text{Zr}$ -DFO-mAb1 administration) and blood was collected via cardiac puncture.

Raji/hPBMC tumors and normal tissues were then excised, placed in counting tubes, and weighed. Count data for  $^{89}\text{Zr}$  in CPM was then collected by measuring samples on an automatic gamma counter (Wizard 2470, Perkin Elmer). The percent-injected dose per gram (% ID/g) was calculated for each sample using standards prepared from the injected material.

### Results, summary, and conclusions:

**[0229]** This study demonstrates antigen-specific targeting of  $^{89}\text{Zr}$ -DFO-mAb1 to LAG3 expressed on human lymphocytes in subcutaneous Raji/hPBMC tumors grown in NSG mice. The blocking dose of 5 mg/kg  $^{89}\text{Zr}$ -DFO-mAb1 showed increased blood uptake (% ID/g) and lower tumor uptake (% ID/g) in Raji/hPBMC tumors compared to the lower doses of 0.3, 0.1, and 0.03 mg/kg  $^{89}\text{Zr}$ -DFO-mAb1 (Table 10). Furthermore, as the protein dose decreased, the average tumor-to-blood ratio increased demonstrating specificity to Lag-3 in vivo (Table 10). In addition to targeting Lag-3 expressed in the Raji/hPBMC tumors, the lower doses of 0.3, 0.1, and 0.03 mg/kg  $^{89}\text{Zr}$ -DFO-mAb1 demonstrated targeting to the spleen and axillary lymph nodes of tumor bearing mice. Representative PET images (Figure 9) at day 6 post  $^{89}\text{Zr}$ -DFO-mAb1 administration demonstrate higher targeting of  $^{89}\text{Zr}$ -DFO-mAb1 to the tumor, spleen, and axillary lymph nodes at 0.03 mg/kg compared 5 mg/kg.

**Table 10: Ex vivo biodistribution at day 6 after administration of  $^{89}\text{Zr}$ -DFO-mAb1 injected at protein doses of 5, 0.3, 0.1, or 0.03 mg/kg in NSG mice bearing Raji/hPBMC tumors. Values are shown as average and standard deviations of % ID/g and tumor-to-blood ratios**

|            | $^{89}\text{Zr}$ -DFO- mAb1<br>5 mg/kg |                     | $^{89}\text{Zr}$ -DFO- mAb1<br>0.3 mg/kg |                     | $^{89}\text{Zr}$ -DFO- mAb1<br>0.1 mg/kg |                     | $^{89}\text{Zr}$ -DFO- mAb1<br>0.03 mg/kg |                     |
|------------|----------------------------------------|---------------------|------------------------------------------|---------------------|------------------------------------------|---------------------|-------------------------------------------|---------------------|
| SAMPL<br>E | Averag<br>e<br>% ID/g                  | STDE<br>V<br>% ID/g | Averag<br>e<br>% ID/g                    | STDE<br>V<br>% ID/g | Averag<br>e<br>% ID/g                    | STDE<br>V<br>% ID/g | Averag<br>e<br>% ID/g                     | STDE<br>V<br>% ID/g |
| Blood      | 18.45                                  | 1.69                | 12.17                                    | 3.20                | 8.13                                     | 4.28                | 7.81                                      | 5.37                |
| Tumor      | 20.52                                  | 5.34                | 40.43                                    | 8.09                | 33.26                                    | 10.81               | 48.92                                     | 28.53               |
| Thymus     | 7.78                                   | 0.64                | 6.57                                     | 2.04                | 7.98                                     | 4.71                | 3.22                                      | 2.43                |
| Heart      | 5.5                                    | 0.45                | 3.74                                     | 0.57                | 2.79                                     | 1.14                | 2.39                                      | 1.47                |
| Lungs      | 10.14                                  | 0.54                | 8.30                                     | 2.40                | 9.72                                     | 1.63                | 8.14                                      | 1.08                |
| Spleen     | 7.74                                   | 0.17                | 22.32                                    | 13.82               | 103.68                                   | 126.79              | 59.20                                     | 40.84               |
| Intestine  | 1.82                                   | 0.23                | 1.43                                     | 0.20                | 0.80                                     | 0.44                | 1.19                                      | 0.23                |
| Liver      | 4.51                                   | 0.26                | 5.56                                     | 1.16                | 9.75                                     | 3.87                | 10.75                                     | 5.58                |
| Kidney     | 6.73                                   | 0.99                | 6.17                                     | 1.28                | 5.77                                     | 1.59                | 5.49                                      | 1.56                |
| Bone       | 8.78                                   | 1.75                | 8.39                                     | 3.10                | 8.87                                     | 2.64                | 9.83                                      | 1.54                |

|                             |      |      |      |      |      |      |      |      |
|-----------------------------|------|------|------|------|------|------|------|------|
|                             |      |      |      |      |      |      |      |      |
| <b>Tumor-to-blood ratio</b> | 1.10 | 0.21 | 3.46 | 1.05 | 5.44 | 3.60 | 9.71 | 8.27 |

### Example 7: LC-PRM-MS Quantitation of LAG3 in Raji/PBMC Xenografts and Clinical Samples

**[0230]** Frozen tissue samples (Raji/PBMC tumors, mouse spleens, and melanoma tissue; see Figure 12 for source and characteristics of melanoma tissues) were lysed with lysis buffer (8 M urea in 50 mM  $\text{NH}_4\text{HCO}_3$  with 1% RapiGest). Tissues were cut into small pieces and were homogenized with 1 mL lysis buffer in a tight fitting dounce homogenizer. The lysate was incubated on ice for 30 mins with sonication for 30 sec every 10 mins to achieve complete protein extraction. The lysate was centrifuged at 14,000g for 10 mins. Protein concentration was measured by BCA assay. Each sample was diluted to 1mg/mL then was centrifuged at 14,000g for 10 mins and was stored in aliquots at -80 °C.

**[0231]** Unimplanted NSG mouse spleen lysate was used as the surrogate matrices to generate the standard curve for LAG3 quantitation. LAG3.Fc was spiked into each of 100  $\mu\text{g}$  of mouse spleen lysate at a final concentration ranging from 0.39 to 50 ng/mg protein (1:2 serial dilution). Standards, xenografts and clinical melanoma lysates were precipitated in 900 $\mu\text{L}$  of cold acetone overnight and then denatured in 90  $\mu\text{L}$  of 8M Urea/TCEP buffer at 37°C for 1hr. Heavy labeled human LAG3 peptide (FVWSSLDTPSQR<sup>13</sup>C6<sup>15</sup>N4) was added to all samples as internal standard. The standards and test samples were alkylated with IAA at room temperature for 30min and digested by lys-C (1:100 w/w) for 4hrs then by trypsin (1:20 w/w) overnight at 37°C. Samples were quenched with 10%FA to reach a final Vol. of 100  $\mu\text{L}$ .

**[0232]** Each processed sample (2 $\mu\text{L}$ ) was injected onto a pre-equilibrated nano C18 trap column and was separated by an easy nano C18 separation column. The flow rate was 250 nL/min (Mobile Phase A: water:formic acid/100:0.1 [V:V] and Mobile Phase B: acetonitrile:formic acid/100:0.1 [V:V]). Retention time and peak area were determined using Skyline software. The calibration curve was generated by plotting the peak area ratio of LAG3.Fc reference standard (unlabeled LAG3 peptide FVWSSLDTPSQR<sup>12</sup>C6<sup>14</sup>N4 generated by tryptic digest of hLAG3) to the internal standard (stable isotope-labeled LAG3 peptide). The concentration of LAG3 in each sample was calculated using linear regression. The lowest concentration of LAG3 reference standard (0.39 ng/mg protein) was within the dynamic range of the assay and was defined as the assay's lower limit of quantification.



## Results summary and conclusions:

**[0233]** LAG3 quantitation was performed on tissue samples from 4 of PBMC/Raji xenografts from 27 days, 5 xenografts from 15 days after tumor implantation and 10 melanoma clinical samples. The tissue weights, protein amounts, extraction yield and LAG3 expression were listed in Table 11. Bmax was calculated based on the following equation with an estimation of tumor density at 1g/mL.

$$B_{\max} \text{ (nM)} = \frac{\text{LAG3 (ng/mg protein)} \times \text{Total Protein Amount (mg)} \times 10E6}{5.74 * 10E4 \times \text{Tumor Weight (mg)}}$$

**[0234]** Five of 10 melanoma tissue samples were detected as LAG3 positive with an average expression level of  $2.52 \pm 1.87$  nM. This expression level is similar to Raji/PBMC model at 27 days ( $3.79 \pm 1.93$  nM) and at 15 days ( $6.06 \pm 4.04$  nM). See Table 11 and also Figure 10.

**Table 11:**

|                                      |                    | Tissue Weight (mg) | Total Protein Amount (mg) | % protein    | Lag3 (ng/mg protein) | Bmax (nM)   |
|--------------------------------------|--------------------|--------------------|---------------------------|--------------|----------------------|-------------|
| <b>Melanoma Tissue</b>               | 131815T2(3)        | 290                | 9.1                       | 3.14%        | BLQ                  | BLQ         |
|                                      | 131719T2(3)        | 230                | 17.6                      | 7.65%        | BLQ                  | BLQ         |
|                                      | <b>13841T2(1)</b>  | <b>220</b>         | <b>20.1</b>               | <b>9.14%</b> | <b>0.73</b>          | <b>1.16</b> |
|                                      | <b>13788T2(4)</b>  | <b>250</b>         | <b>24.1</b>               | <b>9.64%</b> | <b>1.04</b>          | <b>1.75</b> |
|                                      | 13765T2(2)         | 250                | 19.4                      | 7.76%        | BLQ                  | BLQ         |
|                                      | 131778T2(5)        | 180                | 9.2                       | 5.11%        | BLQ                  | BLQ         |
|                                      | <b>131291T2(1)</b> | <b>240</b>         | <b>17.4</b>               | <b>7.25%</b> | <b>0.84</b>          | <b>1.06</b> |
|                                      | 131086T6(1)        | 180                | 9.32                      | 5.18%        | BLQ                  | BLQ         |
|                                      | <b>13547T2(1)</b>  | <b>220</b>         | <b>16.1</b>               | <b>7.32%</b> | <b>2.42</b>          | <b>3.08</b> |
|                                      | <b>13524T2(7)</b>  | <b>200</b>         | <b>13</b>                 | <b>6.50%</b> | <b>4.90</b>          | <b>5.53</b> |
|                                      | <b>Mean</b>        | <b>226</b>         | <b>15.5</b>               | <b>6.87%</b> | <b>1.99</b>          | <b>2.52</b> |
|                                      | <b>SD</b>          | <b>34</b>          | <b>5.2</b>                | <b>1.96%</b> | <b>1.76</b>          | <b>1.87</b> |
| <b>Raji/PBMC Xenograft (27 Days)</b> | 85100_0            | 419.5              | 20.9                      | 4.98%        | 4.74                 | 4.10        |
|                                      | 85101_8            | 248.9              | 10.3                      | 4.14%        | 1.58                 | 1.14        |
|                                      | 85104_23           | 256.5              | 9.74                      | 3.80%        | 6.24                 | 4.12        |
|                                      | 85103_19           | 112.5              | 5.92                      | 5.26%        | 6.32                 | 5.78        |
|                                      | <b>Mean</b>        | <b>259</b>         | <b>11.72</b>              | <b>4.54%</b> | <b>4.72</b>          | <b>3.79</b> |
|                                      | <b>SD</b>          | <b>126</b>         | <b>6.43</b>               | <b>0.69%</b> | <b>2.21</b>          | <b>1.93</b> |
| <b>Raji/PBMC Xenograft (15 Days)</b> | 213_1              | 140                | 8.8                       | 6.29%        | 11.46                | 12.5        |
|                                      | 213_2              | 260                | 10.14                     | 3.90%        | 4.54                 | 3.08        |
|                                      | 213_3              | 230                | 9.3                       | 4.04%        | 7.22                 | 5.09        |
|                                      | 213_4              | 160                | 7.9                       | 4.94%        | 2.95                 | 2.54        |

|  |             |            |             |              |             |             |
|--|-------------|------------|-------------|--------------|-------------|-------------|
|  | 213_5       | 50         | 2.8         | 5.60%        | 7.23        | 7.05        |
|  | <b>Mean</b> | <b>168</b> | <b>7.8</b>  | <b>4.95%</b> | <b>6.68</b> | <b>6.06</b> |
|  | <b>SD</b>   | <b>82</b>  | <b>6.43</b> | <b>0.69%</b> | <b>2.21</b> | <b>1.93</b> |

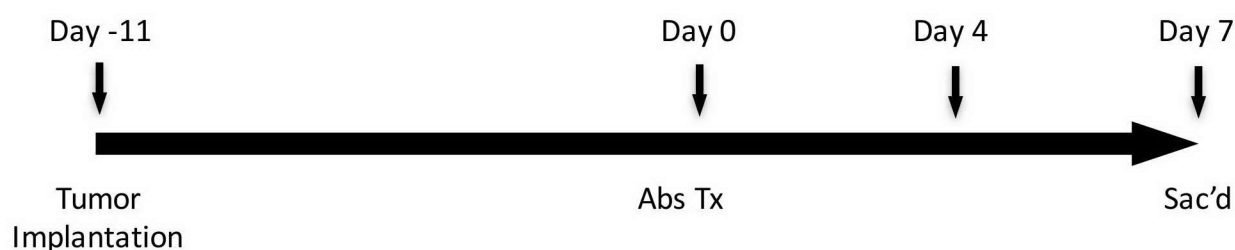
**Example 8: Up-regulation of human LAG-3 and PD-1 expression on T cells in the tumor microenvironment by therapy with REGN2810 (anti-human PD-1 Ab) and mAb1 (anti-human LAG-3 Ab)**

**[0235]** This experiment was carried out to evaluate the modulation of expression levels of human LAG-3 and PD-1 on T cells in the tumor microenvironment upon treatment with REGN2810 and mAb1 using Regeneron's proprietary PD-1<sup>hu/hu</sup>/LAG-3<sup>hu/hu</sup> double humanized immune-competent mice. The tumor cell line used in this experiment is a murine colon carcinoma cell line MC38 (obtained from NCI at Frederick, MD, Laboratory of Tumor Immunology and Biology), which has been engineered in house to express full-length chicken ovalbumin fused with eGFP, thus referred here as MC38-cOVA/eGFP. The expression level of human LAG-3 was evaluated ex vivo on both CD4 and CD8 T cells from enzymatically disassociated tumors extracted from tumor bearing double humanized mice. All surface staining was performed with commercially available fluorochrome directly conjugated to antibodies (anti-human LAG-3 antibody: eBioscience, Clone 3DS223H; anti-human PD-1 antibody: BioLegend, Clone [EH12.2H7](#)), following standard protocol. Briefly, tumor cells were washed with PBS once, washed with ice cold staining buffer once, stained with commercial available fluorochrome directly conjugated anti-human PD-1 or anti-human LAG-3 antibody in staining buffer for 30 min on ice in the dark, washed with 2ml of PBS once again. Fixable dye eFluor506 was also included following manufacturer's protocol (eBioscience). Samples were acquired on BD FACSCanto II™ IVD10 equipped with DIVA v8. Data were further analyzed with FlowJo v10.0.6 or the later version.

**Results summary and conclusions:**

**[0236]** Table 12 provides a schematic presentation of the therapeutic dosing regimen in pre-clinical tumor setting.  $1 \times 10^6$  MC38-cOVA/eGFP cells were implanted s.c. into PD-1<sup>hu/hu</sup>/LAG-3<sup>hu/hu</sup> double humanized immune-competent mice. At about Day 11, mice were randomized into four groups with average tumor volumes of  $\sim 100\text{mm}^3$  and started treatment as indicated. Tumor samples were collected 3 days after the second dose.

Table 12: Schematic presentation of therapeutic dosing regimen.



| Group                   | Treatment                                | # Mice |
|-------------------------|------------------------------------------|--------|
| Isotype                 | 25 mg/kg, 2x week, 2 doses, IP           | 10     |
| REGN2810 (PD-1)         | 10 mg/kg, 2x week, 3 doses, IP           | 12     |
| mAb1 (anti-human LAG-3) | 25 mg/kg, 2x week, 2 doses, IP           | 12     |
| REGN2810 + mAb1         | 10 mg/kg +25 mg/kg, 2x week, 2 doses, IP | 12     |

**[0237]** As shown in Table 13, the combination of anti-human PD-1 (REGN2810) and anti-human LAG-3 (mAb1) significantly inhibited tumor growth in MC38-cOVA/eGFP syngeneic tumor model in double humanized mice. Tumor-bearing mice (tumor sizes of about 100mm<sup>3</sup>) were treated with an hIgG4 isotype control antibody, REGN2810 (anti-human PD-1, hIgG4), mAb1 (anti-human LAG-3, hIgG4s), and combination of REGN2810 and mAb1, twice a week for two doses, and tumor sizes were measured by caliper. Tumor volume was calculated as  $V=L \times W^2/2$ . In the control group, tumor sizes ranged from 300 to 869mm<sup>3</sup> with median value of 548 mm<sup>3</sup>. REGN2810 treated group showed reduced tumor sizes (121 to 721mm<sup>3</sup> with median at 466mm<sup>3</sup>), but the differences did not reach statistical significance. Whereas mAb1-treated group showed no difference from the isotype control group either (203 to 721mm<sup>3</sup> with median at 592mm<sup>3</sup>), the combination treatment significantly delayed tumor growth (113 to 621mm<sup>3</sup> with median at 289mm<sup>3</sup>,  $p<0.01$ ).

**Table 13: Anti-human PD-1 (REGN2810) and anti-Human LAG-3 (mAb1) significantly inhibited tumor growth in MC38-cOVA/GFP syngeneic tumor model in double humanized mice**

|                | Iso** | αhPD-1 | αhLAG-3** | Combo |
|----------------|-------|--------|-----------|-------|
| Mice / group   | 10    | 12     | 12        | 12    |
| Minimum        | 299.9 | 120.9  | 202.6     | 113.4 |
| 25% Percentile | 437.6 | 321.3  | 426.9     | 192.6 |
| Median         | 548.4 | 465.5  | 592.1     | 289.1 |
| 75% Percentile | 617.6 | 597.8  | 631.1     | 349.7 |
| Maximum        | 868.7 | 710.6  | 760.7     | 631.4 |

**[0238]** REGN2810 anti-human PD-1 Ab and mAb1 anti-human LAG-3 respectively increased LAG-3+ T cells and PD-1+ T cells in tumor microenvironment, as can be seen in Figure 11. Tumors from individual mice were dissociated by GentleMACs (Miltenyi Biotech) according to the Manufacturer's protocol. Samples were stained with a panel of Abs and analyzed by flow cytometer. Data presented were pre-gated on FSC/SSC, viability, singlets, CD45+CD3+ cells, then further gated on CD4 or CD8 T cells. The expression of human LAG-3 and human PD-1 were evaluated between different groups. To eliminate the possible Ab cross-competition, REGN2810- and combination-treated groups were excluded from human PD-1 analysis. Similarly, mAb1- and combination-treated groups were also excluded from human LAG-3 analysis. After two therapeutic doses, REGN2810 significantly increased the frequency of human LAG-3+ CD4 T cells in tumor microenvironment by ~ 24% (p=0.0006), though it did seem to have a direct modulatory role for LAG-3 expression on CD8 T cells with the dosing regimen tested. Interestingly, mAb1 also increased the frequency of human PD-1+ CD4 (p=0.0026) and CD8 T cells (p=0.0249) in tumor microenvironment by ~ 28%, respectively. See Figure 11.

**[0239]** The results from the studies performed here clearly demonstrate that anti-LAG3 antibody labeled with <sup>89</sup>Zr can significantly and specifically localize to tumors. One may envision a scenario where the anti-LAG3 antibody is used in the selection of patients with LAG3 positive tumors for subsequent treatment with LAG3 inhibitors, alone or in combination with other anti-cancer therapeutics including inhibitors of the PD-1/PD-L1 signaling axis.

#### **Example 9: Scaled-up manufacturing process for producing DFO-anti-LAG3 antibody conjugates**

**[0240]** This example details the scaled-up manufacturing process for preparing the anti-

LAG3 antibody to be suitable for radiolabeling by attaching p-SCN-bn-Deferoxamine (DFO) to the anti-LAG3 antibody (mAb, H4sH15482P) described herein: (1) ultrafiltration and diafiltration (UFDF) processes prior to mAb conjugation removes excipients that inhibit the conjugation process; (2) following the pre-conjugation UFDF, conjugation of the mAb with p-SCN-Bn-deferoxamine is performed to produce DFO-mAb conjugates; and (3) a post-conjugation UFDF to remove residual salts provides a suitable concentration, excipient level, and pH of the conjugated monoclonal antibody. The resulting DFO-mAb conjugates are then provided in a buffered state with improved stability for subsequent formulation.

### **(1) Pre-Conjugation Ultrafiltration and Diafiltration (UFDF)**

**[0241]** 100 g mAb was buffer exchanged into a 5 mM acetate buffer solution having a pH of 5.50 using a Sius Prostream (TangenX Technology Corporation) membrane (membrane capacity of  $\leq 500 \text{ g/m}^2$ ) to remove residual salts prior to conjugation. The process volume was reduced to further concentrate the antibody, then the antibody was sterile filtered using a Sartopore 2 (Sartorius) membrane having a  $0.45/0.2 \text{ }\mu\text{m}$  (heterogeneous PES double layer) or equivalent pore size. The acetate buffer temperature was kept at a target temperature of  $20\pm 5^\circ\text{C}$ . The solutions were well mixed.

### **(2) Conjugation**

**[0242]** The concentrated and filtered antibody (20 g) was transferred into a conjugation vessel containing an amine free carbonate buffer system (56 mM Carbonate, 167 mM Sodium Chloride, pH 9.40) resulting in negligible levels of residual acetate. DFO (25 mM p-SCN-Bn-Deferoxamine) was solubilized in DMSO and added to the conjugation vessel, along with additional DMSO such that the DMSO was present in a final amount of 5%. DFO was added in molar excess at a ratio of 4.5:1 DFO to mAb. The total reaction volume equaled 2.0 L. The buffer system was mixed throughout the addition of the reaction ingredients and throughout the reaction time.

**[0243]** The reaction temperature was controlled for specific time by using an equation which relates temperature to reaction time. In this instance, the reaction temperature was held at  $20\pm 2^\circ\text{C}$  for 180 minutes. The reaction was quenched by the addition of 2M acetic acid (23 mL/L), resulting in the solution having a pH of 6.

### **(3) Post-Conjugation UFDF**

**[0244]** After the conjugation step, the quenched DFO-mAb conjugation solution was buffer exchanged into histidine buffer (10 mM Histidine, pH 5.50 with 0.0005% (w/v) super refined polysorbate 80 added as a shear protectant) to remove residual process salts, DMSO, and unreacted DFO. Once diafiltered, the solution was then concentrated and subsequently

formulated. The histidine buffer was selected for long term storage of protein at -80°C. The same Sius Prostream membrane mentioned in step (1) was used in the final UFDF step. The resulting concentrated DFO-mAb conjugate solution was sterile filtered using the Sartopore 2 filter mentioned above.

**[0245]** UV-DAR (target of 1.5) and protein concentration determination was performed as described in Example 2.

Table 14. Molar Extinction Coefficients and Molecular Weight

| <b>Antibody</b> | <b>MW<br/>(g mol<sup>-1</sup>)</b> | <b>□<sub>280</sub><br/>(L g<sup>-1</sup>cm<sup>-1</sup>)</b> | <b>□<sub>252</sub><br/>(L g<sup>-1</sup>cm<sup>-1</sup>)</b> |
|-----------------|------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------|
| H4sH15482P      | 145709                             | 223400                                                       | 87077                                                        |

**Example 10: ImmunoPET imaging of LAG3 in tumors using an <sup>89</sup>Zr-DFO-anti-LAG3 antibody conjugate in patients with metastatic melanoma**

**[0246]** The primary objective of this study is to determine the safety and tolerability of <sup>89</sup>Zr-DFO-anti-LAG3 antibody conjugate, in which the anti-LAG3 antibody used in the radiolabeled conjugate is H4sH15482P. Outcome measures monitor adverse events and routine laboratory tests for safety.

**[0247]** The secondary objectives of the study are:

- **Study part A:** To qualify <sup>89</sup>Zr-DFO-anti-LAG3 PET as a biomarker for the evaluation of LAG3 expression in tumors. This will be accomplished by evaluating the safety of the <sup>89</sup>Zr-DFO-anti-LAG3 PET tracer, determining optimal tracer mass dose and optimal post-injection imaging time, establishing the relationship of tumor PET signal with LAG3 tissue-based expression, and evaluating dosimetry in patients. Part A comprises a sequential tracer dose escalation design, with tumor biopsy. Imaging and blood draws at days 1, 4, and 7 post tracer injection permit blood poos SUV with subsequent calculation of tumor: blood ratios at the time of imaging; clinical dosimetry based on tissue radiation absorbed dose and effective dose calculated from PET image acquisition data and tracer activity concentration in blood; standardized uptake values (SUVs – decay-corrected activity concentration in target tissue divided by the mean activity concentration in the body at the time of injection) across the tumor regions of interest; maximal SUVs within tumor regions of interest (ROIs) (SUV<sub>max</sub>); and plasma tracer activity concentration, with calculation of area under the curve (AUC<sub>0-7 days</sub>).

- **Study part B:** To explore the construct and criterion validity of  $^{89}\text{Zr}$ -DFO-anti-LAG3 PET by correlating the PET signal with tissue-based LAG3 expression and clinical outcome (objective response rate and progression-free survival) after IO therapy. Sequential iPET scanning and tumor biopsies are performed before and after treatment with standard of care immunotherapies selected from the following: nivolumab, ipilimumab, pembrolizumab, and combinations as allowed by label.

**[0248]** The utility of the immune-PET (iPET) tracer can be initially assessed by testing for ability to detect the presence of LAG3 tumors, as well as changes in LAG3 signal induced by an established immunotherapy, and by exploring the correlation of the iPET signal with clinical outcomes (criterion validation: against biologically and clinically meaningful outcomes).

**[0249]** A safe, optimal mass dose of  $^{89}\text{Zr}$ -DFO-anti-LAG3 can be identified that shows adequate tumor uptake by PET, tracer PK, and dosimetry. Selection of three tracer mass dose levels is based on preclinical mouse xenograft imaging and biodistribution studies, and on clinical and preclinical data using unlabeled anti-LAG3 therapeutic antibodies. The planned mass dose escalation is 2 mg, 5 mg, and 10 mg. The approach is to use doses that are sub-therapeutic or pharmacologically inert, so as not to interfere with prospective anti-tumor therapy.

**[0250]** The optimal mass dose will demonstrate tumor SUV, maximal SUV ( $\text{SUV}_{\text{max}}$ ) within the tumor lesion region of interest (ROI) and tumor:blood ratio all  $>1$  (and ideally a tumor-blood ratio of 3-4) in at least one lesion (ideally in  $>1$  lesion, in patients with several metastases).

**[0251]** Tracer activity in plasma (or serum) and/or blood pool SUV (the activity PK measures for this study) will be detectable throughout the 7-day imaging window, following dosing, suggesting adequate availability of tracer to compartmentalize into tumor lesions. Ratios of tumor and blood signal will be based on SUVs, although other activity concentration units may be used. The same applies to measurements of blood activity concentration, which could be reported in terms of absolute units or normalized units.

**[0252]** LAG3 PET signal intensity in a biopsied lesion will covary with degree of LAG3 expression in the tissue biopsy using semi-quantitative measures.

**[0253]** The autoradiographic LAG3 PET signal will correlate spatially with LAG3 expression in tissue biopsy samples.

**[0254]** LAG3 PET signal intensity will increase following treatment with an immunotherapy.



**[0255]** LAG3 PET signal intensity increase will correlate with response following treatment with an immunotherapy.

**[0256]** Additionally, exploratory objectives and outcome measures include determining expression of LAG3 in tissue biopsies in correlation with tumor <sup>89</sup>Zr-DFO-anti-LAG3 uptake using immunohistochemistry, RNAscope, liquid chromatography mass spectrometry (LC/MS), and autoradiography. For part B only, exploratory objectives include measuring changes in <sup>89</sup>Zr-DFO-anti-LAG3 signal after treatment and correlation of <sup>89</sup>Zr-DFO-anti-LAG3 signal with clinical outcome after treatment. The outcome measures include SUV, SUVmax, tumor:blood ratio, and clinical outcome following immunotherapy treatment (serial CT for the purpose of calculation of responder status using RECIST 1.1 and tumor volume), objective response rate, and progression-free survival.

### **Patient Target Population**

**[0257]** The target population will consist of patients 18 years of age or older with advanced metastatic melanoma, histologically or cytologically confirmed diagnosis, with at least one lesion amenable to biopsy. The patient must have an ECOG performance status of less than or equal to 2, an anticipated life expectancy of at least 3 months, and adequate organ and bone marrow function.

**[0258]** Inclusion of patients with an indication that has a high prevalence of the target will support assessment of LAG3 iPET tumor localization which is a key outcome of the study. Detection and correlation of post-immunotherapy LAG3 expression with clinical outcomes requires a patient population with well characterized clinical response rates to immunotherapies. Metastatic melanoma patients represent a patient population with established response rates to checkpoint inhibitors as well as the high levels of prevalence and expression of LAG3.

### **Study Design**

**[0259]** The study comprises part A (construct validation) and part B (criterion validation). Duration of the study is 9 weeks for Part A (4 weeks screening, 1 week tracer dosing, scans and biopsy, 4 weeks safety follow up), and 18 weeks for Part B (4 weeks screening, 1 week tracer dosing, scans and biopsy, up to 8 weeks on immunotherapy, 1 week second tracer dose and scan, 4 weeks safety follow up).

### **Part A**

**[0260]** Part A is a dose finding study in which patients receive a single tracer dose, followed by serial scans and a biopsy over a 7 day period. Once the scanning sequence



and biopsy are completed, subjects can immediately be treated with a standard of care immunotherapy regime (anti-PD-1 alone or in combination with anti-CTLA4 according to labeled indication).

### **Dose Cohorts in Part A**

**[0261]** Part A comprises three sequential dose cohorts, consisting of 3 patients, with potential to expand the cohort to a total of 6 patients (3+3 design). Dose escalation decisions will be informed by a) safety and b) evaluation of iPET positivity. Dose limiting toxicity (DLT) is defined as a Grade 3 or higher (NTCAE) adverse event (AE) related to or possibly related to  $^{89}\text{Zr}$ -DFO-anti-LAG3, one week following tracer administration. For hematologic lab AEs, DLT is defined as Grade 4 or higher. Tumor uptake positivity/tumor localization is defined by a tumor:blood ratio greater than 1. Adequate PK is defined by SUV in blood in the range of 1-5 at optimum imaging time (4 or 7 days post-injection).

**[0262]** Cohort expansion to 6 patients will occur if any of the following conditions are met: (a) exactly 1 patient experiences a DLT or (b) at least 1 patient out of 3 shows tumor localization and adequate PK and no more than 1 patient experiences a DLT.

**[0263]** At the completion of a cohort of either 3 or 6 subjects, dose escalation will occur to a higher available dose if fewer than 3 patients in an expanded cohort experience a DLT.

**[0264]** Part A of study will stop if any of the following conditions are met (Part A stopping rules): more than 1 patient in a cohort experiences a DLT; more than 3 patients show visual tumor localization and adequate PK in each of two consecutive expanded cohorts; or no higher doses are available for escalation.

**[0265]** Upon reaching a Part A stopping rule, Part B dose will be selected as follows: a) if two or three expanded cohorts show more than 3 patients with tumor localization and adequate PK, then the dose cohort with tumor localization in more patients, or the highest tumor: blood ratios, will be chosen. When these are similar between cohorts, the lower dose will be chosen. b) if one cohort shows more than 3 patients with tumor localization and adequate PK, this dose will be chosen. c) if no cohorts show more than 3 patients with tumor localization and adequate PK, the study will terminate without progression to Part B.

### **Part B**

**[0266]** Part B will measure LAG3 iPET signal at the defined tracer dose and post-injection time point (determined in part A), both pre- and post-immunotherapy to assess the hypotheses surrounding the role of LAG3 as an indicator of tumor inflammatory response (exploratory objectives). All patients in Part B will receive the optimal tracer mass dose and

post-injection imaging timing as identified in Part A.

**[0267]** Part B patients will receive LAG3 iPET scanning at baseline as well as a biopsy prior to therapy. Patients will then receive a standard of care immunotherapy (currently these are monoclonal antibody-based PD-1 and CTLA-4 pathway blockers), according to the label. Four to eight weeks later an additional iPET scan will be undertaken followed by a second biopsy if feasible.

**[0268]** Patients in Part A who received the optimal tracer mass dose and achieved adequate scan quality may be eligible for Part B and receive a total of two iPET tracer injections. The total number of subjects in Part B (including those that enter from Part A) will not exceed 20.

### **Biopsy Considerations**

**[0269]** Lesions will be selected for biopsy on the basis of accessibility and size (typically at least 20 mm diameter). All patients will undergo a baseline biopsy on the last day of the first set of iPET scans, regardless of whether the iPET study is positive or not. In this way, tissues from patients with a wide range of LAG3 tissue expression will be collected for correlation with LAG3 signal, including negative patients. The biopsy will be scheduled no later than 7 days from date of injection in order to minimize delay of therapy to the patient.

**[0270]** A sequence of assessments that starts with a biopsy followed by the tracer dosing and scans, and then the initiation of therapy may be preferable for practical reasons.

**[0271]** For Part B, a second biopsy after the second scan may be undertaken if feasible and will be optional. Sequential biopsies will be taken from the same site if practicable.

**[0272]** Autoradiography studies will be performed in a subset of biopsied tumors that are positive on iPET scan, with adjacent slices stained against LAG3.

### **Study Interventions**

#### **Part A**

**[0273]** Following screening, each subject will receive a dose of <sup>89</sup>Zr-DFO-anti-LAG3 followed by three sequential iPET scans over 6-7 days. Starting dose will be 2 mg, as determined from animal studies and modeling. No later than 1 day after the last iPET scan, the subject will undergo radiology-guided biopsy. If available, archived biopsy tumor tissue will also be analyzed by IHC for LAG3 expression.

**[0274]** For Part A, biopsy is optional, since not all subjects will receive the eventually identified optimal tracer dose.

**[0275]** Decision to progress to Part B will be made on the basis of Part A data and recruitment rate.

#### **Part B**

**[0276]** Following screening, each melanoma patient will receive a  $^{89}\text{Zr}$ -DFO-anti-LAG3 at the optimized mass dose (from Part A) followed by PET scanning at the optimal post-injection time point (from Part A). Then, no later than 1 day after iPET imaging, the subject will undergo radiology guided biopsy of a lesion. Subsequently, the patient will be treated, open-label, with available approved immunotherapy regimens (dosed as per label). Subjects will receive a second scan 4-8 weeks after commencement of immunotherapy. A second biopsy after the second scan may be undertaken if feasible and will be optional.

**[0277]** All patients will be screened by an  $^{18}\text{F}$ -FDG PET/CT scan. CT portion of the PET/CT scan must be of diagnostic quality or a diagnostic CT scan acquired during the screening period must be available to assess location and dimension of lesions. These scans will be used to evaluate the lesions for metabolic activity/viability and appropriate dimensions.

**[0278]** The embodiments and examples described above are intended to be merely illustrative and non-limiting. Those skilled in the art will recognize or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials and procedures. All such equivalents are considered to be within the scope and are encompassed by the appended claims.

## CLAIMS

What is claimed is:

1. A radiolabeled antibody conjugate comprising an antibody or antigen binding fragment thereof that binds lymphocyte activation gene-3 (LAG3), a chelating moiety, and a positron emitter, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (HCDRs) (HCDR1, HCDR2 and HCDR3) within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO:418 and three light chain complementarity determining regions (LCDRs) (LCDR1, LCDR2 and LCDR3) within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO:426, and wherein the positron emitter is  $^{89}\text{Zr}$ .

2. The radiolabeled antibody conjugate of claim 1, wherein said antibody or antigen-binding fragment thereof is covalently bonded to one or more moieties of Formula (A):

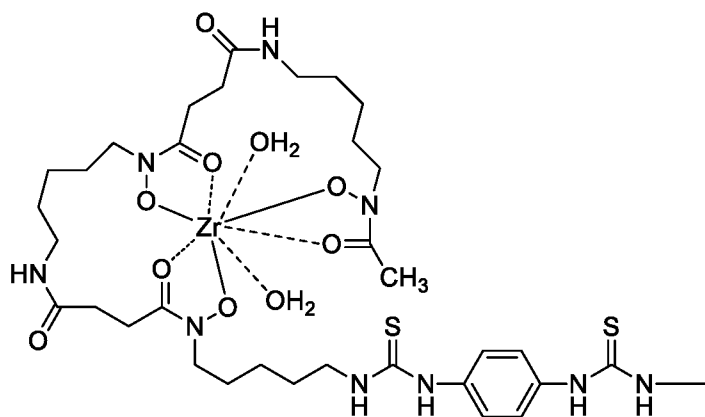


(A)

wherein L is the chelating moiety; M is the positron emitter; and z, independently at each occurrence, is 0 or 1; and wherein at least one of z is 1.

3. The radiolabeled antibody conjugate of claim 2, wherein the chelating moiety comprises desferrioxamine.

4. The radiolabeled antibody conjugate of claim 2, wherein -L-M is



and wherein Zr is the positron emitter  $^{89}\text{Zr}$ .

5. The radiolabeled antibody conjugate of any one of claims 2-4, wherein the antibody or antigen-binding fragment thereof is covalently bonded to one, two, or three moieties of Formula (A).

6. The radiolabeled antibody conjugate of any one of claims 1-5, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region HCDR1 comprising SEQ ID NO: 420; an HCDR2 comprising SEQ ID NO: 422; and an HCDR3 comprising SEQ ID NO: 424; a light chain complementarity determining region LCDR1 comprising SEQ ID NO: 428; an LCDR2 comprising SEQ ID NO: 430; and an LCDR3 comprising SEQ ID NO: 432.

7. The radiolabeled antibody conjugate of any one of claims 1-6, wherein the antibody or antigen-binding fragment thereof comprises the HCVR of SEQ ID NO: 418; and the LCVR of SEQ ID NO: 426.

8. A method of imaging a tissue that expresses LAG3 comprising administering the radiolabeled antibody conjugate of any one of claims 1-7 to the tissue; and visualizing LAG3 expression by positron emission tomography (PET) imaging.

9. A method for determining that a solid tumor comprises LAG3-positive cells, comprising (i) administering the radiolabeled antibody conjugate of any one of claims 1 – 7 to a subject in need thereof; and (ii) imaging localization of the radiolabeled antibody conjugate in the tumor in the subject by positron emission tomography (PET) imaging, wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor comprises LAG3-positive cells.

10. Use of the conjugate of any of one of claims 1 through 7 in the manufacture of a medicament for determining that a solid tumor comprises LAG3-positive cells, the determining comprising imaging localization of the radiolabeled antibody conjugate in the tumor in the subject by positron emission tomography (PET) imaging, wherein presence of the radiolabeled antibody conjugate in the tumor indicates that the tumor comprises LAG3-positive cells.

11. The method of claim 9 or the use of claim 10, wherein upon determining that the solid tumor comprises LAG3-positive cells, an anti-tumor therapy for administration to the subject is selected from the group consisting of an inhibitor of LAG3, an inhibitor of the PD-1/PD-L1 signaling axis, a CTLA-4 inhibitor, a TIM3 inhibitor, a BTLA inhibitor, a TIGIT inhibitor, a CD47 inhibitor, a GITR inhibitor, an antagonist of another T cell co-inhibitor or

ligand, an indoleamine-2,3-dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist, an Ang2 inhibitor, a transforming growth factor beta (TGF $\beta$ ) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a CD20 inhibitor, an antibody to a tumor-specific antigen, a cancer vaccine, a bispecific antibody, a cytotoxin, a chemotherapeutic agent, cyclophosphamide, radiotherapy, an IL-6R inhibitor, an IL-4R inhibitor, an IL-10 inhibitor, IL-2, IL-7, IL-21, IL-15, and an antibody-drug conjugate (ADC).

12. The method or use of claim 11, wherein the anti-tumor therapy is selected from the group consisting of an anti-LAG3 antibody, REGN2810, BGB-A317, nivolumab, pidilizumab, pembrolizumab, atezolizumab, avelumab, durvalumab, MDX-1105, REGN3504, ipilimumab, an anti-CD-28 antibody, an anti-2B4 antibody, an anti-LY108 antibody, an anti-LAIR1 antibody, an anti-ICOS antibody, an anti-CD160 antibody, an anti-VISTA antibody, aflibercept, bevacizumab, ranibizumab, sunitinib, sorafenib, pazopanib, nesvacumab, erlotinib, cetuximab, rituximab, an anti-CA9 antibody, an anti-CA125 antibody, an anti-melanoma-associated antigen 3 (MAGE3) antibody, an anti-carcinoembryonic antigen (CEA) antibody, an anti-vimentin antibody, an anti-tumor-M2-PK antibody, an anti-prostate-specific antigen (PSA) antibody, an anti-mucin-1 antibody, an anti-MART-1 antibody, an anti-CA19-9 antibody, Bacillus Calmette-Guerin, a CD3xCD20 bispecific antibody, a PSMAxCD3 bispecific antibody, dacarbazine, temozolomide, cyclophosphamide, docetaxel, doxorubicin, daunorubicin, cisplatin, carboplatin, gemcitabine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, vincristine, cyclophosphamide, radiotherapy, sarilumab, dupilumab, anti-CD19-DM4 ADC, and anti-DS6-DM4 ADC.

13. The method or use of either of claims 11 or 12, wherein the anti-tumor therapy is selected from the group consisting of an anti-LAG3 antibody or antigen-binding fragment thereof, an anti-PD-1 antibody or antigen-binding fragment thereof, and an anti-PD-L1 antibody or antigen-binding fragment thereof.

14. The method or use of claim 13, wherein the anti-tumor therapy is an anti-LAG3 antibody or antigen-binding fragment thereof comprising three heavy chain complementarity determining regions (HCDRs) and three light chain complementarity determining regions (LCDRs) within the heavy chain variable region (HCVR)/light chain variable region (LCVR) sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330, 338/346,

354/362, 370/378, 386/394, 402/410, 418/426, 434/442, 450/522, 458/522, 466/522, 474/522, 482/522, 490/522, 498/530, 506/530, 514/530, 538/546, and 554/562.

15. The method or use of claim 14, wherein the anti-LAG3 antibody or antigen-binding fragment thereof comprises three HCDRs and three LCDRs selected from the group consisting of SEQ ID NOs: 4/6/8/12/14/16, 20/22/24/28/30/32, 36/38/40/44/46/48, 52/54/56/60/62/64, 68/70/72/76/78/80, 84/86/88/92/94/96, 100/102/104/108/110/112, 116/118/120/124/126/128, 132/134/136/140/142/144, 148/150/152/156/158/160, 164/166/168/172/174/176, 180/182/184/188/190/192, 196/198/200/204/206/208, 212/214/216/220/222/224, 228/230/232/236/238/240, 244/246/248/252/254/256, 260/262/264/268/270/272, 276/278/280/284/286/288, 292/294/296/300/302/304, 308/310/312/316/318/320, 324/326/328/332/334/336, 340/342/344/348/350/352, 356/358/360/364/366/368, 372/374/376/380/382/384, 388/390/392/396/398/400, 404/406/408/412/414/416, 420/422/424/428/430/432, 436/438/440/444/446/448, 452/454/456/524/526/528, 460/462/464/524/526/528, 468/470/472/524/526/528, 476/478/480/524/526/528, 484/486/488/524/526/528, 492/494/496/524/526/528, 500/502/504/532/534/536, 508/510/512/532/534/536, 516/518/520/532/534/536, 540/542/544/548/550/552, and 556/558/560/564/566/568.

16. The method or use of claim 14, wherein the anti-LAG3 antibody or antigen-binding fragment thereof comprises three HCDRs in a HCVR of SEQ ID NO: 418; and three LCDRs in a LCVR of SEQ ID NO: 426.

17. The method or use of claim 13, wherein the anti-tumor therapy is an anti-PD-1 antibody or antigen-binding fragment thereof selected from the group consisting of REGN2810, nivolumab, and pembrolizumab.

18. The method or use of claim 13, wherein the anti-tumor therapy is an anti-PD-L1 antibody or antigen-binding fragment thereof selected from the group consisting of atezolizumab, avelumab, and durvalumab.

19. The method or use of claim 16, wherein the anti-LAG3 antibody is administered in combination with a second anti-tumor therapy.

20. The method or use of claim 19, wherein the second anti-tumor therapy is selected from the group consisting of an inhibitor of the PD-1/PD-L1 signaling axis, a CTLA-4 inhibitor, a TIM3 inhibitor, a BTLA inhibitor, a TIGIT inhibitor, a CD47 inhibitor, a GITR inhibitor, an antagonist of another T cell co-inhibitor or ligand, an indoleamine-2,3-

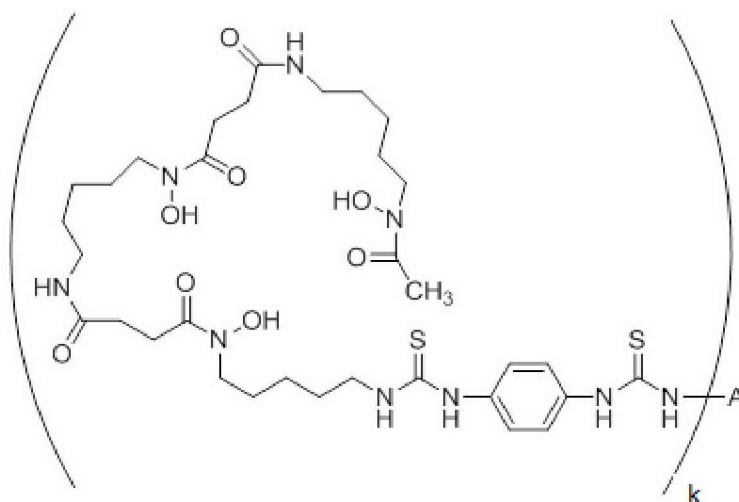
dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist, an Ang2 inhibitor, a transforming growth factor beta (TGF $\beta$ ) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, a CD20 inhibitor, an antibody to a tumor-specific antigen, a cancer vaccine, a bispecific antibody, a cytotoxin, a chemotherapeutic agent, cyclophosphamide, radiotherapy, an IL-6R inhibitor, an IL-4R inhibitor, an IL-10 inhibitor, IL-2, IL-7, IL-21, IL-15, and an antibody-drug conjugate (ADC).

21. The method or use of claim 19, wherein the second anti-tumor therapy is selected from the group consisting of a second anti-LAG3 antibody, REGN2810, BGB-A317, nivolumab, pidilizumab, pembrolizumab, atezolizumab, avelumab, durvalumab, MDX-1105, REGN3504, ipilimumab, an anti-CD-28 antibody, an anti-2B4 antibody, an anti-LY108 antibody, an anti-LAIR1 antibody, an anti-ICOS antibody, an anti-CD160 antibody, an anti-VISTA antibody, aflibercept, bevacizumab, ranibizumab, sunitinib, sorafenib, pazopanib, nesvacumab, erlotinib, cetuximab, rituximab, an anti-CA9 antibody, an anti-CA125 antibody, an anti-melanoma-associated antigen 3 (MAGE3) antibody, an anti-carcinoembryonic antigen (CEA) antibody, an anti-vimentin antibody, an anti-tumor-M2-PK antibody, an anti-prostate-specific antigen (PSA) antibody, an anti-mucin-1 antibody, an anti-MART-1 antibody, an anti-CA19-9 antibody, Bacillus Calmette-Guerin, a CD3xCD20 bispecific antibody, a PSMAxCD3 bispecific antibody, dacarbazine, temozolomide, cyclophosphamide, docetaxel, doxorubicin, daunorubicin, cisplatin, carboplatin, gemcitabine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, vincristine, cyclophosphamide, radiotherapy, sarilumab, dupilumab, anti-CD19-DM4 ADC, and anti-DS6-DM4 ADC.

22. The method or use of any one of claims 9 – 21, wherein the tumor is selected from the group consisting of blood cancer, brain cancer, renal cell cancer, ovarian cancer, bladder cancer, prostate cancer, breast cancer, hepatic cell carcinoma, bone cancer, colon cancer, non-small-cell lung cancer, squamous cell carcinoma of head and neck, colorectal cancer, mesothelioma, B cell lymphoma, and melanoma.

23. A compound of Formula (III):





Wherein A is an antibody or antigen-binding fragment thereof that binds LAG3, k is an integer from 1-30; wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (HCDRs) within a heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 418 and three light chain complementarity determining regions (LCDRs) within a light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 426.

24. The compound of claim 23, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain complementarity determining region HCDR1 comprising SEQ ID NO: 420; an HCDR2 comprising SEQ ID NO: 422; and an HCDR3 comprising SEQ ID NO: 424; a light chain complementarity determining region LCDR1 comprising SEQ ID NO: 428; an LCDR2 comprising SEQ ID NO: 430; and an LCDR3 comprising SEQ ID NO: 432.

25. The compound of either of claim 23 or 24, wherein the antibody or antigen-binding fragment thereof comprises three HCDRs in a HCVR of SEQ ID NO: 418; and the LCVR of SEQ ID NO: 426.

26. The compound of any one of claims 23-25, wherein k is less than or equal to 2.

27. The compound of any one of claims 23-26, wherein k is 1 or 2.

28. A method for identifying T-cell exhaustion in a subject comprising administering the radiolabeled conjugate of any one of claims 1 through 7 to the subject.

29. Use of the conjugate of any one of claims 1 through 7 in the manufacture of a medicament for identifying T-cell exhaustion in a subject.

30. The method of claim 28 or the use of claim 29, wherein the subject suffers from cancer, a viral infection, a bacterial infection, a fungal infection, or a parasitic infection.

31. A composition comprising:

(i) a radiolabeled antibody conjugate comprising an antibody or antigen binding fragment thereof that binds lymphocyte activation gene-3 (LAG3), desferrioxamine, and a  $^{89}\text{Zr}$  positron emitter, wherein the antibody or antigen-binding fragment thereof comprises three heavy chain complementarity determining regions (HCDRs) within a heavy chain variable region (HCVR) amino acid sequence as set forth in SEQ ID NO: 418 and three light chain complementarity determining regions (LCDRs) within a light chain variable region (LCVR) amino acid sequence as set forth in SEQ ID NO: 426; and

(ii) LAG3 expressing T cells.

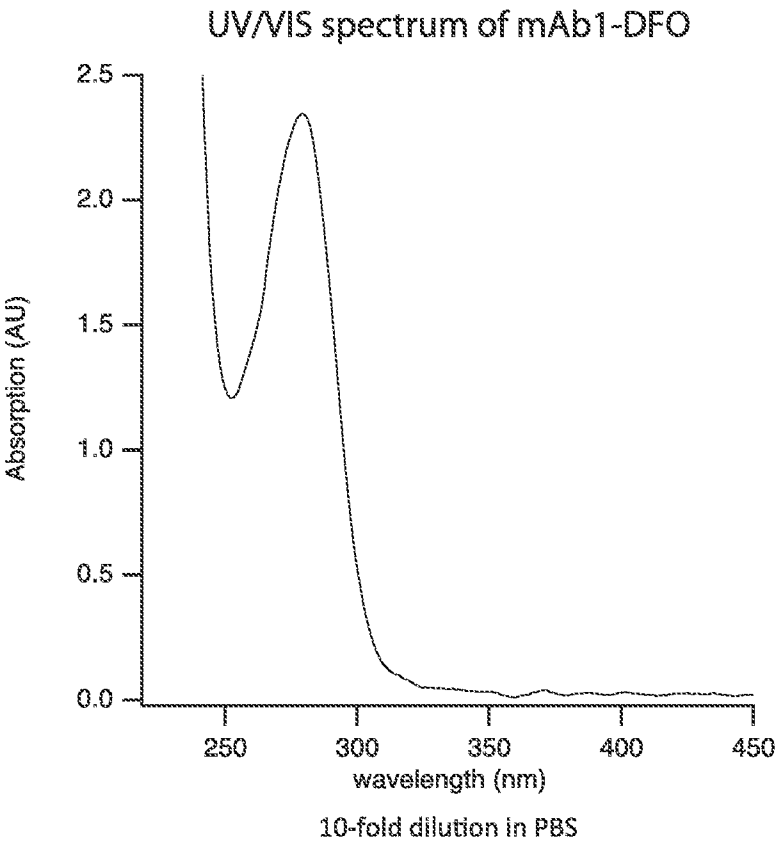


FIGURE 1

2/12

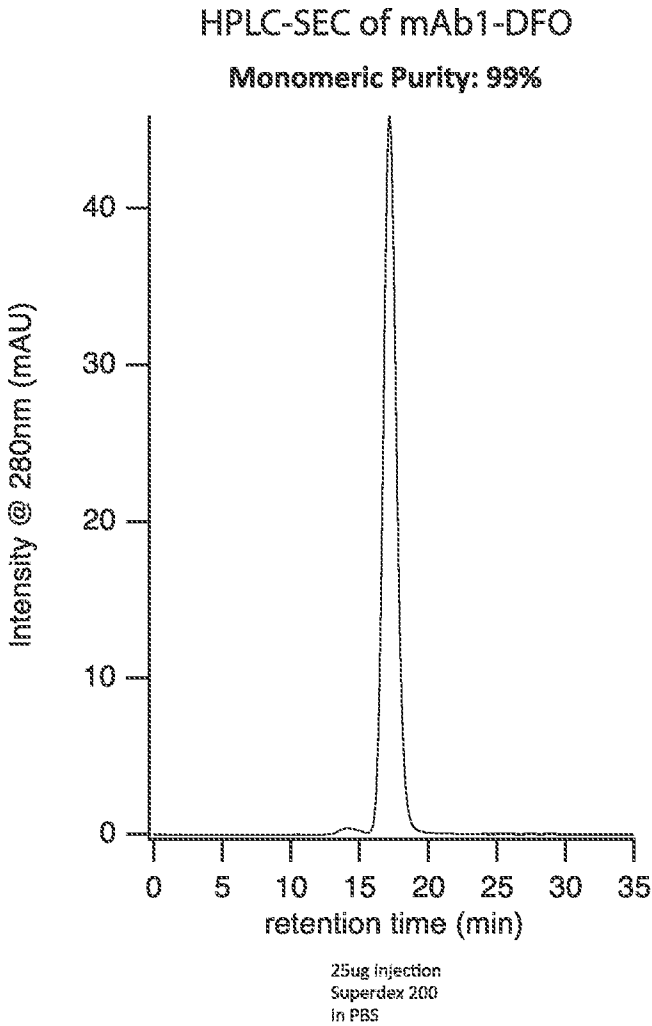


FIGURE 2

3/12

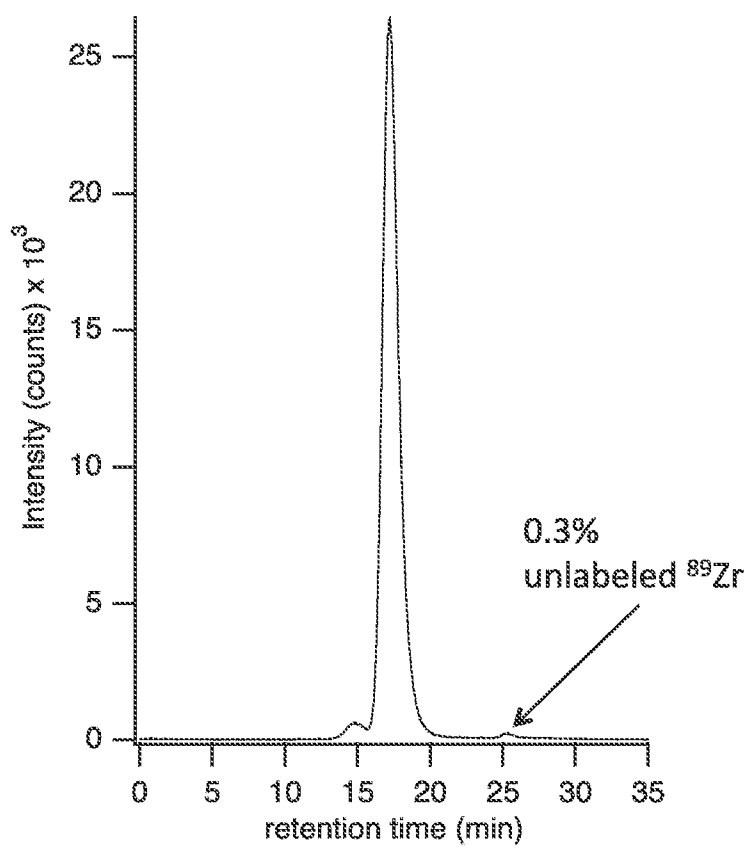
radio-SEC: Isotype-DFO-<sup>89</sup>Zr

FIGURE 3

4/12

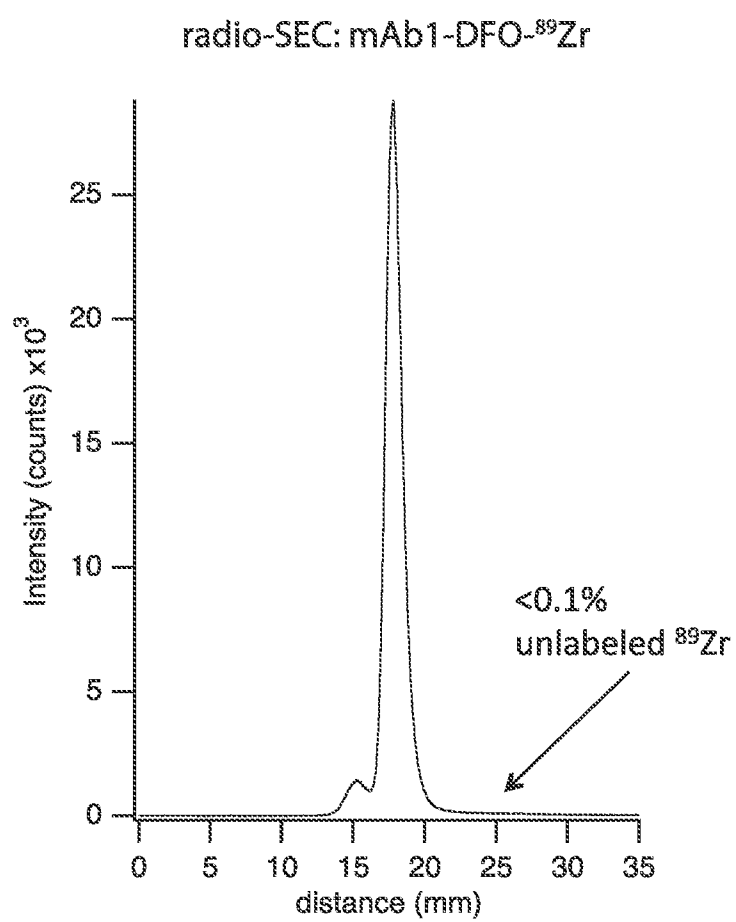


FIGURE 4

5/12

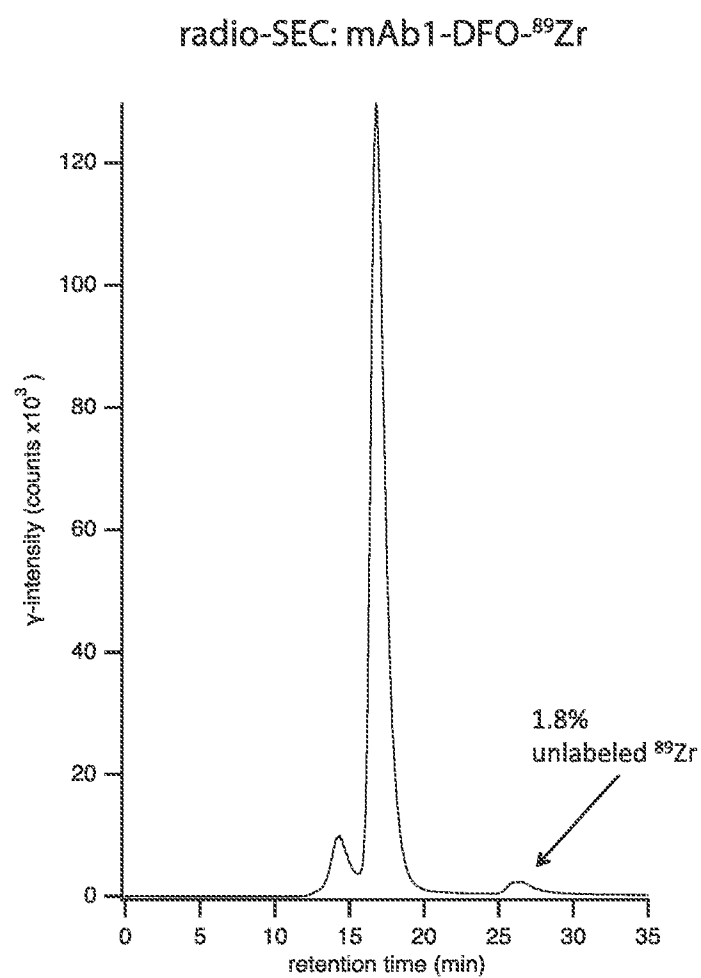


FIGURE 5

6/12

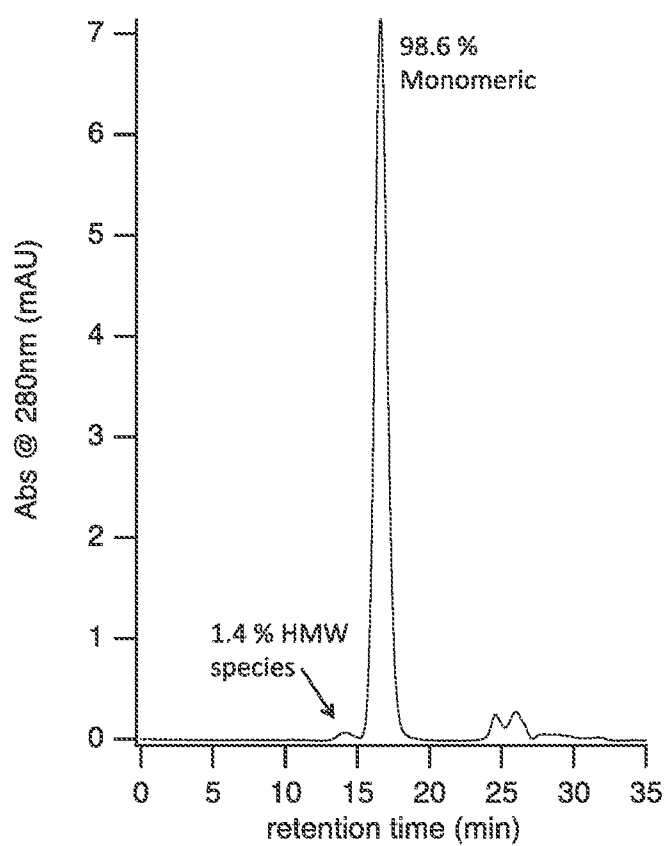
UV-SEC: Isotype-DFO-<sup>89</sup>Zr

FIGURE 6



7/12

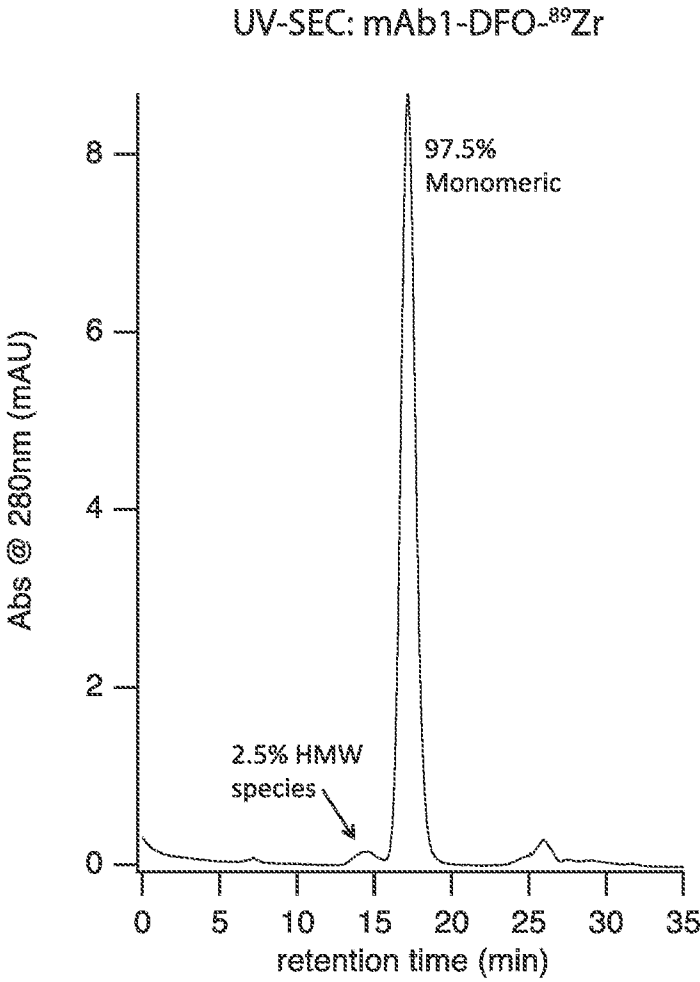


FIGURE 7

8/12

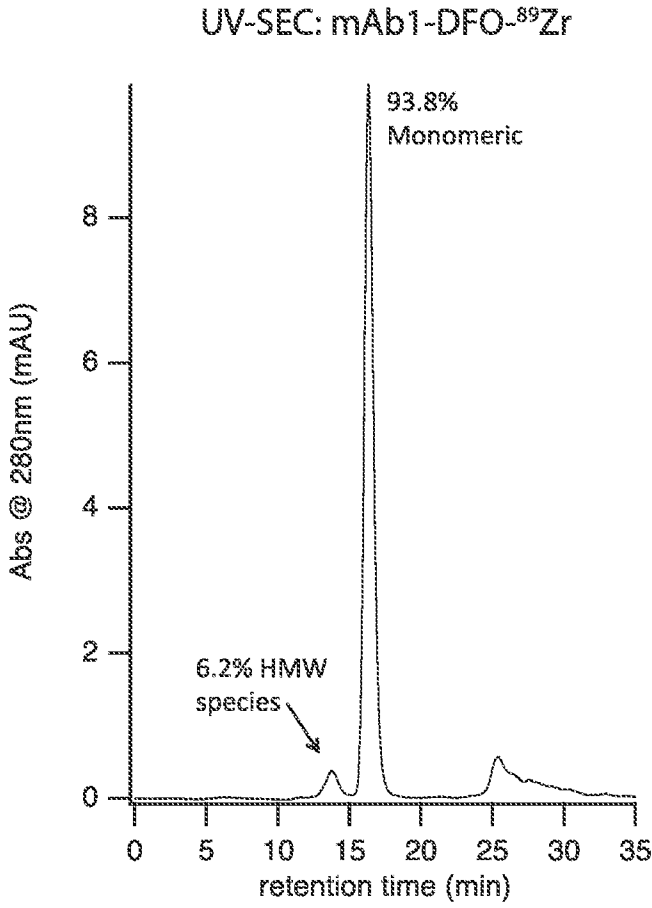


FIGURE 8

9/12

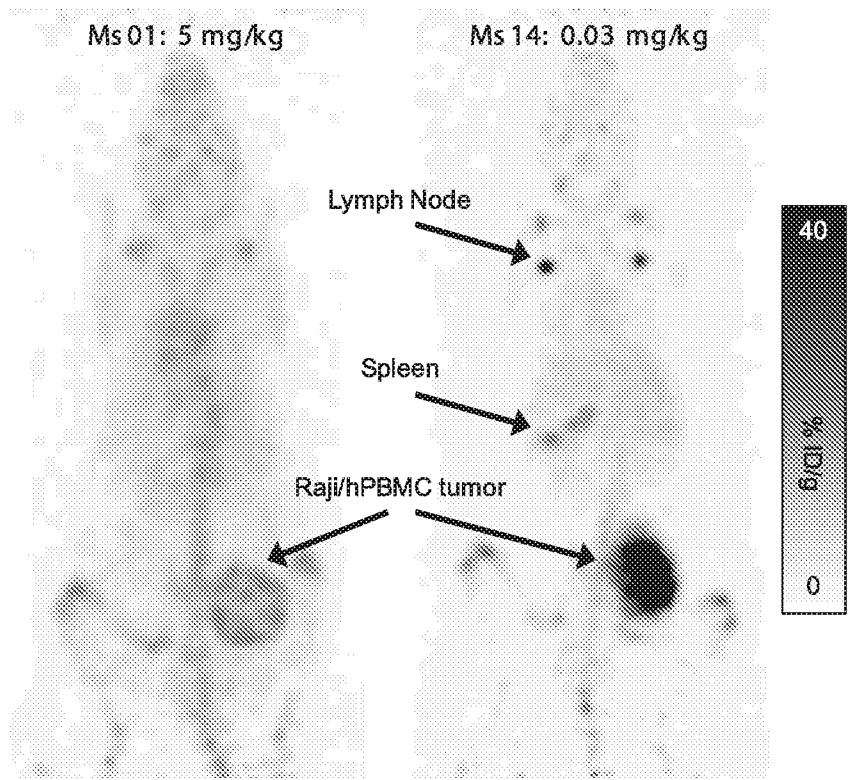


FIGURE 9

10/12

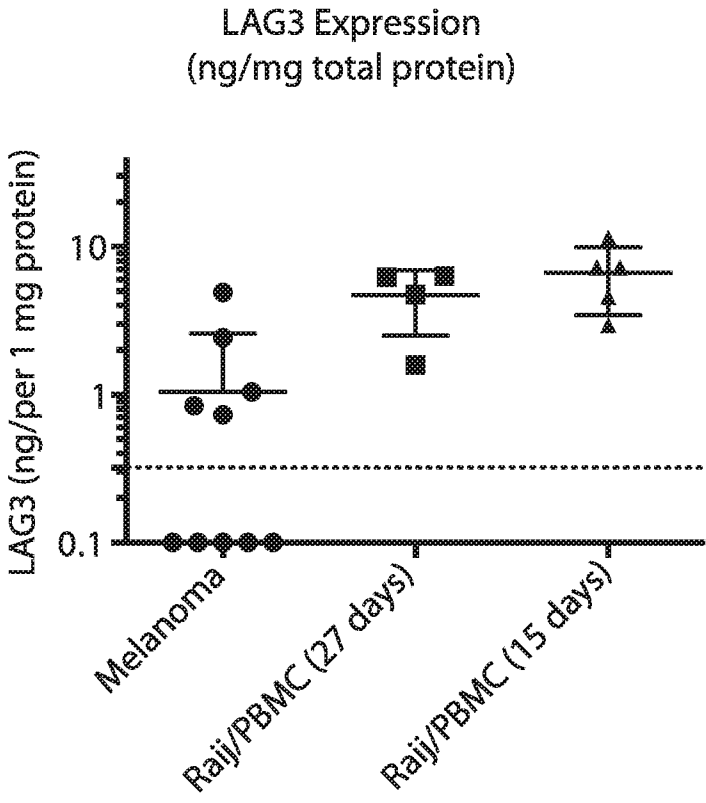
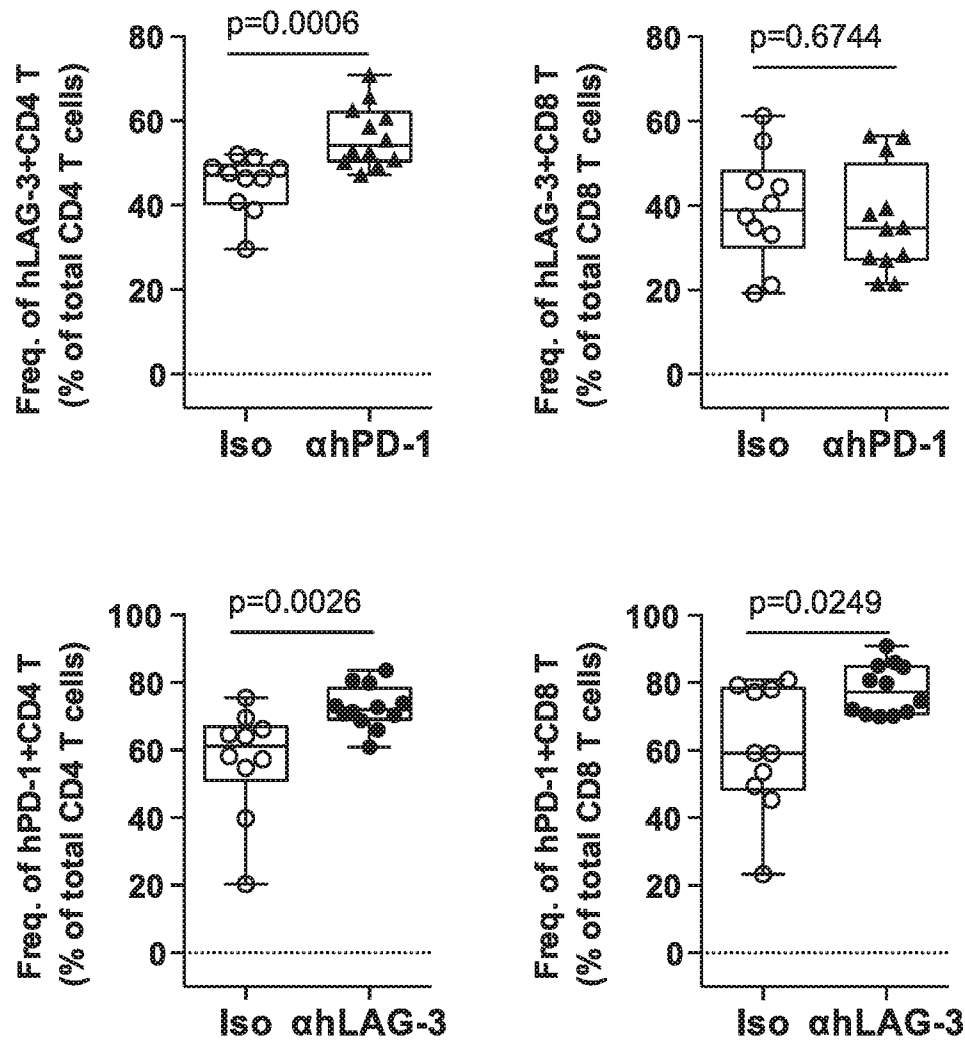


FIGURE 10

11/12



Statistic analysis was performed using Unpaired Mann-Whitney nonparametric T test

FIGURE 11

12/12

Sample information of melanoma tissues

| Sample ID   | Sex | Age | Ethnicity | Sample type | Matrix                  | Diagnosis | Histological diagnosis    | TNM       | Stage     | Clark's level of invasion | Breslow microstaging, cm | Tumor size, cm | Metastases        | Date of surgery | Tumor content % | Weight, g |
|-------------|-----|-----|-----------|-------------|-------------------------|-----------|---------------------------|-----------|-----------|---------------------------|--------------------------|----------------|-------------------|-----------------|-----------------|-----------|
| 131815T2(3) | M   | 45  | Caucasian | FF          | skin                    | melanoma  | epithelioid cell melanoma | T4bN3M0   | IIIC      | V                         | 1                        | 1.8x1x1        | 9/9 lymph nodes   | 03/16/2015      | 95              | 0.9       |
| 131719T2(3) | M   | 58  | Caucasian | FF          | skin                    | melanoma  | spindle cell melanoma     | T4bN0M0   | IIC       | V                         | 1                        | 6x5x1          | no                | 09/23/2014      | 100             | 0.8       |
| 139411T2(1) | F   | 51  | Caucasian | FF          | skin                    | melanoma  | mixed cell melanoma       | T4bN0M0   | IIB       | IV                        | 1.3                      | 3.5x3.5x1.3    | no                | 02/08/2010      | 100             | 0.8       |
| 13798T2(4)  | F   | 63  | Caucasian | FF          | skin                    | melanoma  | spindle cell melanoma     | T4bN1bM0  | IIIC      | III                       | 2.5                      | 7 cm           | 1/1 lymph nodes   | 10/23/2009      | 100             | 0.7       |
| 13765T2(2)  | M   | 56  | Caucasian | FF          | skin                    | melanoma  | epithelioid cell melanoma | T4bN3M0   | IIIC      | III                       | 0.7                      | 2.5x1.5        | 6/6 lymph nodes   | 08/26/2009      | 90              | 0.8       |
| 131778T2(5) | M   | 58  | Caucasian | FF          | skin                    | melanoma  | epithelioid cell melanoma | T4bN3M0   | IIIC      | V                         | 30 mm                    | 5x3x3          | 11/17 lymph nodes | 12/15/2014      | 100             | 0.7       |
| 131291T2(1) | F   | 33  | Caucasian | FF          | skin                    | melanoma  | nevroid cell melanoma     | T4bN3M0   | IIIC      | III                       | 15 mm                    | 3x1.5          | 6/6 lymph nodes   | 03/15/2012      | 100             | 1         |
| 131086T6(1) | M   | 59  | Caucasian | FF          | skin                    | melanoma  | epithelioid cell melanoma | T4pN0M0   | IIB       | V                         | 10 mm                    | 2.5 cm         | no                | 05/12/2011      | 75              | 0.6       |
| 13547T2(1)  | M   | 73  | Caucasian | FF          | skin and adipose tissue | melanoma  | epithelioid cell melanoma | recurrent | recurrent | III                       | 15 mm                    | N/A            | 1/18 lymph nodes  | 05/21/2008      | 100             | 0.9       |
| 13524T2(7)  | F   | 44  | Caucasian | FF          | skin                    | melanoma  | epithelioid cell melanoma | T4bN2aM0  | IIIC      | III                       | 22 mm                    | 2 cm           | 2/12 lymph nodes  | 01/24/2008      | 100             | 0.65      |

FIGURE 12

10329W001\_SEQ\_LIST\_ST25.txt  
SEQUENCE LISTING

<110> Regeneron Pharmaceuticals, Inc.  
Kelly, Marcus  
Ma, Dangshe  
Olson, William  
Thurston, Gavin

<120> RADIOLABELED ANTI-LAG3 ANTIBODIES FOR IMMUNO-PET IMAGING

<130> 10329W001

<140> TBD

<141> 2018-02-09

<150> 62/457,287

<151> 2017-02-10

<160> 589

<170> PatentIn version 3.5

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| tcctgtgtgg cctctggatt cacctttagc acctatgcca tgagttgggt ccgccaggct | 120 |
| ccagggatgg ggctggagtg ggtctcaagt attagtggtg gtggtcgtaa cacatactat | 180 |
| gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctgttt | 240 |
| cttcaaatac acagcctgag agccgaggac acggccgttt attactgtgc gaaagagtcc | 300 |
| gtaactggaa cttcgtccta ctactacggt gtggacgtct ggggccaagg gaccacggtc | 360 |
| accgtctcct cg                                                     | 372 |

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 20 25 30

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

Ser Ser Ile Ser Gly Ser Gly Arg Asn 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 Phe  
 65 70 75 80

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

Ala Lys Glu Ser Val Thr Gly Thr Ser Ser Tyr Tyr Tyr Gly Val Asp  
 100 105 110

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

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&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

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24

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&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence



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<400> 8

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| Ala | Lys | Glu | Ser | Val | Thr | Gly | Thr | Ser | Ser | Tyr | Tyr | Tyr | Gly | Val | Asp |
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| atcacttgcc | gggcaagtca | gagcattagc | agttatttaa | attggtatca | tcagaaacca  | 120 |
| gggaaagccc | caaagctcct | gatctatgct | gcatccagtt | tgcaaaatgg | gggtcccatca | 180 |
| aggttcagt  | gcagtggatc | tgggacagat | ttcactctca | ccatcagcag | tctgcaacct  | 240 |
| gaagattttg | catcttacta | ctgtcaacag | agttacagaa | ccccgctcac | tttcggcgga  | 300 |
| gggaccaagg | tggagatcaa | a          |            |            |             | 321 |

<210> 10

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

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

10329W001\_SEQ\_LIST\_ST25.txt

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

Tyr Ala Ala Ser Ser Leu Gln Asn 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 Ser Tyr Tyr Cys Gln Gln Ser Tyr Arg Thr Pro Leu  
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Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys  
100 105

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9

<210> 14

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<210> 15

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<210> 16

<211> 9

<212> PRT

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Gln Gln Ser Tyr Arg Thr Pro Leu Thr

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5

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| tcctgtgcag cgtctggatt caccttcagt tggatatggca tgcactgggt ccgccaggct | 120 |
| ccaggcaagg ggctggagtg ggtggcactt atatggtatg atggaactaa taaaaagtat  | 180 |
| ggagactccg tgaagggccg attcaccatt tccagagaca attccaagaa cacggtgtat  | 240 |
| ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagattgt  | 300 |
| ggacatagtg gcaacgatcg ggggacttac tattactact acggtatgga cgtctggggc  | 360 |
| caagggacca cggtcaccgt ctcctca                                      | 387 |

<210> 18

<211> 129

<212> PRT

<213> Artificial Sequence

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| 1 5 10 15                                                       |  |

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

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

|                                                                 |  |
|-----------------------------------------------------------------|--|
| Ala Leu Ile Trp Tyr Asp Gly Thr Asn Lys Lys Tyr Gly Asp Ser Val |  |
| 50 55 60                                                        |  |

|                                                                 |  |
|-----------------------------------------------------------------|--|
| Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Val 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 Cys Gly His Ser Gly Asn Asp Arg Gly Thr Tyr Tyr Tyr  
 100 105 110

Tyr Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser  
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Ser

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24

<210> 20  
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Gly Phe Thr Phe Ser Trp Tyr Gly  
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<210> 21  
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24

<210> 22  
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<400> 22

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Tyr Tyr Gly Met Asp Val  
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gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca    180
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct    240
gaagattttg caacttacta ctgtcaacag agttacagta cccctccgat caccttcggc    300
caagggacac gactggagat taaa                                           324

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&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 26

```

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

```

```

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

```

```

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

```

```

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

```

```

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

```

```

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

```

```

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
          100          105

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18

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Gln Ser Ile Ser Ser Tyr  
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9

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Ala Ala Ser  
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<400> 32

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 ccagggaagg ggctggagtg ggttggggaa atcagtcata gaggaaccac caactacaac 180  
 ccgtccctca agagtcgagt caccatatca ctggacacgt ccaagaacca gttctccctg 240  
 aaactgacct ctgtgaccgc cgcggacacg gctgtgtatt actgttcgag agacgaggaa 300  
 ctggaattcc gtttctttga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

<210> 34  
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&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 34

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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 Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45

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

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

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

Arg Asp Glu Glu Leu Glu Phe Arg Phe Phe Asp Tyr Trp Gly Gln Gly  
 100 105 110

Thr Leu Val Thr Val Ser Ser  
 115

&lt;210&gt; 35

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 35

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Ile Ser His Arg Gly Thr Thr  
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 ggccaggctc ccaggctcct cgtctatggt gcatccaaca gggccactgg catcccagcc 180  
 aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240  
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Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Tyr  
 20 25 30

10329W001\_SEQ\_LIST\_ST25.txt

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

Tyr Gly 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 Phe Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu  
 85 90 95

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

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18

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<210> 46

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27

<210> 48

<211> 9

<212> PRT

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Gln Gln Arg Ser Asn Trp Pro Leu Thr

1

5

<210> 49

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<212> DNA

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|                                                                   |     |
|-------------------------------------------------------------------|-----|
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| acctgcactg tctctggtga ctccatcatc agtaatagtt attactgggg ctggatccgc | 120 |
| cagccccag ggaaggggct ggagtggatt ggcaatttct tttatactgg ggccacctac  | 180 |
| tacaaccgt ccctcaagag tcgagtcacc atatccgctg acacgtccaa gaatcagttc  | 240 |
| tccctgaagc tgagctctgt gaccgccgca gacacggctc tgtattattg tgcgagttat | 300 |
| aataggaatt accggttcga cccctggggc cagggaacct tggtcaccgt ctctca     | 357 |

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<212> PRT

<213> Artificial Sequence

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<400> 50

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 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 | Asp | Ser | Ile | Ile | Ser | Asn |
|     |     |     | 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 | Asn | Phe | Phe | Tyr | Thr | Gly | Ala | Thr | Tyr | Tyr | Asn | Pro | Ser |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

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

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



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

Thr Leu Val Thr Val Ser Ser  
 115

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30

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<400> 52

Gly Asp Ser Ile Ile Ser Asn Ser Tyr Tyr  
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21

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Phe Phe Tyr Thr Gly Ala Thr  
1 5

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gcgagttata ataggaatta ccggttcgac ccc

33

<210> 56

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Ala Ser Tyr Asn Arg Asn Tyr Arg Phe Asp Pro  
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<211> 324

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gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240

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caagggacac gactggagat taaa

324

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 <211> 108  
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<400> 58

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

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

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

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

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

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

Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
 100 105

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18

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<400> 60

Gln Ser Ile Ser Ser Tyr  
 1 5

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9

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Ala Ala Ser  
 1

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Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr  
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| acctgcgctg tctatgggtg gtccttcagt acttactact ggagctggat ccgccagccc  | 120 |
| ccaggggaagg ggctggagtg gattggagag atcaatcata gtggaaacgc cgactacaac | 180 |
| ccgtccctca agagtcgagt ctccatatca gtggacacgt ccaagaacca gttctccctg  | 240 |
| aggctgagct ctgtgaccgc cgcggacacg gctattttatt actgtgcgag agcgggctat | 300 |
| tgtagtagtc ccacctgcta ttctactac tacttcggta tggacgtctg gggccaaggg   | 360 |
| accacgggtca ccgtctcctc a                                           | 381 |

<210> 66  
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<400> 66

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

10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

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

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

Arg Ala Gly Tyr Cys Ser Ser Pro Thr Cys Tyr Ser Tyr Tyr Tyr Phe  
100 105 110

Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
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Gly Gly Ser Phe Ser Thr Tyr Tyr  
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Ile Asn His Ser Gly Asn Ala  
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gtc 63

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Ala Arg Ala Gly Tyr Cys Ser Ser Pro Thr Cys Tyr Ser Tyr Tyr Tyr  
 1 5 10 15

Phe Gly Met Asp Val  
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&lt;210&gt; 73

&lt;211&gt; 324

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 73

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 cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcttccca 180  
 gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatccg cagactggag 240  
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 caagggacca aggtggagat caaa 324

&lt;210&gt; 74

&lt;211&gt; 108

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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&lt;223&gt; synthetic

&lt;400&gt; 74

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

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

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



Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Phe Pro Asp Arg Phe Ser  
50 55 60

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

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

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

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21

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Gln Ser Val Ile Ser Ser Phe  
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9

<210> 78  
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Gly Ala Ser  
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27

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Gln Gln Tyr Gly Asn Ser Pro Trp Thr  
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10329W001\_SEQ\_LIST\_ST25.txt

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cagccccctg ggaaggccct ggagtggctt gcacacattt tttcgaatga cgagaagtcc 180  
tacagcacat ctctgaggac cagactcacc atctccaagg acacctcaa aagccaggtg 240  
gtccttaccg tgaccaactt ggaccctgtg gacacagcca catatttctg tgcacggata 300  
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Thr Leu Thr Leu Thr Cys Thr Val Ser Gly Phe Ser Leu Ser Asn Ala  
20 25 30

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

Trp Leu Ala His Ile Phe Ser Asn Asp Glu Lys Ser Tyr Ser Thr Ser  
50 55 60

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

Val Leu Thr Val Thr Asn Leu Asp Pro Val Asp Thr Ala Thr Tyr Phe  
85 90 95

Cys Ala Arg Ile Pro Glu Phe Thr Ser Ser Ser Trp Ala Leu Tyr Tyr  
100 105 110

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

Ser

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<400> 84

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&lt;223&gt; synthetic

&lt;400&gt; 86

Ile Phe Ser Asn Asp Glu Lys

1 5

&lt;210&gt; 87

&lt;211&gt; 63

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 87

gcacggatac cagagtttac cagctcgtcg tgggctctct actacttcta cggatatggac 60

gtc 63

&lt;210&gt; 88

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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&lt;223&gt; synthetic

&lt;400&gt; 88

Ala Arg Ile Pro Glu Phe Thr Ser Ser Ser Trp Ala Leu Tyr Tyr Phe

1 5 10 15

Tyr Gly Met Asp Val

20

&lt;210&gt; 89

&lt;211&gt; 324

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 89

gaaattgtgt tgacgcagtc tccaggcacc ctgtctttgt ctccagggga aagcgccacc 60

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| cctggccagg | ctcccaggct | cctcatctat | gctacatcca | gcagggccac | tggcgtccca | 180 |
| gacaggttca | gtggcagtgg | gtctgggacg | gacttcactc | tcaccatcag | cagactggag | 240 |
| cctgatgatt | ttgcagtgta | ttactgtcag | caatatggta | ggtcaccttg | gacgttcggc | 300 |
| caagggacca | aggtggaagt | caaa       |            |            |            | 324 |

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| <211> | 108                 |
| <212> | PRT                 |
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Glu Ser Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Thr Ser Thr  
20 25 30

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

Ile Tyr Ala Thr Ser Ser Arg Ala Thr Gly Val 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 Asp Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Arg Ser Pro  
85 90 95

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

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&lt;223&gt; synthetic

&lt;400&gt; 95

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&lt;212&gt; PRT

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&lt;223&gt; synthetic

&lt;400&gt; 96

Gln Gln Tyr Gly Arg Ser Pro Trp Thr

1 5

&lt;210&gt; 97

&lt;211&gt; 363

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 97

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cctggacaag ggcttgagtg gatgggatgg atcagcgctt acaatgataa cacaaactat 180

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&lt;211&gt; 121

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence



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Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala  
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr  
20 25 30

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

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

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

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

Val Arg Trp Asn Trp Gly Ser Val Tyr Trp Tyr Phe Asp Leu Trp Gly  
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Arg Gly Thr Leu Val Thr Val Ser Ser  
115 120

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Gly Tyr Thr Phe Thr Ser Tyr Gly  
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<210> 101  
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Ile Ser Ala Tyr Asn Asp Asn Thr  
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<212> PRT  
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Val Arg Trp Asn Trp Gly Ser Val Tyr Trp Tyr Phe Asp Leu  
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Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ile Ile Ser Ser Ser  
 20 25 30

10329W001\_SEQ\_LIST\_ST25.txt

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

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

Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys  
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Gln Ile Ile Ser Ser Ser Tyr  
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9

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<223> synthetic

<400> 112

Gln Gln Tyr Gly Asn Ser Pro Trp Thr

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5

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<212> DNA

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&lt;400&gt; 113

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cagccccag gaaaggccct ggagtggctt gcactcattt atgggaatga tgtaagaac      180
tacagcccat ctctggagac caggctcacc atcgccaagg acacctcaa aaaccaggtg      240
gtccttacia tgaccaacat ggacctgtg gacacagcca catatttctg ttcgtacata      300
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&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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&lt;400&gt; 114

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Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
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Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Asn Thr His
          20           25           30

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

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

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

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Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Phe
          85           90           95

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Cys Ser Tyr Ile Thr Gly Glu Gly Met Tyr Trp Gly Gln Gly Thr Leu
          100          105          110

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Val Thr Val Ser Ser  
115

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<400> 116

Gly Phe Ser Leu Asn Thr His Arg Val Gly  
1 5 10

<210> 117  
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<400> 117  
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21

<210> 118  
<211> 7  
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<220>  
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&lt;400&gt; 118

Ile Tyr Gly Asn Asp Val Lys  
 1 5

&lt;210&gt; 119

&lt;211&gt; 27

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 119

tcgtacataa cgggggaagg aatgtac

27

&lt;210&gt; 120

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 120

Ser Tyr Ile Thr Gly Glu Gly Met Tyr  
 1 5

&lt;210&gt; 121

&lt;211&gt; 333

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 121

gatgttgtga tgactcagtc tccactctcc ctgtccgtca cccttggaca gccggcctcc 60

atttcctgta ggtctagtca aaacctcatg tacagtgatg gaaacaccta cttgaattgg 120

tttcaccaga ggccaggcca atctccaagg cgtctaattt ataaggtttc taaccgggac 180

tctgggggtcc cagacagatt cagcggcagt gggtcaggca ctgatttcac actgaaaatc 240

agcagggtgg aggctgagga tgttgggggtt tattactgca tgcaaggtag acactggtac 300

acatttggcc aggggaccaa gctggagatc aaa 333



<210> 122  
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<220>  
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<400> 122

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

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Leu Met Tyr Ser  
 20 25 30

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

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

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

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

Thr His Trp Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys  
 100 105 110

<210> 123  
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 <212> DNA  
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<220>  
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<400> 123

caaaacctca tgtacagtga tggaaacacc tac

33

<210> 124  
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 <212> PRT  
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<220>  
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<400> 124

Gln Asn Leu Met Tyr Ser Asp Gly Asn Thr Tyr  
 1 5 10

<210> 125  
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 <212> DNA  
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<220>  
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<400> 125  
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9

<210> 126  
 <211> 3  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 126

Lys Val Ser  
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<210> 127  
 <211> 24  
 <212> DNA  
 <213> Artificial Sequence

<220>  
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<400> 127  
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24

<210> 128  
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<220>  
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<400> 128

Met Gln Gly Thr His Trp Tyr Thr  
 1 5

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 acctgcgctg tctatggtgg gtctttcagt ggttattact ggagctggat ccgccagccc 120  
 ccaggaagg gtctggaatg gattggggaa atcaatcata gaggaacac caactacaac 180  
 ccgtccctca agagtcgagt caccatatca ctcgacacgt ccaagaaaca gttctccctg 240  
 aacctgagtt ctgtgaccgc cgcggacacg gctatgtatt actgtacgag agacgaagaa 300  
 caggaactac gtttccttga ctactggggc caggaaccc tggtcaccgt ctcctca 357

<210> 130  
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<400> 130

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

10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

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

Arg Asp Glu Glu Gln Glu Leu Arg Phe Leu Asp Tyr Trp Gly Gln Gly  
100 105 110

Thr Leu Val Thr Val Ser Ser  
115

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<400> 131  
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24

<210> 132  
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<212> PRT  
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<220>  
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<400> 132

Gly Gly Ser Phe Ser Gly Tyr Tyr  
1 5

<210> 133  
 <211> 21  
 <212> DNA  
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<220>  
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<400> 133  
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21

<210> 134  
 <211> 7  
 <212> PRT  
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<220>  
 <223> synthetic

<400> 134

Ile Asn His Arg Gly Asn Thr  
 1 5

<210> 135  
 <211> 39  
 <212> DNA  
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<400> 135  
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39

<210> 136  
 <211> 13  
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<220>  
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<400> 136

Thr Arg Asp Glu Glu Gln Glu Leu Arg Phe Leu Asp Tyr  
 1 5 10

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<210> 137  
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<400> 137  
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ctctcctgca gggccagtca ggatattagc acctacttag cctggtacca acagagagct 120  
ggccaggctc ccaggctcct catctatggt gcttccaaca gggccactgg catcccagcc 180  
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240  
gaagattttg cattttatta ctgtcaacag cgcagcaact ggccgctcac tttcggcgga 300  
gggaccgagg tggagatcaa a 321

<210> 138  
<211> 107  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 138

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 Asp Ile Ser Thr Tyr  
20 25 30

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

Tyr Gly 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

10329W001\_SEQ\_LIST\_ST25.txt

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

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

<210> 139  
<211> 18  
<212> DNA  
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<220>  
<223> synthetic

<400> 139  
caggatatta gcacctac 18

<210> 140  
<211> 6  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 140

Gln Asp Ile Ser Thr Tyr  
1 5

<210> 141  
<211> 9  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 141  
ggtgcttcc 9

<210> 142  
<211> 3  
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<213> Artificial Sequence

<220>

<223> synthetic

<400> 142

Gly Ala Ser

1

<210> 143

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 143

caacagcgca gcaactggcc gctcact

27

<210> 144

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 144

Gln Gln Arg Ser Asn Trp Pro Leu Thr

1

5

<210> 145

<211> 366

<212> DNA

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<223> synthetic

<400> 145

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acctgcgttg tccatggtgg gtccttcagt ggttactact ggaactggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gaggaaacac caactacaac 180

ccgtccctca agagtcgagt caccgtatca gaagacacgt ccaagaacca gttctccctg 240

aagctgagct ctttgaccgc cgcggacacg gctgtgtatt actgtgtgag aggagaggat 300



tacgattttt ggagtgatta ttataatgac tactggggcc agggaaccct ggtcaccgtc 360  
tcctca 366

<210> 146  
<211> 122  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 146

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 Val Val His Gly Gly Ser Phe Ser Gly Tyr  
20 25 30

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

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

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

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

Arg Gly Glu Asp Tyr Asp Phe Trp Ser Asp Tyr Tyr Asn Asp Tyr Trp  
100 105 110

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

<210> 147  
<211> 24  
<212> DNA  
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<220>

<223> synthetic

<400> 147

ggtgggtcct tcagtggta ctac

24

<210> 148

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 148

Gly Gly Ser Phe Ser Gly Tyr Tyr

1 5

<210> 149

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 149

atcaatcata gaggaacac c

21

<210> 150

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 150

Ile Asn His Arg Gly Asn Thr

1 5

<210> 151

<211> 48

<212> DNA

<213> Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 151

gtgagaggag aggattacga tttttggagt gattattata atgactac

48

&lt;210&gt; 152

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 152

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Arg | Gly | Glu | Asp | Tyr | Asp | Phe | Trp | Ser | Asp | Tyr | Tyr | Asn | Asp | Tyr |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

&lt;210&gt; 153

&lt;211&gt; 321

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 153

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gactattagc agctacttag cctggcacca acagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaaa gggccacggg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcaccag cctagagcct 240

gaagattttg cagtttatta ctgtcagcag cgtagcaact ggcctctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

&lt;210&gt; 154

&lt;211&gt; 107

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 154

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 Thr Ile Ser Ser Tyr  
 20 25 30

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu  
 85 90 95

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

&lt;210&gt; 155

&lt;211&gt; 18

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 155

cagactatta gcagctac

18

&lt;210&gt; 156

&lt;211&gt; 6

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 156

Gln Thr Ile Ser Ser Tyr  
1 5

<210> 157  
<211> 9  
<212> DNA  
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<220>  
<223> synthetic

<400> 157  
gatgcatcc

9

<210> 158  
<211> 3  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 158

Asp Ala Ser  
1

<210> 159  
<211> 27  
<212> DNA  
<213> Artificial Sequence

<220>  
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<400> 159  
cagcagcgta gcaactggcc tctcact

27

<210> 160  
<211> 9  
<212> PRT  
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<400> 160

10329W001\_SEQ\_LIST\_ST25.txt

Gln Gln Arg Ser Asn Trp Pro Leu Thr

1 5

<210> 161

<211> 372

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 161

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atctgcgctg tctatggtgg gtccttcagt ggttactact ggagctggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcata gaggaagcac caactacaac 180

ccgtccctca agagtcgagc caccatatca gttgacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc cgcggacacg gctgtgtatt actgttcgag aggcgaggat 300

tactatgata gtagtggtta ctcgtactac ttgactact ggggccaggg aaccctggtc 360

accgtctcct ca 372

<210> 162

<211> 124

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 162

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Pro Pro Ser Glu

1 5 10 15

Thr Leu Ser Leu Ile Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr

20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile

35 40 45

Gly Glu Ile Asn His Arg Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys

50 55 60

10329W001\_SEQ\_LIST\_ST25.txt

Ser Arg Ala 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 Ser  
85 90 95

Arg Gly Glu Asp Tyr Tyr Asp Ser Ser Gly Tyr Ser Tyr Tyr Phe Asp  
100 105 110

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

<210> 163  
<211> 24  
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<220>  
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<400> 163  
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24

<210> 164  
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<220>  
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<400> 164

Gly Gly Ser Phe Ser Gly Tyr Tyr  
1 5

<210> 165  
<211> 21  
<212> DNA  
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<220>  
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<400> 165  
atcaatcata gaggaagcac c

21

<210> 166  
<211> 7  
<212> PRT  
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<220>  
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<400> 166

Ile Asn His Arg Gly Ser Thr  
1 5

<210> 167  
<211> 54  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 167  
tcgagaggcg aggattacta tgatagtagt gggttactcgt actactttga ctac

54

<210> 168  
<211> 18  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 168

Ser Arg Gly Glu Asp Tyr Tyr Asp Ser Ser Gly Tyr Ser Tyr Tyr Phe  
1 5 10 15

Asp Tyr

<210> 169  
<211> 321  
<212> DNA  
<213> Artificial Sequence



&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 169

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ctctcctgca gggccagtca gagtgttagc agctacttag cctggtacca acagaaacct 120

ggccaggctc ccaggctcct catctatgat gcatccaaca gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttactctca ccatcagcag cctagagcct 240

gaagattttg cagtttatta ctgtcagcag cgtagcaact ggccgctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

&lt;210&gt; 170

&lt;211&gt; 107

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 170

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 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 | Arg | Ser | Asn | Trp | Pro | Leu |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

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

<210> 171  
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<400> 171  
 cagagtgtta gcagctac

18

<210> 172  
 <211> 6  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 172

Gln Ser Val Ser Ser Tyr  
 1 5

<210> 173  
 <211> 9  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 173  
 gatgcatcc

9

<210> 174  
 <211> 3  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 174

Asp Ala Ser

1

<210> 175  
 <211> 27  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 175  
 cagcagcgta gcaactggcc gctcact

27

<210> 176  
 <211> 9  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 176

Gln Gln Arg Ser Asn Trp Pro Leu Thr

1

5

<210> 177  
 <211> 366  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 177  
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 ccagggacgg ggctggagtg gattggggaa atcaatcata gagggaacat caacttcaac 180  
 ccgtcccctca agatcgagt caccatatca gaggacacgt ccaaaaacca attctccctg 240  
 aggctgaact ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag aggagaggat 300  
 tacgatattt ggagtgggta ttataggag tactggggcc agggaaccct ggtcaccgtc 360  
 tcctca 366

<210> 178  
 <211> 122  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 178

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Arg 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 Asn Trp Ile Arg Gln Ser Pro Gly Thr Gly Leu Glu Trp Ile  
 35 40 45

Gly Glu Ile Asn His Arg Gly Asn Ile Asn Phe Asn Pro Ser Leu Lys  
 50 55 60

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

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

Arg Gly Glu Asp Tyr Asp Ile Trp Ser Gly Tyr Tyr Arg Glu Tyr Trp  
 100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
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<400> 180  
 Gly Gly Ser Phe Ser Gly Tyr Tyr  
 1 5

<210> 181  
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 Ile Asn His Arg Gly Asn Ile  
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<400> 183  
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Ala Arg Gly Glu Asp Tyr Asp Ile Trp Ser Gly Tyr Tyr Arg Glu Tyr  
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ggccaggctc ccaggctcct catctatgat gcatccaaga gggccactgg catcccagcc 180  
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240  
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gggaccaagg tggagatcaa a 321

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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 Lys 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 Arg Ser Asn Trp Pro Leu  
 85 90 95

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

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Gln Ser Val Ser Ser Tyr  
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Asp Ala Ser  
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Gln Gln Arg Ser Asn Trp Pro Leu Ala  
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 ccagagaagg gcctggagtg gattggggaa atcaatcatc gtggaaacac caactacaac 180  
 ccgtccctca agagtcgagt caccatatca gtagacatgt ccaagaacca gttctccctg 240  
 cagctgaact ctgtgaccgt cgcggacacg gctctgtatt actgtgcgtt tggctacgat 300  
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Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu  
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Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Glu Phe  
 20 25 30

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

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

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

10329W001\_SEQ\_LIST\_ST25.txt

Gln Leu Asn Ser Val Thr Val Ala Asp Thr Ala Leu Tyr Tyr Cys Ala  
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Phe Gly Tyr Asp Phe Arg Ser Ser Tyr Glu Asp Val Trp Gly Gln Gly  
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Thr Thr Val Thr Val Ser Ser  
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<400> 196

Gly Gly Ser Phe Ser Glu Phe Tyr  
1 5

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Ile Asn His Arg Gly Asn Thr  
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Ala Phe Gly Tyr Asp Phe Arg Ser Ser Tyr Glu Asp Val  
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 ggccagcctc ccaggctcct catctatggt tcatccaaca gggccactgg catcccagcc 180

10329W001\_SEQ\_LIST\_ST25.txt

aggttcagtgc gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240  
gaagattttg cagtttatta ctgtcagcag cgtagcaact ggctctcac tttcggcgga 300  
gggaccaagg tggagatcaa a 321

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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 Asp Ile Ser Thr Tyr  
20 25 30

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

Tyr Gly Ser 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 Arg Ser Asn Trp Pro Leu  
85 90 95

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

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Gln Asp Ile Ser Thr Tyr  
1 5

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Gly Ser Ser  
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Gln Gln Arg Ser Asn Trp Pro Leu Thr

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ccagggaagg ggctggagtg ggtctcagtt attagtgggtg gtggtggtag gacatactac 180

acagactccg tgaagggccg gttcaccatc tccagagaca attccaagag catgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggccattt attactgtgc gaaagagagg 300

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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 Arg 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 Val Ile Ser Gly Gly Gly Gly Arg Thr Tyr Tyr Thr Asp Ser Val  
 50 55 60

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

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

Ala Lys Glu Arg Val Thr Gly Ile Asp His Tyr Tyr Tyr Gly Val Asp  
 100 105 110

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

&lt;210&gt; 211

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 211

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24

&lt;210&gt; 212

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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Gly Phe Thr Phe Arg Ser Tyr Ala  
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<400> 213

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<210> 214

<211> 8

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<211> 51

<212> DNA

<213> Artificial Sequence

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<400> 215

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<211> 17

<212> PRT

<213> Artificial Sequence

<220>



<223> synthetic

<400> 216

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Lys | Glu | Arg | Val | Thr | Gly | Ile | Asp | His | Tyr | Tyr | Tyr | Gly | Val | Asp |
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<211> 321

<212> DNA

<213> Artificial Sequence

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<223> synthetic

<400> 217

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| atcacttgcc | gggcaagtca | gagcattagt | agctatttaa | attggtatca | gcagaaacca | 120 |
| gggaaagccc | ctaagctcct | gatctatgct | acatccagtt | tgcaaagtgg | ggtcccatca | 180 |
| cggttcagtg | gcagtgcac  | tggaacagat | ttcactctcg | ccatcagcag | tctgcaacct | 240 |
| gaagattttg | caacttacta | ctgtcaacag | agttacacta | ccccctcac  | tttcggcgga | 300 |
| gggaccaagg | tgagatcaa  | a          |            |            |            | 321 |

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<400> 218

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

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

10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

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

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

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18

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<400> 220

Gln Ser Ile Ser Ser Tyr  
1 5

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<400> 221

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9

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<212> PRT

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Ala Thr Ser

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Gln Gln Ser Tyr Thr Thr Pro Leu Thr

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&lt;400&gt; 225

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ccagggaagg ggctggagtg ggtttcatat atcagtagta gtggtataac caaagactac      180
gcaggctctg tgaagggccg agtcaccatc tccagagaca acgccaagaa cttactgtat      240
ctgcaaatga acagcctgag agccgaggac acggctgttt atcactgtgc gagagatgga      300
gggcattacg atattttgac tggttccatg tcctactact actacgcttt ggacgtctgg      360
ggccaaggga ccacgggtcac cgtctcctca      390

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&lt;210&gt; 226

&lt;211&gt; 130

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 226

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Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
          20           25           30

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```

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

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```

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

```

```

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

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

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10329W001\_SEQ\_LIST\_ST25.txt

Ala Arg Asp Gly Gly His Tyr Asp Ile Leu Thr Gly Ser Met Ser Tyr  
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Tyr Tyr Tyr Ala Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val  
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Ser Ser  
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<400> 228

Gly Phe Thr Phe Ser Ser Tyr Glu  
1 5

<210> 229  
<211> 24  
<212> DNA  
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24

<210> 230  
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<212> PRT  
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<400> 230

Ile Ser Ser Ser Gly Asn Thr Lys  
 1 5

<210> 231  
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<400> 232

Ala Arg Asp Gly Gly His Tyr Asp Ile Leu Thr Gly Ser Met Ser Tyr  
 1 5 10 15

Tyr Tyr Tyr Ala Leu Asp Val  
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10329W001\_SEQ\_LIST\_ST25.txt

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gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccgta 180  
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240  
gaagattttg caacttacta ctgtcaacag agttacagta cccctccgat caccttcggc 300  
caagggacac gactggagat taaa 324

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<400> 234  
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Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr  
20 25 30  
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile  
35 40 45  
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly  
50 55 60  
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro  
65 70 75 80  
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Pro  
85 90 95  
Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
100 105

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Gln Ser Ile Ser Ser Tyr  
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<220>  
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9

<210> 238  
 <211> 3  
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<220>  
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<400> 238

Ala Ala Ser  
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<210> 239  
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Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr  
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 ccagggaggg ggctggagtg ggtctcaggt attagtggta gtggtagtag ctcatactac 180  
 gcagactccg tgaagggccg gttcaccatc tccagagaca attacaagaa gacgctgtct 240  
 ctgcaaatga acagtctgag agccgaggac acggccgttt attactgtgc gctggatata 300  
 atggcaacgg taggaggtct ctttaacaac tggggccagg gaaccctggt caccgtctcc 360  
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&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 242

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

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

Ser Gly Ile Ser Gly Ser Gly Ser Thr Ser Tyr Tyr Ala Asp Ser Val  
 50 55 60

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

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

Ala Leu Asp Ile Met Ala Thr Val Gly Gly Leu Phe Asn Asn Trp Gly  
 100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser  
 115 120

&lt;210&gt; 243

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 243

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24

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<400> 244

Gly Phe Thr Phe Lys Thr Tyr Ala  
 1 5

<210> 245  
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<400> 245  
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24

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<400> 246

Ile Ser Gly Ser Gly Ser Thr Ser  
 1 5

<210> 247  
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<400> 247  
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42

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<400> 248

Ala Leu Asp Ile Met Ala Thr Val Gly Gly Leu Phe Asn Asn  
 1 5 10

<210> 249  
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 <212> DNA  
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<220>  
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<400> 249

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 cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180  
 gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240  
 cctgaagatt ttgcagtgtg ttactgtcag cagtatggta gctcaccttg gacgttcggc 300  
 caagggacca aggtggaaat caaa 324

<210> 250  
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<220>  
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<400> 250

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

10329W001\_SEQ\_LIST\_ST25.txt

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> 251  
<211> 21  
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<400> 251  
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21

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<211> 7  
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<220>  
<223> synthetic

<400> 252

Gln Ser Val Ser Ser Ser Tyr  
1 5

<210> 253  
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<220>

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<400> 253

ggtgcatcc

9

<210> 254

<211> 3

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<400> 254

Gly Ala Ser

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<210> 255

<211> 27

<212> DNA

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<400> 255

cagcagtatg gtagctcacc ttggacg

27

<210> 256

<211> 9

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<400> 256

Gln Gln Tyr Gly Ser Ser Pro Trp Thr

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5

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<211> 360

<212> DNA

<213> Artificial Sequence

10329W001\_SEQ\_LIST\_ST25.txt

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<223> synthetic

<400> 257

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| tcctgcaagg | cttctggagg | caccttcagc | agacatacta | tcagctgggt | gcgacaggcc  | 120 |
| cctggacaag | ggcttgagtg | gatgggaggg | atcatcccta | tctttggtac | agcaaactac  | 180 |
| gcacacaagt | tccagggcag | agtcacgatt | accacggacg | aatccacgag | cacagcctac  | 240 |
| atggagctga | gcagcctgag | atctgaggac | acggccgtat | attattgtgc | gagagcccct  | 300 |
| tatacccgac | aggggtactt | cgatctctgg | ggccgtggca | ccctggtcac | cgctctcctca | 360 |

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<211> 120

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 258

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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 | Arg | His |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | 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 | His | Lys | Phe |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Gly | Arg | Val | Thr | Ile | Thr | Thr | 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 Ala Pro Tyr Thr Arg Gln Gly Tyr Phe Asp Leu Trp Gly Arg  
 100 105 110

Gly Thr Leu Val Thr Val Ser Ser  
 115 120

<210> 259  
 <211> 24  
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 <223> synthetic

<400> 259  
 ggaggcacct tcagcagaca tact

24

<210> 260  
 <211> 8  
 <212> PRT  
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 <223> synthetic

<400> 260

Gly Gly Thr Phe Ser Arg His Thr  
 1 5

<210> 261  
 <211> 24  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 261  
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24

<210> 262  
 <211> 8  
 <212> PRT  
 <213> Artificial Sequence

<220>



<223> synthetic

<400> 262

Ile Ile Pro Ile Phe Gly Thr Ala  
1 5

<210> 263

<211> 39

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 263

gcgagagccc cttatacccg acaggggtac ttcgatctc 39

<210> 264

<211> 13

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 264

Ala Arg Ala Pro Tyr Thr Arg Gln Gly Tyr Phe Asp Leu  
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<210> 265

<211> 339

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 265

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atcaactgca agtccagcca gagtgtttta tacagctcca acaataagaa ctacttagct 120

tggtaccagc agaaaccagg acagcctcct aagctactca ttactgggc atctaccgg 180

gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240

atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaaga ttatagtact 300

ccgtggacgt tcggccaagg gaccaaggtg gaaatcaaa

339

<210> 266  
 <211> 113  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 266

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

Asp Tyr Ser Thr Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile  
 100 105 110

Lys

<210> 267  
 <211> 36  
 <212> DNA  
 <213> Artificial Sequence

<220>

<223> synthetic

<400> 267

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36

<210> 268

<211> 12

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 268

Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Tyr  
1 5 10

<210> 269

<211> 9

<212> DNA

<213> Artificial Sequence

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<223> synthetic

<400> 269

tgggcatct

9

<210> 270

<211> 3

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<213> Artificial Sequence

<220>

<223> synthetic

<400> 270

Trp Ala Ser  
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<210> 271

<211> 27

<212> DNA

<213> Artificial Sequence

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<223> synthetic

<400> 271

cagcaagatt atagtactcc gtggacg

27

<210> 272

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<212> PRT

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<400> 272

Gln Gln Asp Tyr Ser Thr Pro Trp Thr

1

5

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<211> 354

<212> DNA

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<223> synthetic

<400> 273

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cctggacaag ggcttgactg gatgggaatt atcaaccctg gtggtggtaa cacaaactac 180

gcacagaagt tcctgggcag agtcaccatg accagggaca cgtccacgac cacagtctac 240

atggagctga gcagcctgag atctgaggac acggccatat attactgtgc gagagaaaac 300

tggaactctt actttgacaa ctggggccag ggaaccctgg tcaccgtctc ctca 354

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<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 274

10329W001\_SEQ\_LIST\_ST25.txt

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 Asn Tyr  
20 25 30

Tyr Ile His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Asp Trp Met  
35 40 45

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

Leu Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Thr Thr Val Tyr  
65 70 75 80

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

Ala Arg Glu Asn Trp Asn Ser Tyr Phe Asp Asn Trp Gly Gln Gly Thr  
100 105 110

Leu Val Thr Val Ser Ser  
115

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<400> 275  
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<210> 276  
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&lt;400&gt; 276

Gly Tyr Thr Phe Thr Asn Tyr Tyr  
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&lt;210&gt; 277

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 277

atcaaccctg gtggtggtaa caca

24

&lt;210&gt; 278

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 278

Ile Asn Pro Gly Gly Gly Asn Thr  
 1 5

&lt;210&gt; 279

&lt;211&gt; 33

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 279

gcgagagaaa actggaactc ttactttgac aac

33

&lt;210&gt; 280

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 280

Ala Arg Glu Asn Trp Asn Ser Tyr Phe Asp Asn  
 1 5 10

&lt;210&gt; 281

&lt;211&gt; 339

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 281

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 atcaactgca agtccagcca gagtgtttta tacagctcca acaataagaa cttcttagct 120  
 tggtagcagc agaaaccagg acagcctcct aagctgctca tttactgggc atctaccg 180  
 gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240  
 atcagcagcc tgcaggctga agatgtggca ctttattact gtcagcaata ttatggtgct 300  
 ccgtggacgt tcggccaagg gaccaaggtg gaaatcaaa 339

&lt;210&gt; 282

&lt;211&gt; 113

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 282

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 Phe 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 Leu Tyr Tyr Cys Gln Gln  
85 90 95

Tyr Tyr Gly Ala Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile  
100 105 110

Lys

<210> 283  
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<212> DNA  
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<400> 283  
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36

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<400> 284

Gln Ser Val Leu Tyr Ser Ser Asn Asn Lys Asn Phe  
1 5 10

<210> 285  
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<400> 285  
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9

<210> 286  
<211> 3  
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<220>  
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<400> 286

Trp Ala Ser  
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<210> 287  
<211> 27  
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<400> 287  
cagcaatatt atggtgctcc gtggacg

27

<210> 288  
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<220>  
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<400> 288

Gln Gln Tyr Tyr Gly Ala Pro Trp Thr  
1 5

<210> 289  
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<212> DNA  
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10329W001\_SEQ\_LIST\_ST25.txt

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cctggacaag ggcttgagtg gatgggaggg atcatcccta tcttttggtat agcaaaactac 180  
gcacagaagt tccagggcag agtcacgatt accacggacg aatccacgaa cacagcctac 240  
atggagctga gcagcctgag atctgaggac acggccattt attactgtgc gagagcgaga 300  
tatggttcgg ggagttatga ctactggggc cagggaaccc tggtcaccgt ctcctca 357

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<400> 290  
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr  
20 25 30  
Thr Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met  
35 40 45  
Gly Gly Ile Ile Pro Ile Phe Gly Ile Ala Asn Tyr Ala Gln Lys Phe  
50 55 60  
Gln Gly Arg Val Thr Ile Thr Thr Asp Glu Ser Thr Asn Thr Ala Tyr  
65 70 75 80  
Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Ile Tyr Tyr Cys  
85 90 95  
Ala Arg Ala Arg Tyr Gly Ser Gly Ser Tyr Asp Tyr Trp Gly Gln Gly  
100 105 110

Thr Leu Val Thr Val Ser Ser  
115

<210> 291  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 291  
ggaggcacct tcagcagcta tact

24

<210> 292  
<211> 8  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 292

Gly Gly Thr Phe Ser Ser Tyr Thr  
1 5

<210> 293  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 293  
atcatcccta tctttggtat agca

24

<210> 294  
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<213> Artificial Sequence

<220>  
<223> synthetic

<400> 294

Ile Ile Pro Ile Phe Gly Ile Ala  
1 5

<210> 295  
<211> 36  
<212> DNA  
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<400> 295  
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<210> 296  
<211> 12  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 296

Ala Arg Ala Arg Tyr Gly Ser Gly Ser Tyr Asp Tyr  
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<210> 297  
<211> 339  
<212> DNA  
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<223> synthetic

<400> 297  
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tggtaccagc agaaaccagg acagcctcct aagctgctca tttactgggc atctaccgg 180  
gaatccggggg tccctgaccg attcagtggc agcgggtctg ggacagattt cactctcacc 240  
atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttataatact 300  
ccatggacgt tcggccaagg gaccaaggtg gaaatcaaa 339

10329W001\_SEQ\_LIST\_ST25.txt

<210> 298  
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<220>  
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<400> 298

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

Lys

<210> 299  
 <211> 36  
 <212> DNA  
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<220>  
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<400> 299

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<400> 300

Gln Ser Val Leu Tyr Thr Ser Asn Asn Lys Asn Tyr  
 1 5 10

<210> 301  
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<220>  
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<400> 301  
 tgggcatct

9

<210> 302  
 <211> 3  
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<220>  
 <223> synthetic

<400> 302

Trp Ala Ser  
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<210> 303  
 <211> 27  
 <212> DNA  
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<220>  
 <223> synthetic

<400> 303  
 cagcaatatt ataatactcc atggacg

27

<210> 304  
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 <212> PRT  
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<220>  
 <223> synthetic

<400> 304

Gln Gln Tyr Tyr Asn Thr Pro Trp Thr  
 1 5

<210> 305  
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<220>  
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<400> 305  
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 cagccccag gaaaggccct ggagtggctt ggaatcattt attggaatga tgataagcgc 180  
 tacagcccat ctctgaggag cagactcacc atcaccaagg acacctcaa aaaccaggtg 240  
 gtccttacia tgaccaacat ggaccctgtg gacacagcca catattactg tgcacacaga 300  
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<210> 306  
 <211> 120  
 <212> PRT  
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<220>  
 <223> synthetic

<400> 306

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

10329W001\_SEQ\_LIST\_ST25.txt

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Asn  
20 25 30

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

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

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

Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Ala His Arg Gly Leu Phe Gly Gly Trp Phe Asp Pro Trp Gly Gln  
100 105 110

Gly Thr Leu Val Thr Val Ser Ser  
115 120

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<400> 307  
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30

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<400> 308

Gly Phe Ser Leu Ser Thr Asn Gly Val Gly  
1 5 10



<210> 309  
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<400> 309  
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21

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<400> 310

Ile Tyr Trp Asn Asp Asp Lys  
 1 5

<210> 311  
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<400> 311  
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36

<210> 312  
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<220>  
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<400> 312

Ala His Arg Gly Leu Phe Gly Gly Trp Phe Asp Pro  
 1 5 10

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<400> 313  
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 gggaaagccc ctaacctcct gatctttgct gcatccagtt tgcaaagtgg ggtcccatca 180  
 aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 240  
 gaagattttg caacttactt ctgtcaacag agttacaata ccccgctcac tttcggcgga 300  
 gggaccaagg tggagatcaa a 321

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<220>  
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<400> 314

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

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

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

Phe 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 Phe Cys Gln Gln Ser Tyr Asn Thr Pro Leu  
85 90 95

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

<210> 315  
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<212> DNA  
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<220>  
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<400> 315  
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18

<210> 316  
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<400> 316

Gln Ser Ile Ser Arg Tyr  
1 5

<210> 317  
<211> 9  
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<220>  
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<400> 317  
gctgcatcc

9

<210> 318  
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&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 318

Ala Ala Ser

1

&lt;210&gt; 319

&lt;211&gt; 27

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 319

caacagagtt acaatacccc gtcact

27

&lt;210&gt; 320

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 320

Gln Gln Ser Tyr Asn Thr Pro Leu Thr

1

5

&lt;210&gt; 321

&lt;211&gt; 366

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 321

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tcctgtgcaa tctctggatt cacctttagg agttatgccca tgacctgggt ccgccaggct 120

ccagggaagg cgctggagtg ggtctcagtt attagtggtta gcggtggtaa cacatactac 180

gcagactccg tgaagggccg gttcaccgtc tccagagaca attccaggaa cacgctgtat 240

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ctgcaaatga acagcctgag agccgaggac acggccgtat atttctgttc gaaagttgca 300  
gcagctaata attactatta cgctttggac gtctggggcc aaggggaccac ggtcaccgtc 360  
tcctca 366

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<400> 322

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 Ile Ser Gly Phe Thr Phe Arg Ser Tyr  
20 25 30

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

Ser Val Ile Ser Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val  
50 55 60

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

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

Ser Lys Val Ala Ala Ala Asn Asn Tyr Tyr Tyr Ala Leu Asp Val Trp  
100 105 110

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

<210> 323  
<211> 24

<212> DNA  
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<220>  
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<400> 323  
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24

<210> 324  
 <211> 8  
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<220>  
 <223> synthetic

<400> 324

Gly Phe Thr Phe Arg Ser Tyr Ala  
 1 5

<210> 325  
 <211> 24  
 <212> DNA  
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<220>  
 <223> synthetic

<400> 325  
 attagtggta gcggtggtaa caca

24

<210> 326  
 <211> 8  
 <212> PRT  
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<220>  
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<400> 326

Ile Ser Gly Ser Gly Gly Asn Thr  
 1 5

<210> 327  
 <211> 45

<212> DNA  
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 <400> 327  
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<210> 328  
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<220>  
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<400> 328  
 Ser Lys Val Ala Ala Ala Asn Asn Tyr Tyr Tyr Ala Leu Asp Val  
 1 5 10 15

<210> 329  
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 <213> Artificial Sequence

<220>  
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 tacctgcaga agccagggca gtctccacaa ctctgatct atttggtttc taatcgggcc 180  
 tccgggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240  
 agcagagtgg aggctgagga tgttgggggtt tattattgca tgcaagctct acaaactccg 300  
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<210> 330  
 <211> 112  
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<220>

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&lt;400&gt; 330

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

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

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

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

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

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

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

&lt;210&gt; 331

&lt;211&gt; 33

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 331

cagagcctcc tgcataagtaa tggatacaag tat

33

&lt;210&gt; 332

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic



&lt;400&gt; 332

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

&lt;210&gt; 333

&lt;211&gt; 9

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 333

ttggtttct

9

&lt;210&gt; 334

&lt;211&gt; 3

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 334

Leu Val Ser  
 1

&lt;210&gt; 335

&lt;211&gt; 27

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 335

atgcaagctc tacaaactcc gtacact

27

&lt;210&gt; 336

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 336

Met Gln Ala Leu Gln Thr Pro Tyr Thr  
 1 5

&lt;210&gt; 337

&lt;211&gt; 381

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 337

caggtgcagc tgggtggagtc tggggggaggc gtggtccagc ctgggaggtc cctgagactc 60  
 tcctgtgtag cgtctggatt caccttcagt aactatggca tgcactgggt ccgccaggct 120  
 ccaggcaagg ggctggagtg ggtggcagtt atatggaatg atggaagtaa taaatactat 180  
 gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240  
 ctccaagtga gcagcctgag agccgatgac acggctgtat attactgtgc gagggacgga 300  
 gaggtcgaat atagcagctc gaattacaac tactacggtc tggatgtctg gggccaaggg 360  
 accacggtca ccgtctcctc a 381

&lt;210&gt; 338

&lt;211&gt; 127

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 338

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 Val Ala Ser Gly Phe Thr Phe Ser Asn Tyr  
 20 25 30

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

10329W001\_SEQ\_LIST\_ST25.txt

Ala Val Ile Trp Asn 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 Val Ser Ser Leu Arg Ala Asp Asp Thr Ala Val Tyr Tyr Cys  
85 90 95

Ala Arg Asp Gly Glu Val Glu Tyr Ser Ser Ser Asn Tyr Asn Tyr Tyr  
100 105 110

Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
115 120 125

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<220>  
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<400> 339  
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24

<210> 340  
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<220>  
<223> synthetic

<400> 340

Gly Phe Thr Phe Ser Asn Tyr Gly  
1 5

<210> 341  
<211> 24  
<212> DNA  
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<220>

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<400> 341  
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24

<210> 342  
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<220>  
<223> synthetic

<400> 342

Ile Trp Asn Asp Gly Ser Asn Lys  
1 5

<210> 343  
<211> 60  
<212> DNA  
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<400> 343  
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<210> 344  
<211> 20  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 344

Ala Arg Asp Gly Glu Val Glu Tyr Ser Ser Ser Asn Tyr Asn Tyr Tyr  
1 5 10 15

Gly Leu Asp Val  
20

<210> 345  
<211> 321

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 345

gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 120

gggaaagccc ctaaactcct gatctacgat gcatccaatt tggaaacagg ggtcccatca 180

aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 240

gaagatattg taacatatta ctgtcaacag tatgatgatc tcccgatcac cttcggccaa 300

gggacacgac tggagattaa a 321

&lt;210&gt; 346

&lt;211&gt; 107

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 346

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

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

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

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Asp | Ala | Ser | Asn | Leu | Glu | Thr | Gly | Val | Pro | Ser | Arg | Phe | Ser | Gly |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

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

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Asp | Ile | Val | Thr | Tyr | Tyr | Cys | Gln | Gln | Tyr | Asp | Asp | Leu | Pro | Ile |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys  
100 105

<210> 347  
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<213> Artificial Sequence

<220>  
<223> synthetic

<400> 347  
caggacatta gcaactat 18

<210> 348  
<211> 6  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 348

Gln Asp Ile Ser Asn Tyr  
1 5

<210> 349  
<211> 9  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 349  
gatgcatcc 9

<210> 350  
<211> 3  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

&lt;400&gt; 350

Asp Ala Ser  
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&lt;210&gt; 351

&lt;211&gt; 27

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 351

caacagtatg atgatctccc gatcacc

27

&lt;210&gt; 352

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 352

Gln Gln Tyr Asp Asp Leu Pro Ile Thr  
1 5

&lt;210&gt; 353

&lt;211&gt; 375

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 353

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60

tcctgtgcag cctctggatt ctcttttcat aattttgcc a tgaactgggt ccgccaggct 120

ccaggggaagg ggctggagtg ggtctcagtt attactggta gtggtactag cacacactac 180

gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa aacgctatat 240

ctgcaaatga atagcctgag agccgaggac acggccgtat attactgtgc gaaagatcgg 300

ggctatgatt atagtgttc ttactacaac tggttcgacc cctggggcca gggaaccctg 360

gtcaccgtct cctca

375

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 <211> 125  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 354

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 His Asn Phe  
 20 25 30

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

Ser Val Ile Thr Gly Ser Gly Thr Ser Thr His Tyr Ala Asp Ser Val  
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Lys 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 Tyr Asp Tyr Ser Gly Ser Tyr Tyr Asn Trp Phe  
 100 105 110

Asp Pro Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser  
 115 120 125

<210> 355  
 <211> 24  
 <212> DNA  
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<220>



<223> synthetic

<400> 355  
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24

<210> 356  
<211> 8  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 356  
  
Gly Phe Ser Phe His Asn Phe Ala  
1 5

<210> 357  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 357  
attactggta gtggtactag caca

24

<210> 358  
<211> 8  
<212> PRT  
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<220>  
<223> synthetic

<400> 358  
  
Ile Thr Gly Ser Gly Thr Ser Thr  
1 5

<210> 359  
<211> 54  
<212> DNA  
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<220>

<223> synthetic

<400> 359

gcgaaagatc ggggctatga ttatagtggt tcttactaca actgggtcga cccc

54

<210> 360

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<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 360

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Lys | Asp | Arg | Gly | Tyr | Asp | Tyr | Ser | Gly | Ser | Tyr | Tyr | Asn | Trp | Phe |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

Asp Pro

<210> 361

<211> 327

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 361

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gggaaagccc ctaaactcct gatctttgct gcatcaaatt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagtag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta ccccatcctt attcactttc 300

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<211> 109

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 362

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

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

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

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

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

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

Leu Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys  
100 105

<210> 363

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 363

cagagtatta gcagctat

18

<210> 364

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 364

Gln Ser Ile Ser Ser Tyr  
1 5

<210> 365

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 365

gctgcatca

9

<210> 366

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 366

Ala Ala Ser  
1

<210> 367

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 367

caacagagtt acagtacccc atccttattc act

33

<210> 368

<211> 11

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

&lt;400&gt; 368

Gln Gln Ser Tyr Ser Thr Pro Ser Leu Phe Thr  
 1 5 10

&lt;210&gt; 369

&lt;211&gt; 384

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 369

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggagggtc cctgagactc 60  
 tcctgtgcag tctctggatt caccttcagt agttacgaga tgaactgggt ccgccaggct 120  
 ccagggaagg ggctggaatg ggtttcacac attagtagta gtggaagtac catatactac 180  
 gcagactctg tgaagggccg attcaccatg tccagagaca acgccaagaa ctactgtat 240  
 ctgcaaatga acagcctgag agccgaggac acggctgttt attactgtgc gagagatggg 300  
 aatatctgga gtggttatta tgccgcctac tacttctacg gtatggacgt ctggggccaa 360  
 gggaccacgg tcaccgtctc ctca 384

&lt;210&gt; 370

&lt;211&gt; 128

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 370

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 Val Ser Gly Phe Thr Phe Ser Ser Tyr  
 20 25 30

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

10329W001\_SEQ\_LIST\_ST25.txt

Ser His Ile Ser Ser Ser Gly Ser Thr Ile Tyr Tyr Ala Asp Ser Val  
50 55 60

Lys Gly Arg Phe Thr Met 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 Asp Gly Asn Ile Trp Ser Gly Tyr Tyr Ala Ala Tyr Tyr Phe  
100 105 110

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

<210> 371  
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<400> 371  
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24

<210> 372  
<211> 8  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 372

Gly Phe Thr Phe Ser Ser Tyr Glu  
1 5

<210> 373  
<211> 24  
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<220>

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<400> 373

attagtagta gtggaagtac cata

24

<210> 374

<211> 8

<212> PRT

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<223> synthetic

<400> 374

Ile Ser Ser Ser Gly Ser Thr Ile

1 5

<210> 375

<211> 63

<212> DNA

<213> Artificial Sequence

<220>

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<400> 375

gcgagagatg ggaatatctg gagtgggttat tatgccgcct actacttcta cggtatggac

60

gtc

63

<210> 376

<211> 21

<212> PRT

<213> Artificial Sequence

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<223> synthetic

<400> 376

Ala Arg Asp Gly Asn Ile Trp Ser Gly Tyr Tyr Ala Ala Tyr Tyr Phe

1 5

10

15

Tyr Gly Met Asp Val

20

10329W001\_SEQ\_LIST\_ST25.txt

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<220>  
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<400> 377  
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 cttcagcaga ggccaggcca gcctccaaga ctctaattt ataagatttc taaccggttc 180  
 tctgggggtcc cagacagaat cagtggcagt ggggcaggga cagatttcac actgaaaatc 240  
 agcaggggtgg aagctgagga tgtcgggggtt tattactgca tgcaagctgt acaatttcct 300  
 cggacgttcg gccaaaggac caaggtggaa atcaaa 336

<210> 378  
 <211> 112  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 378

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

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

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

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

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



10329W001\_SEQ\_LIST\_ST25.txt

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

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

<210> 379  
<211> 33  
<212> DNA  
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<400> 379  
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33

<210> 380  
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<220>  
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<400> 380

Gln Ser Leu Val His Ser Asp Gly Lys Thr Tyr  
1 5 10

<210> 381  
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<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 381  
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9

<210> 382  
<211> 3  
<212> PRT  
<213> Artificial Sequence

<220>

<223> synthetic

<400> 382

Lys Ile Ser  
1

<210> 383

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 383

atgcaagctg tacaatttcc tcggacg

27

<210> 384

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 384

Met Gln Ala Val Gln Phe Pro Arg Thr  
1 5

<210> 385

<211> 366

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 385

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acctgcgctg tctatggtgg ggccttcagt gattactact ggaattggat ccgccagccc 120

ccagggaagg ggctggagtg gattggggaa atcaatcatc gcggaagcac caactacaac 180

ccgtccctca agagtcgtgt caccatttca gttgacacgt ccaagaacca gttctccctg 240

aggatgagct ctgtgaccgc cgcggacgcg gctgtgtatt actgtgcgag aggagaggat 300

tacgatattt ggaatgggta ttatcaggaa aaatggggcc agggaaccct ggtcaccgtc 360  
tcctca 366

<210> 386  
<211> 122  
<212> PRT  
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<220>  
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<400> 386

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

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

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

Gly Glu Ile Asn His Arg 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

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

Arg Gly Glu Asp Tyr Asp Ile Trp Asn Gly Tyr Tyr Gln Glu Lys Trp  
100 105 110

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

<210> 387  
<211> 24  
<212> DNA  
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&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 387

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24

&lt;210&gt; 388

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 388

Gly Gly Ala Phe Ser Asp Tyr Tyr

1 5

&lt;210&gt; 389

&lt;211&gt; 21

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 389

atcaatcatc gcggaagcac c

21

&lt;210&gt; 390

&lt;211&gt; 7

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 390

Ile Asn His Arg Gly Ser Thr

1 5

&lt;210&gt; 391

&lt;211&gt; 48

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 391

gcgagaggag aggattacga tatttggaat gggttattatc aggaaaaa

48

&lt;210&gt; 392

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 392

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Arg | Gly | Glu | Asp | Tyr | Asp | Ile | Trp | Asn | Gly | Tyr | Tyr | Gln | Glu | Lys |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

&lt;210&gt; 393

&lt;211&gt; 321

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 393

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtattagc acctacttag cctggtacca acagaagcct 120

ggccaggctc ccaggctcct catctatgat gcatccaaga gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg tagtttatta ctgtcaccag cgtagcaact ggcctctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

&lt;210&gt; 394

&lt;211&gt; 107

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 394

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 Ile Ser Thr 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 Lys 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 Val Val Tyr Tyr Cys His Gln Arg Ser Asn Trp Pro Leu  
 85 90 95

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

&lt;210&gt; 395

&lt;211&gt; 18

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 395

cagagtatta gcacctac

18

&lt;210&gt; 396

&lt;211&gt; 6

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 396

Gln Ser Ile Ser Thr Tyr  
1 5

<210> 397  
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<212> DNA  
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<400> 397  
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9

<210> 398  
<211> 3  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 398

Asp Ala Ser  
1

<210> 399  
<211> 27  
<212> DNA  
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<220>  
<223> synthetic

<400> 399  
caccagcgta gcaactggcc tctcact

27

<210> 400  
<211> 9  
<212> PRT  
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<400> 400

10329W001\_SEQ\_LIST\_ST25.txt

His Gln Arg Ser Asn Trp Pro Leu Thr

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<212> DNA  
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<400> 401  
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ccaggaaagg ggctggagtg gattggatat atcttttaca gtgggagtac cgactacaac 180  
ccctccctca agagtcgagt caccatttca gtagacacgt ccaagaagca gttctccctg 240  
aagctgacct ctgtgaccgc tgcggacacg gccgtctatt actgtgcgcg aacaataagt 300  
acgtggtggt tcgccccctg gggccaggga accctgggtca ccgtctcctc a 351

<210> 402  
<211> 117  
<212> PRT  
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<220>  
<223> synthetic

<400> 402

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

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

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

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



10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

Val Thr Val Ser Ser  
115

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<212> DNA  
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<400> 403  
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24

<210> 404  
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<220>  
<223> synthetic

<400> 404

Gly Gly Ser Phe Ser Ser Tyr Tyr  
1 5

<210> 405  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 405  
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21

<210> 406  
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 <212> PRT  
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<220>  
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<400> 406

Ile Phe Tyr Ser Gly Ser Thr  
 1 5

<210> 407  
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<210> 408  
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<400> 408

Ala Arg Thr Ile Ser Thr Trp Trp Phe Ala Pro  
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 <212> DNA  
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<400> 409  
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60

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aggttcagtg gcagtgggtc tggaacagag ttcactctca ccatcagcag cctgcagtct 240  
gaagattttg cagtttattc ctgtcagcag tataataact ggctcacttt cggcggaggg 300  
accaaggtgg agatcaaa 318

<210> 410  
<211> 106  
<212> PRT  
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<220>  
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<400> 410

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

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

Val 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 Gly 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 Ser Cys Gln Gln Tyr Asn Asn Trp Leu Thr  
85 90 95

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

<210> 411  
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<212> DNA  
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18

<210> 412  
 <211> 6  
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<220>  
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<400> 412

Gln Ser Val Ser Asn Asn  
 1 5

<210> 413  
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 <212> DNA  
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<220>  
 <223> synthetic

<400> 413  
 ggtgcatcc

9

<210> 414  
 <211> 3  
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<220>  
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<400> 414

Gly Ala Ser  
 1

<210> 415  
 <211> 24

<212> DNA  
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<220>  
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<400> 415  
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24

<210> 416  
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<220>  
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<400> 416

Gln Gln Tyr Asn Asn Trp Leu Thr  
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 <212> DNA  
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<400> 417  
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 gcagactccg tgaagggccg attcaccata tccagagaca attccaagaa cacacagtat 240  
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<210> 418  
 <211> 123  
 <212> PRT  
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&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 418

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

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

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

Ala Ser Val Ala Thr Ser Gly Asp Phe Asp Tyr Tyr Gly Met Asp Val  
 100 105 110

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

&lt;210&gt; 419

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 419

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24

&lt;210&gt; 420

&lt;211&gt; 8

<212> PRT  
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<220>  
 <223> synthetic

<400> 420

Gly Phe Thr Phe Ser Ser Tyr Gly  
 1 5

<210> 421  
 <211> 24  
 <212> DNA  
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<220>  
 <223> synthetic

<400> 421  
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24

<210> 422  
 <211> 8  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 422

Ile Trp Tyr Asp Gly Ser Asn Lys  
 1 5

<210> 423  
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 <212> DNA  
 <213> Artificial Sequence

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<400> 423  
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48

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<212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 424

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| Ala | Ser | Val | Ala | Thr | Ser | Gly | Asp | Phe | Asp | Tyr | Tyr | Gly | Met | Asp | Val |
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<220>  
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<400> 425

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| ctctcctgca | gggccagtca | gagaattagc | acctacttag | cctggatatca | acagaaacct | 120 |
| ggccaggctc | ccaggctcct | catctatgat | gcatccaaaa | gggccactgg  | catcccagcc | 180 |
| aggttcagtg | gtagtgggtc | tgggacaggc | ttcactctca | ccatcagcag  | cctagagcct | 240 |
| gaagattttg | cagtttatta | ctgtcagcag | cgtagtaact | ggcctctcac  | tttcggcgga | 300 |
| gggaccaagg | tggagatcaa | a          |            |             |            | 321 |

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 <211> 107  
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<220>  
 <223> synthetic

<400> 426

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

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Arg | Thr | Thr | Leu | Ser | Cys | Arg | Ala | Ser | Gln | Arg | Ile | Ser | Thr | Tyr |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |



10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu  
 85 90 95

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

<210> 427  
 <211> 18  
 <212> DNA  
 <213> Artificial Sequence

<220>  
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<400> 427  
 cagagaatta gcacctac

18

<210> 428  
 <211> 6  
 <212> PRT  
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<220>  
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<400> 428

Gln Arg Ile Ser Thr Tyr  
 1 5

<210> 429  
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<220>

<223> synthetic

<400> 429

gatgcatcc

9

<210> 430

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

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<400> 430

Asp Ala Ser

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<210> 431

<211> 27

<212> DNA

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<220>

<223> synthetic

<400> 431

cagcagcgta gtaactggcc tctcact

27

<210> 432

<211> 9

<212> PRT

<213> Artificial Sequence

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<223> synthetic

<400> 432

Gln Gln Arg Ser Asn Trp Pro Leu Thr

1

5

<210> 433

<211> 357

<212> DNA

<213> Artificial Sequence

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&lt;223&gt; synthetic

&lt;400&gt; 433

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gaggtgcagc tgggtgcagtc tggagcagag gtgagaaagc ccggggagtc tctgaagatc      60
tcctgtaagg gttctggata cagctttact aactactgga tcgtctgggt gcgccagatg      120
cccgggaaag gcctggagtg gatggggatc atctatcctg gtgactctga taccagatac      180
agcccgctcct tccaaggcca ggtcaccatc tcagccgaca agtccatcag caccgcctac      240
ctgcagtgga gcagcctgaa ggcctcggac accgccatgt attactgtgc gagacgggat      300
acgattttcc cttcctatcc cctctggggc cagggaaccc tggtcaccgt ctcctca      357

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&lt;210&gt; 434

&lt;211&gt; 119

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 434

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

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```

Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr
          20           25           30

```

```

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

```

```

Gly Ile Ile Tyr Pro Gly Asp Ser Asp Thr Arg Tyr Ser Pro Ser Phe
50           55           60

```

```

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

```

```

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

```

```

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

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Thr Leu Val Thr Val Ser Ser  
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24

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<400> 436

Gly Tyr Ser Phe Thr Asn Tyr Trp  
1 5

<210> 437  
<211> 24  
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24

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&lt;400&gt; 438

Ile Tyr Pro Gly Asp Ser Asp Thr  
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&lt;210&gt; 439

&lt;211&gt; 36

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 439

gcgagacggg atacgatttt cccttcctat cccctc

36

&lt;210&gt; 440

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 440

Ala Arg Arg Asp Thr Ile Phe Pro Ser Tyr Pro Leu  
 1 5 10

&lt;210&gt; 441

&lt;211&gt; 336

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 441

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atctcctgca ggtctagtca gagcctctg aatagtaatg gatacaactt tttggattgg 120

tacctgcaga agccagggca gtctccacaa ctctgatct atttggtttc taatcgggcc 180

tccgggggtcc ctgacagggt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

agcagagtgg aggctgagga tattgggggtt tattactgca tgcaagctct ccaaactccg 300

atcaccttcg gccaaaggac acgactggag attaaa 336

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<400> 442

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

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu Asn Ser  
 20 25 30

Asn Gly Tyr Asn Phe Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser  
 35 40 45

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

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

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

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

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33

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<400> 444

Gln Ser Leu Leu Asn Ser Asn Gly Tyr Asn Phe  
 1 5 10

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9

<210> 446  
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<400> 446

Leu Val Ser  
 1

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<400> 447  
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27

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<400> 448

Met Gln Ala Leu Gln Thr Pro Ile Thr  
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<400> 449

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| acctgcacct tctctgggtt ctactcagc actaatggag tgggtgtggg ctggatccgt  | 120 |
| cagccccag gaaaggccct ggagtggctt acactcattt attggaatga aaataagcac  | 180 |
| tacagcccat ctctgaaaaa caggatcacc atcaccaagg acacctcaa aaaccagggtg | 240 |
| gtccttacia tgaccaactt ggaccctgtg gacacagcca cttattactg tgtacacagg | 300 |
| ggatggttgg gagcaatctt tgcctactgg ggccaggga ccctgggtcac cgtctcctca | 360 |

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 <212> PRT  
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<220>  
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<400> 450

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

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Asn  
 20 25 30



10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

Val Leu Thr Met Thr Asn Leu Asp Pro Val Asp Thr Ala Thr Tyr Tyr  
85 90 95

Cys Val His Arg Gly Trp Leu Gly Ala Ile Phe Ala Tyr Trp Gly Gln  
100 105 110

Gly Thr Leu Val Thr Val Ser Ser  
115 120

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30

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<400> 452

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<210> 453  
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<400> 453  
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21

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<400> 454

Ile Tyr Trp Asn Glu Asn Lys  
 1 5

<210> 455  
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 <212> DNA  
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36

<210> 456  
 <211> 12  
 <212> PRT  
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<400> 456

Val His Arg Gly Trp Leu Gly Ala Ile Phe Ala Tyr  
 1 5 10

10329W001\_SEQ\_LIST\_ST25.txt

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 tcctgtgcag cctctggatt cacctttact agttatgcca tgacctgggt ccgccaggct 120  
 ccagggaagg ggctggagtg ggtctcagat attagtggta gtggtggtag aacatattac 180  
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa tatgctgtat 240  
 ctgcaaataa acatcctgag agccgaagac acggccgtat atcattgtgc gaagggaaca 300  
 ggccagcagg tggaccttta caactactac tatgctttgg acgtctgggg ccaagggacc 360  
 acggtcaccg tctcctca 378

<210> 458  
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 <212> PRT  
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<220>  
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<400> 458  
 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 Thr Ser Tyr  
 20 25 30  
 Ala Met Thr Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
 35 40 45  
 Ser Asp Ile Ser Gly Ser Gly Gly Arg Thr Tyr Tyr Ala Asp Ser Val  
 50 55 60  
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Met Leu Tyr  
 65 70 75 80

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

Ala Lys Gly Thr Gly Gln Gln Val Asp Leu Tyr Asn Tyr Tyr Tyr Ala  
100 105 110

Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser  
115 120 125

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<220>  
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<400> 459  
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24

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<220>  
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<400> 460

Gly Phe Thr Phe Thr Ser Tyr Ala  
1 5

<210> 461  
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<400> 461  
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24

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<400> 462

Ile Ser Gly Ser Gly Gly Arg Thr  
 1 5

<210> 463  
 <211> 57  
 <212> DNA  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 463  
 gcgaaggga caggccagca ggtggacctt tacaactact actatgcttt ggacgtc 57

<210> 464  
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 <212> PRT  
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<220>  
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<400> 464

Ala Lys Gly Thr Gly Gln Gln Val Asp Leu Tyr Asn Tyr Tyr Tyr Ala  
 1 5 10 15

Leu Asp Val

<210> 465  
 <211> 387  
 <212> DNA  
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10329W001\_SEQ\_LIST\_ST25.txt

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ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa taaacactat 180  
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240  
ctgcaaatac acagcctgag agccgacgac acggctgtct attactgtgc gagagataag 300  
gggtataagt gaattaaggg gggttcttac tactactact atgccatgga cgtctggggc 360  
caagggacca cggtcacctg ctcctca 387

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<211> 129  
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<400> 466  
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg  
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Tyr Tyr  
20 25 30  
Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45  
Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys His 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 Asp Asp Thr Ala Val Tyr Tyr Cys  
85 90 95  
Ala Arg Asp Lys Gly Ile Ser Gly Ile Lys Gly Gly Ser Tyr Tyr Tyr  
100 105 110

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

Ser

<210> 467  
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<212> DNA  
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<400> 467  
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<210> 468  
<211> 8  
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<213> Artificial Sequence

<220>  
<223> synthetic

<400> 468

Gly Phe Thr Phe Ser Tyr Tyr Gly  
1 5

<210> 469  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 469  
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<210> 470  
<211> 8  
<212> PRT  
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&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 470

Ile Trp Tyr Asp Gly Ser Asn Lys

1 5

&lt;210&gt; 471

&lt;211&gt; 66

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 471

gcgagagata aggggtataag tggaattaag ggggggttctt actactacta ctatgccatg 60

gacgtc 66

&lt;210&gt; 472

&lt;211&gt; 22

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 472

Ala Arg Asp Lys Gly Ile Ser Gly Ile Lys Gly Gly Ser Tyr Tyr Tyr

1 5 10 15

Tyr Tyr Ala Met Asp Val

20

&lt;210&gt; 473

&lt;211&gt; 360

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 473

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## 10329W001 SEQ LIST ST25.txt

|            |            |            |            |            |            |     |
|------------|------------|------------|------------|------------|------------|-----|
| tcctgtgcag | cctctggatt | cactttcagt | aacgcctgga | tgacctgggt | ccgccaggct | 120 |
| ccaggaagg  | ggctggagt  | ggttggccgt | attaaaaaca | aaattgatgg | tgggacaaca | 180 |
| gactacgctg | cacccgtgaa | aggcagattc | accatctcaa | gagatgattc | aaaaaacacg | 240 |
| gtttatctgc | aatgaacag  | cctgaaaacc | gaggacacag | ccgtttatta | ctgttcacg  | 300 |
| gtggactaca | attggtactt | cgatttctgg | ggccgtggca | ccctggtcac | tgtctcctca | 360 |

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|-------|---------------------|
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| <211> | 120                 |
| <212> | PRT                 |
| <213> | Artificial Sequence |

<220>  
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<400> 474

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 Asn Ala  
20 25 30

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

Gly Arg Ile Lys Asn Lys Ile Asp Gly Gly Thr Thr Asp Tyr Ala Ala  
50 55 60

Pro Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr  
65 70 75 80

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

Tyr Cys Ser Thr Val Asp Tyr Asn Trp Tyr Phe Asp Phe Trp Gly Arg  
100 105 110

Gly Thr Leu Val Thr Val Ser Ser  
115 120

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<400> 475  
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<400> 476

Gly Phe Thr Phe Ser Asn Ala Trp  
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30

<210> 478  
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<400> 478

Ile Lys Asn Lys Ile Asp Gly Gly Thr Thr  
 1 5 10

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<400> 479  
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<400> 480  
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 ccaggcaagg ggctggagtg ggtggcactt atatggtatg atggaactaa tgaaaactat 180  
 gcagactccg tgaagggccg attcaccatc tccagagaca attccaagtc cacgctgtat 240  
 ctgcaaatac acagtctgag agccgaggac acggctgttt actactgtgc gagagatagg 300  
 ggagtggcga catttacgag ggggaattac tactacaact acggtatgga cgtctggggc 360  
 caagggacca cggtcaccgt ctcctca 387

10329W001\_SEQ\_LIST\_ST25.txt

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 <211> 129  
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<220>  
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<400> 482

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 Phe Phe  
 20 25 30

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

Ala Leu Ile Trp Tyr Asp Gly Thr Asn Glu Asn Tyr Ala Asp Ser Val  
 50 55 60

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

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

Ala Arg Asp Arg Gly Val Ala Thr Phe Thr Arg Gly Asn Tyr Tyr Tyr  
 100 105 110

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

Ser

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 <212> DNA  
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<223> synthetic

<400> 483

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24

<210> 484

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 484

Gly Phe Thr Phe Ser Phe Phe Gly  
1 5

<210> 485

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 485

atatggtatg atggaactaa tgaa

24

<210> 486

<211> 8

<212> PRT

<213> Artificial Sequence

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<223> synthetic

<400> 486

Ile Trp Tyr Asp Gly Thr Asn Glu  
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<210> 487

<211> 66

<212> DNA

<213> Artificial Sequence

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<223> synthetic

<400> 487

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gacgtc 66

<210> 488

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<212> PRT

<213> Artificial Sequence

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<400> 488

Ala Arg Asp Arg Gly Val Ala Thr Phe Thr Arg Gly Asn Tyr Tyr Tyr  
1 5 10 15

Asn Tyr Gly Met Asp Val  
20

<210> 489

<211> 387

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 489

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ccaggcaagg ggctggaggg ggtggcagtt atatggtatg atggaagtaa taaatactat 180

gcagactccg tgaagggccg attcaccata tccagagaca attccaagaa catgctgtat 240

ctacaaatga ccagcctgag agccgaggac acggctgtgt attactgtgc gagagattcg 300

ggtaaaactg gaactgggat aactgggtac tcctactact acggtatgga cgtctggggc 360

caagggacca cggtcaccgt ctcctca 387

<210> 490

<211> 129

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 490

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 Phe Tyr  
 20 25 30

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

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

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

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

Ala Arg Asp Ser Gly Lys Thr Gly Thr Gly Ile Thr Gly Tyr Ser Tyr  
 100 105 110

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

Ser

&lt;210&gt; 491

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

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24

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<400> 492

Gly Phe Thr Phe Ser Phe Tyr Gly  
1 5

<210> 493  
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<220>  
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<400> 493  
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24

<210> 494  
<211> 8  
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<220>  
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<400> 494

Ile Trp Tyr Asp Gly Ser Asn Lys  
1 5

<210> 495  
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10329W001\_SEQ\_LIST\_ST25.txt

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gacgtc 66

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<220>  
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<400> 496  
Ala Arg Asp Ser Gly Lys Thr Gly Thr Gly Ile Thr Gly Tyr Ser Tyr  
1 5 10 15

Tyr Tyr Gly Met Asp Val  
20

<210> 497  
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cagccccag ggaagggtct ggagtggatt ggtagtatct attatagtgg gaggacctac 180  
tacaaccgt ccctcgagag tcgagtcacc atatccgtgg acacgtccaa gaaccagttc 240  
tccctgaagt tgacctctgt gaccgccgca gacacggcta tatattactg tgcgagggaa 300  
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&lt;400&gt; 498

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Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ile Thr Asn  
 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 Arg Thr Tyr Tyr Asn Pro Ser  
 50 55 60

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

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

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

Leu Val Thr Val Ser Ser  
 115

&lt;210&gt; 499

&lt;211&gt; 30

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 499

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30

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&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

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Gly Gly Ser Ile Ile Thr Asn Ser Tyr Tyr  
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21

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<400> 502

Ile Tyr Tyr Ser Gly Arg Thr  
1 5

<210> 503

<211> 30

<212> DNA

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<400> 503

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<211> 10

<212> PRT

<213> Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 504

Ala Arg Glu Gly Asp Pro Ser Leu Asp Pro  
 1 5 10

&lt;210&gt; 505

&lt;211&gt; 363

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 505

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 ccaggggaagg ggctggagtg ggtctcacat attagtggta gtggtggtaa ttcatactcc 180  
 gcagactccg tgaagggccg gttcaccatc tccagagaca attccaagaa cacgctatat 240  
 ctgcaaatac acagcctgag agccgaggac acggccatat attactgttc gctggatata 300  
 atggctacag taggcggtct ctttgcctac tggggccagg gaaccctggt caccgtctcc 360  
 tca 363

&lt;210&gt; 506

&lt;211&gt; 121

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 506

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

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

10329W001\_SEQ\_LIST\_ST25.txt

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

Ser His Ile Ser Gly Ser Gly Gly Asn Ser Tyr Ser 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 Ile Tyr Tyr Cys  
85 90 95

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

Gln Gly Thr Leu Val Thr Val Ser Ser  
115 120

<210> 507  
<211> 24  
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<400> 507  
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24

<210> 508  
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<400> 508

Gly Phe Thr Phe Ser Thr Tyr Ala  
1 5

<210> 509  
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24

<210> 510  
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<400> 510

Ile Ser Gly Ser Gly Gly Asn Ser  
 1 5

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42

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<400> 512

Ser Leu Asp Ile Met Ala Thr Val Gly Gly Leu Phe Ala Tyr  
 1 5 10

<210> 513  
 <211> 393

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 513

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caggtgcagc tggatggagtc tgggggaggc gtgggtccagc ctgggaggtc cctgagactc      60
tcctgtgtag cgtctggatt catcttcagt ttctatggca tgcactgggt ccgccaggct      120
ccagacaagg ggctggagtg ggtggcagtt atatggatat atggaagtaa tgaatactat      180
gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat      240
ctgcaaatac acagcctgag agccgaggac acggctgtgt attactgtgg gagagatcaa      300
ggatatttcgt attacgatat tttagctggg aattataact attactacgg tgtggacgtc      360
tggggccaag ggaccacggt caccgtctcc tca                                     393

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&lt;210&gt; 514

&lt;211&gt; 131

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 514

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

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

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

Ala Val Ile Trp Tyr Asp Gly Ser Asn Glu 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

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10329W001\_SEQ\_LIST\_ST25.txt

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

Gly Arg Asp Gln Gly Ile Ser Tyr Tyr Asp Ile Leu Thr Gly Asn Tyr  
100 105 110

Asn Tyr Tyr Tyr Gly Val Asp Val Trp Gly Gln Gly Thr Thr Val Thr  
115 120 125

Val Ser Ser  
130

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24

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<400> 516

Gly Phe Ile Phe Ser Phe Tyr Gly  
1 5

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24



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<400> 518

Ile Trp Tyr Asp Gly Ser Asn Glu  
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 ggtgtggacg tc 72

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<400> 520

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

Asn Tyr Tyr Tyr Gly Val Asp Val  
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<210> 521  
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&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 521

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atcacttgcc gggcaagtca gagcattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccgta 180

aggttcagtg gcagtggatc tgggacagat ttactctca ccatcagcag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta cccctccgat caccttcggc 300

caagggacac gactggagat taaa 324

&lt;210&gt; 522

&lt;211&gt; 108

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 522

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

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

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

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

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

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Asp | Phe | Ala | Thr | Tyr | Tyr | Cys | Gln | Gln | Ser | Tyr | Ser | Thr | Pro | Pro |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

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 100 105

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18

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Gln Ser Ile Ser Ser Tyr  
 1 5

<210> 525  
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<220>  
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<400> 525  
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9

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Ala Ala Ser

1

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<400> 528

Gln Gln Ser Tyr Ser Thr Pro Pro Ile Thr  
 1 5 10

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<400> 529  
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 cctggccagg ctcccaggct cctcatctat ggtgcatcca gcagggccac tggcatccca 180  
 gacaggttca gtggcagtgg gtctgggaca gacttcactc tcaccatcag cagactggag 240  
 cctgaagatt ttgcagtgtg ttactgtcag cagtatggta gctcaccttg gacgttcggc 300  
 caagggacca aggtggaaat caaa 324

10329W001\_SEQ\_LIST\_ST25.txt

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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

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Gln Ser Val Ser Ser Ser Tyr  
 1 5

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 ggtgcatcc

9

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Gly Ala Ser  
 1

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<400> 536

Gln Gln Tyr Gly Ser Ser Pro Trp Thr  
 1 5

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 ccaggggaagg ggctggagtg ggttggggaa atcagtcata gaggaagcac caactacaac 180  
 ccgtccctca agagtcgagt caccatatca ctggacacgt ccaagaacca gttctccctg 240  
 aagctgacct ctgtgaccgc cgcggacacg gctgtgtatt actgttcgag agacgaggaa 300  
 ctggaattcc gtttctttga ctactggggc cagggaaacc tggtcaccgt ctcctca 357

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<220>  
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<400> 538

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu  
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Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Gly Tyr  
 20 25 30

10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

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

Arg Asp Glu Glu Leu Glu Phe Arg Phe Phe Asp Tyr Trp Gly Gln Gly  
100 105 110

Thr Leu Val Thr Val Ser Ser  
115

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Gly Gly Ser Phe Ser Gly Tyr Tyr  
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<210> 541  
<211> 21



<212> DNA  
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<400> 542

Ile Ser His Arg Gly Ser Thr  
 1 5

<210> 543  
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<220>  
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<400> 543  
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39

<210> 544  
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<400> 544

Ser Arg Asp Glu Glu Leu Glu Phe Arg Phe Phe Asp Tyr  
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&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 545

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ctctcctgca gggccagtca gagtgtttagc agctatttag cctggtacca aaaaaaacct 120

ggccaggctc ccaggctcct cgtctatggt gcatccaaca gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg cattttatta ctgtcagcag cgtagcaact ggccgctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

&lt;210&gt; 546

&lt;211&gt; 107

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 546

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 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 | Val |
|     |     | 35  |     |     |     |     | 40  |     |     |     | 45  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Gly | 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 | Phe | Tyr | Tyr | Cys | Gln | Gln | Arg | Ser | Asn | Trp | Pro | Leu |
|     |     |     | 85  |     |     |     |     |     | 90  |     |     |     |     | 95  |     |

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

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<212> DNA  
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<220>  
<223> synthetic

<400> 547  
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18

<210> 548  
<211> 6  
<212> PRT  
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<220>  
<223> synthetic

<400> 548

Gln Ser Val Ser Ser Tyr  
1 5

<210> 549  
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<212> DNA  
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<220>  
<223> synthetic

<400> 549  
ggtgcatcc

9

<210> 550  
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<220>  
<223> synthetic

&lt;400&gt; 550

Gly Ala Ser  
1

&lt;210&gt; 551

&lt;211&gt; 27

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 551

cagcagcgta gcaactggcc gctcact

27

&lt;210&gt; 552

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 552

Gln Gln Arg Ser Asn Trp Pro Leu Thr  
1 5

&lt;210&gt; 553

&lt;211&gt; 372

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 553

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggggtc cctgagactc 60

tcctgtgtag cctctggatt caccttttagc ctctatgcca tgacctgggt ccgccagggt 120

ccaggggaagg ggctggaatg ggtctcaact attagtggta gtggtggtgg cacatactac 180

acagactccg ttaagggccg gttcaccatc tccagagaca attccaagaa cacactgtat 240

ctgcaaatga acagcctgag agccgacgac acggccgttt tttactgtac gaaagagagt 300

acaactggaa cttactccta cttctacggt atggacgtct ggggccaagg gaccacggtc 360

accgtctcct ca

372

<210> 554  
 <211> 124  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 554

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

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

Ser Thr Ile Ser Gly Ser Gly Gly Gly Thr Tyr 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 Asp Asp Thr Ala Val Phe Tyr Cys  
 85 90 95

Thr Lys Glu Ser Thr Thr Gly Thr Tyr Ser Tyr Phe Tyr Gly Met Asp  
 100 105 110

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

<210> 555  
 <211> 24  
 <212> DNA  
 <213> Artificial Sequence

<220>

<223> synthetic

<400> 555

ggattcacct ttagcctcta tgcc

24

<210> 556

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 556

Gly Phe Thr Phe Ser Leu Tyr Ala

1 5

<210> 557

<211> 24

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 557

attagtggtgta gtggtggtgg caca

24

<210> 558

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 558

Ile Ser Gly Ser Gly Gly Gly Thr

1 5

<210> 559

<211> 51

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 559

acgaaagaga gtacaactgg aacttactcc tacttctacg gtatggacgt c 51

<210> 560

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 560

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Lys | Glu | Ser | Thr | Thr | Gly | Thr | Tyr | Ser | Tyr | Phe | Tyr | Gly | Met | Asp |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     | 15  |     |     |

Val

<210> 561

<211> 321

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 561

gacatccaga tgaccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gaccattagc agctatttaa attggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttactctca ccctcagcgg tctccaacct 240

gaagattttg caacttacta ctgtcaacag agttacagta ccccgctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> 562

<211> 107

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 562

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 Thr Ile Ser Ser Tyr  
20 25 30

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

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

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

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

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

<210> 563

<211> 18

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 563

cagaccatta gcagctat

18

<210> 564

<211> 6

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic



<400> 564

Gln Thr Ile Ser Ser Tyr  
1 5

<210> 565

<211> 9

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 565

gctgcatcc

9

<210> 566

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

<400> 566

Ala Ala Ser  
1

<210> 567

<211> 27

<212> DNA

<213> Artificial Sequence

<220>

<223> synthetic

<400> 567

caacagagtt acagtacccc gtcact

27

<210> 568

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> synthetic

&lt;400&gt; 568

Gln Gln Ser Tyr Ser Thr Pro Leu Thr  
 1 5

&lt;210&gt; 569

&lt;211&gt; 327

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 569

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

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

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

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr  
 65 70 75 80

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

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro  
 100 105 110

Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys  
 115 120 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val  
 130 135 140

10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu  
195 200 205

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

Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys  
225 230 235 240

Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp  
245 250 255

Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys  
260 265 270

Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser  
275 280 285

Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser  
290 295 300

Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser  
305 310 315 320

Leu Ser Leu Ser Leu Gly Lys  
325

<210> 570  
<211> 326  
<212> PRT  
<213> Artificial Sequence

10329W001\_SEQ\_LIST\_ST25.txt

<220>

<223> synthetic

<400> 570

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

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

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

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr  
65 70 75 80

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

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro  
100 105 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp  
115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp  
130 135 140

Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly  
145 150 155 160

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

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp  
180 185 190

10329W001\_SEQ\_LIST\_ST25.txt

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro  
195 200 205

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

Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn  
225 230 235 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile  
245 250 255

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

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg  
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys  
290 295 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu  
305 310 315 320

Ser Leu Ser Leu Gly Lys  
325

<210> 571  
<211> 326  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 571

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

10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr  
65 70 75 80

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

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro  
100 105 110

Pro Val Ala Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp  
115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp  
130 135 140

Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly  
145 150 155 160

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

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp  
180 185 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro  
195 200 205

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

10329W001\_SEQ\_LIST\_ST25.txt

Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn  
225 230 235 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile  
245 250 255

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

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg  
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys  
290 295 300

Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln Lys Ser Leu  
305 310 315 320

Ser Leu Ser Pro Gly Lys  
325

<210> 572  
<211> 326  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 572

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

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

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

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

10329W001\_SEQ\_LIST\_ST25.txt

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr  
65 70 75 80

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

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro  
100 105 110

Gly Gly Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp  
115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp  
130 135 140

Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly  
145 150 155 160

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

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp  
180 185 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro  
195 200 205

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

Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn  
225 230 235 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile  
245 250 255

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



10329W001\_SEQ\_LIST\_ST25.txt

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg  
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys  
290 295 300

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu  
305 310 315 320

Ser Leu Ser Leu Gly Lys  
325

<210> 573  
<211> 326  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 573

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

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

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

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

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr  
65 70 75 80

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

10329W001\_SEQ\_LIST\_ST25.txt

Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro  
100 105 110

Gly Gly Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp  
115 120 125

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp  
130 135 140

Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly  
145 150 155 160

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

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp  
180 185 190

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro  
195 200 205

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

Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn  
225 230 235 240

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile  
245 250 255

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

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg  
275 280 285

Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys  
290 295 300

10329W001\_SEQ\_LIST\_ST25.txt

Ser Val Met His Glu Ala Leu His Asn Arg Phe Thr Gln Lys Ser Leu  
305 310 315 320

Ser Leu Ser Pro Gly Lys  
325

<210> 574  
<211> 450  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> aa 1-478: Human Lag3 (aa 29 through 450 of NP\_002277.4) aa  
451-478: myc-myc-hexahistidine tag

<400> 574

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

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

Val Thr Trp Gln His Gln Pro Asp Ser Gly Pro Pro Ala Ala Ala Pro  
35 40 45

Gly His Pro Leu Ala Pro Gly Pro His Pro Ala Ala Pro Ser Ser Trp  
50 55 60

Gly Pro Arg Pro Arg Arg Tyr Thr Val Leu Ser Val Gly Pro Gly Gly  
65 70 75 80

Leu Arg Ser Gly Arg Leu Pro Leu Gln Pro Arg Val Gln Leu Asp Glu  
85 90 95

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

Arg Ala Asp Ala Gly Glu Tyr Arg Ala Ala Val His Leu Arg Asp Arg  
115 120 125

Ala Leu Ser Cys Arg Leu Arg Leu Arg Leu Gly Gln Ala Ser Met Thr

130

135

140

Ala Ser Pro Pro Gly Ser Leu Arg Ala Ser Asp Trp Val Ile Leu Asn  
 145 150 155 160

Cys Ser Phe Ser Arg Pro Asp Arg Pro Ala Ser Val His Trp Phe Arg  
 165 170 175

Asn Arg Gly Gln Gly Arg Val Pro Val Arg Glu Ser Pro His His His  
 180 185 190

Leu Ala Glu Ser Phe Leu Phe Leu Pro Gln Val Ser Pro Met Asp Ser  
 195 200 205

Gly Pro Trp Gly Cys Ile Leu Thr Tyr Arg Asp Gly Phe Asn Val Ser  
 210 215 220

Ile Met Tyr Asn Leu Thr Val Leu Gly Leu Glu Pro Pro Thr Pro Leu  
 225 230 235 240

Thr Val Tyr Ala Gly Ala Gly Ser Arg Val Gly Leu Pro Cys Arg Leu  
 245 250 255

Pro Ala Gly Val Gly Thr Arg Ser Phe Leu Thr Ala Lys Trp Thr Pro  
 260 265 270

Pro Gly Gly Gly Pro Asp Leu Leu Val Thr Gly Asp Asn Gly Asp Phe  
 275 280 285

Thr Leu Arg Leu Glu Asp Val Ser Gln Ala Gln Ala Gly Thr Tyr Thr  
 290 295 300

Cys His Ile His Leu Gln Glu Gln Gln Leu Asn Ala Thr Val Thr Leu  
 305 310 315 320

Ala Ile Ile Thr Val Thr Pro Lys Ser Phe Gly Ser Pro Gly Ser Leu  
 325 330 335

Gly Lys Leu Leu Cys Glu Val Thr Pro Val Ser Gly Gln Glu Arg Phe

340

345

350

Val Trp Ser Ser Leu Asp Thr Pro Ser Gln Arg Ser Phe Ser Gly Pro  
 355 360 365

Trp Leu Glu Ala Gln Glu Ala Gln Leu Leu Ser Gln Pro Trp Gln Cys  
 370 375 380

Gln Leu Tyr Gln Gly Glu Arg Leu Leu Gly Ala Ala Val Tyr Phe Thr  
 385 390 395 400

Glu Leu Ser Ser Pro Gly Ala Gln Arg Ser Gly Arg Ala Pro Gly Ala  
 405 410 415

Leu Pro Ala Gly His Leu Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu  
 420 425 430

Gly Gly Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu His His His His  
 435 440 445

His His  
 450

<210> 575  
 <211> 655  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> aa 1-683: Human Lag3 (aa 29 through 450 of NP\_002277.4) aa  
 451-683: mIgG2aFc

<400> 575

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

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

Val Thr Trp Gln His Gln Pro Asp Ser Gly Pro Pro Ala Ala Ala Pro  
 35 40 45

10329W001\_SEQ\_LIST\_ST25.txt

Gly His Pro Leu Ala Pro Gly Pro His Pro Ala Ala Pro Ser Ser Trp  
50 55 60

Gly Pro Arg Pro Arg Arg Tyr Thr Val Leu Ser Val Gly Pro Gly Gly  
65 70 75 80

Leu Arg Ser Gly Arg Leu Pro Leu Gln Pro Arg Val Gln Leu Asp Glu  
85 90 95

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

Arg Ala Asp Ala Gly Glu Tyr Arg Ala Ala Val His Leu Arg Asp Arg  
115 120 125

Ala Leu Ser Cys Arg Leu Arg Leu Arg Leu Gly Gln Ala Ser Met Thr  
130 135 140

Ala Ser Pro Pro Gly Ser Leu Arg Ala Ser Asp Trp Val Ile Leu Asn  
145 150 155 160

Cys Ser Phe Ser Arg Pro Asp Arg Pro Ala Ser Val His Trp Phe Arg  
165 170 175

Asn Arg Gly Gln Gly Arg Val Pro Val Arg Glu Ser Pro His His His  
180 185 190

Leu Ala Glu Ser Phe Leu Phe Leu Pro Gln Val Ser Pro Met Asp Ser  
195 200 205

Gly Pro Trp Gly Cys Ile Leu Thr Tyr Arg Asp Gly Phe Asn Val Ser  
210 215 220

Ile Met Tyr Asn Leu Thr Val Leu Gly Leu Glu Pro Pro Thr Pro Leu  
225 230 235 240

Thr Val Tyr Ala Gly Ala Gly Ser Arg Val Gly Leu Pro Cys Arg Leu  
245 250 255

10329W001\_SEQ\_LIST\_ST25.txt

Pro Ala Gly Val Gly Thr Arg Ser Phe Leu Thr Ala Lys Trp Thr Pro  
260 265 270

Pro Gly Gly Gly Pro Asp Leu Leu Val Thr Gly Asp Asn Gly Asp Phe  
275 280 285

Thr Leu Arg Leu Glu Asp Val Ser Gln Ala Gln Ala Gly Thr Tyr Thr  
290 295 300

Cys His Ile His Leu Gln Glu Gln Gln Leu Asn Ala Thr Val Thr Leu  
305 310 315 320

Ala Ile Ile Thr Val Thr Pro Lys Ser Phe Gly Ser Pro Gly Ser Leu  
325 330 335

Gly Lys Leu Leu Cys Glu Val Thr Pro Val Ser Gly Gln Glu Arg Phe  
340 345 350

Val Trp Ser Ser Leu Asp Thr Pro Ser Gln Arg Ser Phe Ser Gly Pro  
355 360 365

Trp Leu Glu Ala Gln Glu Ala Gln Leu Leu Ser Gln Pro Trp Gln Cys  
370 375 380

Gln Leu Tyr Gln Gly Glu Arg Leu Leu Gly Ala Ala Val Tyr Phe Thr  
385 390 395 400

Glu Leu Ser Ser Pro Gly Ala Gln Arg Ser Gly Arg Ala Pro Gly Ala  
405 410 415

Leu Pro Ala Gly His Leu Glu Pro Arg Gly Pro Thr Ile Lys Pro Cys  
420 425 430

Pro Pro Cys Lys Cys Pro Ala Pro Asn Leu Leu Gly Gly Pro Ser Val  
435 440 445

Phe Ile Phe Pro Pro Lys Ile Lys Asp Val Leu Met Ile Ser Leu Ser  
450 455 460

10329W001\_SEQ\_LIST\_ST25.txt

Pro Ile Val Thr Cys Val Val Val Asp Val Ser Glu Asp Asp Pro Asp  
465 470 475 480

Val Gln Ile Ser Trp Phe Val Asn Asn Val Glu Val His Thr Ala Gln  
485 490 495

Thr Gln Thr His Arg Glu Asp Tyr Asn Ser Thr Leu Arg Val Val Ser  
500 505 510

Ala Leu Pro Ile Gln His Gln Asp Trp Met Ser Gly Lys Glu Phe Lys  
515 520 525

Cys Lys Val Asn Asn Lys Asp Leu Pro Ala Pro Ile Glu Arg Thr Ile  
530 535 540

Ser Lys Pro Lys Gly Ser Val Arg Ala Pro Gln Val Tyr Val Leu Pro  
545 550 555 560

Pro Pro Glu Glu Glu Met Thr Lys Lys Gln Val Thr Leu Thr Cys Met  
565 570 575

Val Thr Asp Phe Met Pro Glu Asp Ile Tyr Val Glu Trp Thr Asn Asn  
580 585 590

Gly Lys Thr Glu Leu Asn Tyr Lys Asn Thr Glu Pro Val Leu Asp Ser  
595 600 605

Asp Gly Ser Tyr Phe Met Tyr Ser Lys Leu Arg Val Glu Lys Lys Asn  
610 615 620

Trp Val Glu Arg Asn Ser Tyr Ser Cys Ser Val Val His Glu Gly Leu  
625 630 635 640

His Asn His His Thr Thr Lys Ser Phe Ser Arg Thr Pro Gly Lys  
645 650 655

<210> 576

<211> 516



&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

<223> aa 1-533 (aa 18 through 533 of cynomolgus XP\_005570011.1 modified to replace amino acid at position 74 with a P based on Rhesus macaque XP\_001108923.1)

&lt;400&gt; 576

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

Ala Gln Glu Gly Ala Pro Ala Gln Leu Pro Cys Ser Pro Thr Ile Pro  
20 25 30

Leu Gln Asp Leu Ser Leu Leu Arg Arg Ala Gly Val Thr Trp Gln His  
35 40 45

Gln Pro Asp Ser Gly Pro Pro Ala Pro Ala Pro Gly His Pro Pro Val  
50 55 60

Pro Gly His Arg Pro Ala Ala Pro Tyr Ser Trp Gly Pro Arg Pro Arg  
65 70 75 80

Arg Tyr Thr Val Leu Ser Val Gly Pro Gly Gly Leu Arg Ser Gly Arg  
85 90 95

Leu Pro Leu Gln Pro Arg Val Gln Leu Asp Glu Arg Gly Arg Gln Arg  
100 105 110

Gly Asp Phe Ser Leu Trp Leu Arg Pro Ala Arg Arg Ala Asp Ala Gly  
115 120 125

Glu Tyr Arg Ala Thr Val His Leu Arg Asp Arg Ala Leu Ser Cys Arg  
130 135 140

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

Ser Leu Arg Thr Ser Asp Trp Val Ile Leu Asn Cys Ser Phe Ser Arg  
165 170 175

10329W001\_SEQ\_LIST\_ST25.txt

Pro Asp Arg Pro Ala Ser Val His Trp Phe Arg Ser Arg Gly Gln Gly  
180 185 190

Arg Val Pro Val Gln Gly Ser Pro His His His Leu Ala Glu Ser Phe  
195 200 205

Leu Phe Leu Pro His Val Gly Pro Met Asp Ser Gly Leu Trp Gly Cys  
210 215 220

Ile Leu Thr Tyr Arg Asp Gly Phe Asn Val Ser Ile Met Tyr Asn Leu  
225 230 235 240

Thr Val Leu Gly Leu Glu Pro Ala Thr Pro Leu Thr Val Tyr Ala Gly  
245 250 255

Ala Gly Ser Arg Val Glu Leu Pro Cys Arg Leu Pro Pro Ala Val Gly  
260 265 270

Thr Gln Ser Phe Leu Thr Ala Lys Trp Ala Pro Pro Gly Gly Gly Pro  
275 280 285

Asp Leu Leu Val Ala Gly Asp Asn Gly Asp Phe Thr Leu Arg Leu Glu  
290 295 300

Asp Val Ser Gln Ala Gln Ala Gly Thr Tyr Ile Cys His Ile Arg Leu  
305 310 315 320

Gln Gly Gln Gln Leu Asn Ala Thr Val Thr Leu Ala Ile Ile Thr Val  
325 330 335

Thr Pro Lys Ser Phe Gly Ser Pro Gly Ser Leu Gly Lys Leu Leu Cys  
340 345 350

Glu Val Thr Pro Ala Ser Gly Gln Glu His Phe Val Trp Ser Pro Leu  
355 360 365

Asn Thr Pro Ser Gln Arg Ser Phe Ser Gly Pro Trp Leu Glu Ala Gln  
370 375 380

10329W001\_SEQ\_LIST\_ST25.txt

Glu Ala Gln Leu Leu Ser Gln Pro Trp Gln Cys Gln Leu His Gln Gly  
385 390 395 400

Glu Arg Leu Leu Gly Ala Ala Val Tyr Phe Thr Glu Leu Ser Ser Pro  
405 410 415

Gly Ala Gln Arg Ser Gly Arg Ala Pro Gly Ala Leu Arg Ala Gly His  
420 425 430

Leu Pro Leu Phe Leu Ile Leu Gly Val Leu Phe Leu Leu Leu Leu Val  
435 440 445

Thr Gly Ala Phe Gly Phe His Leu Trp Arg Arg Gln Trp Arg Pro Arg  
450 455 460

Arg Phe Ser Ala Leu Glu Gln Gly Ile His Pro Pro Gln Ala Gln Ser  
465 470 475 480

Lys Ile Glu Glu Leu Glu Gln Glu Pro Glu Leu Glu Pro Glu Pro Glu  
485 490 495

Leu Glu Arg Glu Leu Gly Pro Glu Pro Glu Pro Gly Pro Glu Pro Glu  
500 505 510

Pro Glu Gln Leu  
515

<210> 577  
<211> 449  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 577

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

10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

Ala Ser Val Ala Thr Ser Gly Asp Phe Asp Tyr Tyr Gly Met Asp Val  
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly  
115 120 125

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

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val  
145 150 155 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe  
165 170 175

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

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val  
195 200 205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys  
210 215 220

10329W001\_SEQ\_LIST\_ST25.txt

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro  
225 230 235 240

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

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp  
260 265 270

Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn  
275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val  
290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu  
305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys  
325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr  
340 345 350

Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr  
355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu  
370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu  
385 390 395 400

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

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

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

Lys

<210> 578  
 <211> 214  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 578

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

Glu Arg Thr Thr Leu Ser Cys Arg Ala Ser Gln Arg Ile Ser Thr 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 Lys Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly  
 50 55 60

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

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu  
 85 90 95

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

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

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

10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

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

Phe Asn Arg Gly Glu Cys  
210

<210> 579  
<211> 450  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 579

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

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

## 10329W001\_SEQ\_LIST\_ST25.txt

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

Ala Ser Val Ala Thr Ser Gly Asp Phe Asp Tyr Tyr Gly Met Asp Val  
           100                  105                  110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly  
           115                  120                  125

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

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val  
   145                  150                  155                  160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe  
                   165                  170                  175

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

Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val  
       195                  200                  205

Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys  
       210                  215                  220

Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe 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 Gln Glu  
           260                  265                  270

Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His  
       275                  280                  285



10329W001\_SEQ\_LIST\_ST25.txt

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe 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 Gly Leu Pro Ser Ser Ile Glu  
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr  
340 345 350

Thr Leu Pro Pro Ser Gln Glu Glu Met 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 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp  
405 410 415

Lys Ser Arg Trp Gln Glu 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 Leu  
435 440 445

Gly Lys  
450

<210> 580  
<211> 445  
<212> PRT  
<213> Artificial Sequence  
  
<220>  
<223> synthetic

&lt;400&gt; 580

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 Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Val  
35 40 45

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

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

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

Arg Asp Glu Glu Leu Glu Phe Arg Phe Phe Asp Tyr Trp Gly Gln Gly  
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe  
115 120 125

Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu  
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp  
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu  
165 170 175

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

Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys Pro  
195 200 205

10329W001\_SEQ\_LIST\_ST25.txt

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro  
210 215 220

Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe Leu  
225 230 235 240

Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu  
245 250 255

Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln  
260 265 270

Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys  
275 280 285

Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu  
290 295 300

Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys  
305 310 315 320

Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys  
325 330 335

Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser  
340 345 350

Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys  
355 360 365

Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln  
370 375 380

Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly  
385 390 395 400

Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln  
405 410 415

10329W001\_SEQ\_LIST\_ST25.txt

Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn  
 420 425 430

His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys  
 435 440 445

<210> 581  
 <211> 214  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> synthetic

<400> 581

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 Val  
 35 40 45

Tyr Gly 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 Phe Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu  
 85 90 95

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

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

10329W001\_SEQ\_LIST\_ST25.txt

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

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

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

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

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

Phe Asn Arg Gly Glu Cys  
210

<210> 582  
<211> 525  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 582

Met Trp Glu Ala Gln Phe Leu Gly Leu Leu Phe Leu Gln Pro Leu Trp  
1 5 10 15

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

Trp Ala Gln Glu Gly Ala Pro Ala Gln Leu Pro Cys Ser Pro Thr Ile  
35 40 45

Pro Leu Gln Asp Leu Ser Leu Leu Arg Arg Ala Gly Val Thr Trp Gln  
50 55 60

His Gln Pro Asp Ser Gly Pro Pro Ala Ala Ala Pro Gly His Pro Leu  
65 70 75 80

10329W001\_SEQ\_LIST\_ST25.txt

Ala Pro Gly Pro His Pro Ala Ala Pro Ser Ser Trp Gly Pro Arg Pro  
85 90 95

Arg Arg Tyr Thr Val Leu Ser Val Gly Pro Gly Gly Leu Arg Ser Gly  
100 105 110

Arg Leu Pro Leu Gln Pro Arg Val Gln Leu Asp Glu Arg Gly Arg Gln  
115 120 125

Arg Gly Asp Phe Ser Leu Trp Leu Arg Pro Ala Arg Arg Ala Asp Ala  
130 135 140

Gly Glu Tyr Arg Ala Ala Val His Leu Arg Asp Arg Ala Leu Ser Cys  
145 150 155 160

Arg Leu Arg Leu Arg Leu Gly Gln Ala Ser Met Thr Ala Ser Pro Pro  
165 170 175

Gly Ser Leu Arg Ala Ser Asp Trp Val Ile Leu Asn Cys Ser Phe Ser  
180 185 190

Arg Pro Asp Arg Pro Ala Ser Val His Trp Phe Arg Asn Arg Gly Gln  
195 200 205

Gly Arg Val Pro Val Arg Glu Ser Pro His His His Leu Ala Glu Ser  
210 215 220

Phe Leu Phe Leu Pro Gln Val Ser Pro Met Asp Ser Gly Pro Trp Gly  
225 230 235 240

Cys Ile Leu Thr Tyr Arg Asp Gly Phe Asn Val Ser Ile Met Tyr Asn  
245 250 255

Leu Thr Val Leu Gly Leu Glu Pro Pro Thr Pro Leu Thr Val Tyr Ala  
260 265 270

Gly Ala Gly Ser Arg Val Gly Leu Pro Cys Arg Leu Pro Ala Gly Val  
275 280 285

10329W001\_SEQ\_LIST\_ST25.txt

Gly Thr Arg Ser Phe Leu Thr Ala Lys Trp Thr Pro Pro Gly Gly Gly  
290 295 300

Pro Asp Leu Leu Val Thr Gly Asp Asn Gly Asp Phe Thr Leu Arg Leu  
305 310 315 320

Glu Asp Val Ser Gln Ala Gln Ala Gly Thr Tyr Thr Cys His Ile His  
325 330 335

Leu Gln Glu Gln Gln Leu Asn Ala Thr Val Thr Leu Ala Ile Ile Thr  
340 345 350

Val Thr Pro Lys Ser Phe Gly Ser Pro Gly Ser Leu Gly Lys Leu Leu  
355 360 365

Cys Glu Val Thr Pro Val Ser Gly Gln Glu Arg Phe Val Trp Ser Ser  
370 375 380

Leu Asp Thr Pro Ser Gln Arg Ser Phe Ser Gly Pro Trp Leu Glu Ala  
385 390 395 400

Gln Glu Ala Gln Leu Leu Ser Gln Pro Trp Gln Cys Gln Leu Tyr Gln  
405 410 415

Gly Glu Arg Leu Leu Gly Ala Ala Val Tyr Phe Thr Glu Leu Ser Ser  
420 425 430

Pro Gly Ala Gln Arg Ser Gly Arg Ala Pro Gly Ala Leu Pro Ala Gly  
435 440 445

His Leu Leu Leu Phe Leu Ile Leu Gly Val Leu Ser Leu Leu Leu Leu  
450 455 460

Val Thr Gly Ala Phe Gly Phe His Leu Trp Arg Arg Gln Trp Arg Pro  
465 470 475 480

Arg Arg Phe Ser Ala Leu Glu Gln Gly Ile His Pro Pro Gln Ala Gln  
485 490 495

Ser Lys Ile Glu Glu Leu Glu Gln Glu Pro Glu Pro Glu Pro Glu Pro  
500 505 510

Glu Pro Glu Pro Glu Pro Glu Pro Glu Pro Glu Gln Leu  
515 520 525

<210> 583  
<211> 15  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 583

Glu Asn Pro Val Val His Phe Phe Lys Asn Ile Val Thr Pro Arg  
1 5 10 15

<210> 584  
<211> 17  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 584

agcagctctg ccctcat

17

<210> 585  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> synthetic

<400> 585

gctctggctg gtcttcagta tg

22

<210> 586  
<211> 22  
<212> DNA  
<213> Artificial Sequence



&lt;220&gt;

&lt;223&gt; synthetic

&lt;400&gt; 586

ttgccgtatg gttggtttga ac

22

&lt;210&gt; 587

&lt;211&gt; 665

&lt;212&gt; PRT

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; hLAG3.Fc

&lt;400&gt; 587

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

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

Leu Leu Arg Arg Ala Gly Val Thr Trp Gln His Gln Pro Asp Ser Gly  
 35 40 45

Pro Pro Ala Ala Ala Pro Gly His Pro Leu Ala Pro Gly Pro His Pro  
 50 55 60

Ala Ala Pro Ser Ser Trp Gly Pro Arg Pro Arg Arg Tyr Thr Val Leu  
 65 70 75 80

Ser Val Gly Pro Gly Gly Leu Arg Ser Gly Arg Leu Pro Leu Gln Pro  
 85 90 95

Arg Val Gln Leu Asp Glu Arg Gly Arg Gln Arg Gly Asp Phe Ser Leu  
 100 105 110

Trp Leu Arg Pro Ala Arg Arg Ala Asp Ala Gly Glu Tyr Arg Ala Ala  
 115 120 125

Val His Leu Arg Asp Arg Ala Leu Ser Cys Arg Leu Arg Leu Arg Leu  
 130 135 140

10329W001\_SEQ\_LIST\_ST25.txt

Gly Gln Ala Ser Met Thr Ala Ser Pro Pro Gly Ser Leu Arg Ala Ser  
145 150 155 160

Asp Trp Val Ile Leu Asn Cys Ser Phe Ser Arg Pro Asp Arg Pro Ala  
165 170 175

Ser Val His Trp Phe Arg Asn Arg Gly Gln Gly Arg Val Pro Val Arg  
180 185 190

Glu Ser Pro His His His Leu Ala Glu Ser Phe Leu Phe Leu Pro Gln  
195 200 205

Val Ser Pro Met Asp Ser Gly Pro Trp Gly Cys Ile Leu Thr Tyr Arg  
210 215 220

Asp Gly Phe Asn Val Ser Ile Met Tyr Asn Leu Thr Val Leu Gly Leu  
225 230 235 240

Glu Pro Pro Thr Pro Leu Thr Val Tyr Ala Gly Ala Gly Ser Arg Val  
245 250 255

Gly Leu Pro Cys Arg Leu Pro Ala Gly Val Gly Thr Arg Ser Phe Leu  
260 265 270

Thr Ala Lys Trp Thr Pro Pro Gly Gly Gly Pro Asp Leu Leu Val Thr  
275 280 285

Gly Asp Asn Gly Asp Phe Thr Leu Arg Leu Glu Asp Val Ser Gln Ala  
290 295 300

Gln Ala Gly Thr Tyr Thr Cys His Ile His Leu Gln Glu Gln Gln Leu  
305 310 315 320

Asn Ala Thr Val Thr Leu Ala Ile Ile Thr Val Thr Pro Lys Ser Phe  
325 330 335

Gly Ser Pro Gly Ser Leu Gly Lys Leu Leu Cys Glu Val Thr Pro Val  
340 345 350

10329W001\_SEQ\_LIST\_ST25.txt

Ser Gly Gln Glu Arg Phe Val Trp Ser Ser Leu Asp Thr Pro Ser Gln  
355 360 365

Arg Ser Phe Ser Gly Pro Trp Leu Glu Ala Gln Glu Ala Gln Leu Leu  
370 375 380

Ser Gln Pro Trp Gln Cys Gln Leu Tyr Gln Gly Glu Arg Leu Leu Gly  
385 390 395 400

Ala Ala Val Tyr Phe Thr Glu Leu Ser Ser Pro Gly Ala Gln Arg Ser  
405 410 415

Gly Arg Ala Pro Gly Ala Leu Pro Ala Gly His Leu Ile Glu Gly Arg  
420 425 430

Met Asp Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro  
435 440 445

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

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val  
465 470 475 480

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr  
485 490 495

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu  
500 505 510

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His  
515 520 525

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys  
530 535 540

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln  
545 550 555 560

10329W001\_SEQ\_LIST\_ST25.txt

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu  
565 570 575

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro  
580 585 590

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn  
595 600 605

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu  
610 615 620

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val  
625 630 635 640

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln  
645 650 655

Lys Ser Leu Ser Leu Ser Pro Gly Lys  
660 665

<210> 588  
<211> 422  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> hLAG3 extracellular domain P18627

<400> 588

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

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

Val Thr Trp Gln His Gln Pro Asp Ser Gly Pro Pro Ala Ala Ala Pro  
35 40 45

## 10329W001\_SEQ\_LIST\_ST25.txt

Gly His Pro Leu Ala Pro Gly Pro His Pro Ala Ala Pro Ser Ser Trp  
 50 55 60

Gly Pro Arg Pro Arg Arg Tyr Thr Val Leu Ser Val Gly Pro Gly Gly  
 65 70 75 80

Leu Arg Ser Gly Arg Leu Pro Leu Gln Pro Arg Val Gln Leu Asp Glu  
 85 90 95

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

Arg Ala Asp Ala Gly Glu Tyr Arg Ala Ala Val His Leu Arg Asp Arg  
 115 120 125

Ala Leu Ser Cys Arg Leu Arg Leu Arg Leu Gly Gln Ala Ser Met Thr  
 130 135 140

Ala Ser Pro Pro Gly Ser Leu Arg Ala Ser Asp Trp Val Ile Leu Asn  
 145 150 155 160

Cys Ser Phe Ser Arg Pro Asp Arg Pro Ala Ser Val His Trp Phe Arg  
 165 170 175

Asn Arg Gly Gln Gly Arg Val Pro Val Arg Glu Ser Pro His His His  
 180 185 190

Leu Ala Glu Ser Phe Leu Phe Leu Pro Gln Val Ser Pro Met Asp Ser  
 195 200 205

Gly Pro Trp Gly Cys Ile Leu Thr Tyr Arg Asp Gly Phe Asn Val Ser  
 210 215 220

Ile Met Tyr Asn Leu Thr Val Leu Gly Leu Glu Pro Pro Thr Pro Leu  
 225 230 235 240

Thr Val Tyr Ala Gly Ala Gly Ser Arg Val Gly Leu Pro Cys Arg Leu  
 245 250 255

10329W001\_SEQ\_LIST\_ST25.txt

Pro Ala Gly Val Gly Thr Arg Ser Phe Leu Thr Ala Lys Trp Thr Pro  
260 265 270

Pro Gly Gly Gly Pro Asp Leu Leu Val Thr Gly Asp Asn Gly Asp Phe  
275 280 285

Thr Leu Arg Leu Glu Asp Val Ser Gln Ala Gln Ala Gly Thr Tyr Thr  
290 295 300

Cys His Ile His Leu Gln Glu Gln Gln Leu Asn Ala Thr Val Thr Leu  
305 310 315 320

Ala Ile Ile Thr Val Thr Pro Lys Ser Phe Gly Ser Pro Gly Ser Leu  
325 330 335

Gly Lys Leu Leu Cys Glu Val Thr Pro Val Ser Gly Gln Glu Arg Phe  
340 345 350

Val Trp Ser Ser Leu Asp Thr Pro Ser Gln Arg Ser Phe Ser Gly Pro  
355 360 365

Trp Leu Glu Ala Gln Glu Ala Gln Leu Leu Ser Gln Pro Trp Gln Cys  
370 375 380

Gln Leu Tyr Gln Gly Glu Arg Leu Leu Gly Ala Ala Val Tyr Phe Thr  
385 390 395 400

Glu Leu Ser Ser Pro Gly Ala Gln Arg Ser Gly Arg Ala Pro Gly Ala  
405 410 415

Leu Pro Ala Gly His Leu  
420

<210> 589  
<211> 44  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> hLAG3 epitope

&lt;400&gt; 589

Leu Arg Arg Ala Gly Val Thr Trp Gln His Gln Pro Asp Ser Gly Pro  
1 5 10 15

Pro Ala Ala Ala Pro Gly His Pro Leu Ala Pro Gly Pro His Pro Ala  
20 25 30

Ala Pro Ser Ser Trp Gly Pro Arg Pro Arg Arg Tyr  
35 40