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(54) Title: METHODS FOR TREATING VASCULAR LEAK SYNDROME AND CANCER

(57) Abstract: Disclosed are methods for treating Vascular Leak Syndrome and preventing cancer metastasis. Further disclosed are methods for treating vascular leakage due to inflammatory diseases, sepsis, cancer or the presence of pathogens.



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METHODS FOR TREATING VASCULAR LEAK SYNDROME AND CANCER**CROSS-REFERENCE TO RELATED APPLICATION**

[00001] This application claims priority to U.S. Provisional Application Serial No. 61/546,748 filed October 13, 2011 and to U.S. Provisional Application Serial No. 61/546,697 filed October 13, 2011. The entire content of U.S. Provisional Application Serial No. 61/546,748 and U.S. Provisional Application Serial No. 61/546,697 is incorporated herein by reference.

**INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED
ELECTRONICALLY**

[00002] Incorporated by reference in its entirety is a computer-readable sequence listing submitted concurrently herewith and identified as follows: One 92 KB ASCII (Text) file named "233106-331560_Seq_Listing_ST25," created on October 15, 2012, at 11:52 am.

FIELD

[00003] Methods for treating cancer, preventing metastasis and vascular leak syndrome by administration of a HPTP β inhibitor.

BACKGROUND

[00004] Vascular leak syndrome (VLS) is characterized by hypotension, peripheral edema and hypoalbuminemia. VLS can occur as a side effect of illness especially illnesses due to pathogens, *inter alia*, viruses and bacteria. Vascular leak complicates the healing process and can itself be a direct result of certain therapies. For example, patients suffering from malignant renal carcinoma are given Interleukin-2 (IL-2) to help boost their immune system. However, this treatment must be withdrawn in many patients due to the onset of severe VLS well before the full course of treatment can be administered. VLS restricts the doses of IL-2 which can be administered to humans and, in some cases, necessitates the cessation of therapy before the therapy is maximally effective.

[00005] VLS is characterized by an increase in vascular permeability accompanied by extravasation of fluids and proteins resulting in interstitial edema and organ failure. Manifestations of VLS include fluid retention, increase in body weight, peripheral edema, pleural and pericardial effusions, ascites, anasarca and, in severe form, signs of pulmonary and

cardiovascular failure. Symptoms are highly variable among patients and the causes are poorly understood. Endothelial cell modifications or damage are thought to be important is vascular leak. The pathogenesis of endothelial cell (EC) damage is complex and can involve activation or damage to ECs and leukocytes, release of cytokines and of inflammatory mediators, alteration in cell-cell and cell-matrix adhesion and in cytoskeleton function.

[00006] One of the most frightening aspects of cancer is its ability to spread, or metastasize. Initially, cancer cells are found grouped together thereby forming one or more tumors. After formation of the primary tumor, cancer cells can gain the ability to separate from the original tumor and travel to other areas of the body. Lung cancer cells that take up in the liver and form tumors are still lung cancer cells. Thus, the propensity for one particular form of cancer to metastasize is dependent on many factors, including type of cancer; however, the overall process of how cells begin the process of metastasis is still not completely understood.

[00007] If a single localized tumor is discovered before it has had a chance to metastasize, then the prognosis of patient survival is higher. This is because the tumor can be effectively excised or destroyed by radiation or chemotherapy. There is, therefore, a difference between tumor growth and metastasis of the tumor cells; the first does not always lead to the other. Cancers that have metastasized, however, are difficult to cure because of extent to which they have spread throughout the body.

[00008] In order to metastasize, a cancer cell must break away from its tumor and invade either the circulatory or lymph system. The free cells are then carried to a new location where they establish themselves. Although the body has natural safeguards that prevent cell from surviving after being detached from their natural location, some cancer cells have the ability to overcome these safeguards. Therefore, if metastasis is stopped or significantly reduced, the extent of cancer can be determined and subsequently treated. As such, a follow up treatment to cancer therapy wherein a tumor has been excised or radiation/chemotherapy has been used, would be the treatment of the patient to an anti-metastasizing agent. There is a long felt need for methods of preventing cancer cell metastasis.

[00009] The growth of primary tumors also presents a challenge to treatment. If the growth of a primary tumor goes unchecked, the initial tumor can grow to a size that adversely effects organ function at the primary site and in nearby tissues. Metastasis of the primary tumor are also more

likely if the primary tumor's growth is uncontrolled. There is a need for methods of slowing or preventing tumor growth.

[00010] During the course of antiviral and antibacterial infections, patients can develop vascular leak that is induced as result of the initial infection. There is now a long felt need for a method of preventing vascular leak due to viral or bacterial infection, and for providing methods of increasing the survival of humans or other mammals infected with one or more pathogens. In addition, there is a long felt need for a method of preventing vascular leakage due to certain anticancer drugs or other anticancer therapies such that the administration of anticancer drugs or anticancer therapies can be given to humans or other mammals for a longer course of treatment or therapy.

SUMMARY

[00011] The present disclosure provides methods for treating a patient having vascular leak syndrome comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof.

[00012] Also provided are methods for treating a patient having vascular leak syndrome comprising administering to the patient, a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipient.

[00013] The present disclosure provides for methods of treating vascular leak wherein the patient being treated is suffering from an inflammatory disease or condition, trauma, shock, adult respiratory distress syndrome, acute lung injury, or sepsis comprising administering to the patient, a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof.

[00014] The present disclosure also provides for methods of treating vascular leak wherein the patient being treated is suffering from an inflammatory disease or condition, trauma, shock, adult respiratory distress syndrome, acute lung injury, or sepsis comprising administering to the patient, a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipient.

[00015] Another method provided by the present disclosure, is a method for determining the course of treatment for a patient suffering from vascular leak syndrome, comprising:

a) administering to a patient a composition comprising an effective amount of an HPTP β -ECD binding agent; b) monitoring the level of angiopoietin-2 present in the patient during the course of treatment; and c) discontinuing treatment when the angiopoietin-2 level returns to within a normal range.

[00016] A further method provided by the present disclosure is a method for treating cancer in a patient, comprising administering to a patient a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof.

[00017] A further method provided by the present is a method for treating cancer in a patient, comprising administering to a patient a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00018] Still another method provided by the present disclosure is a method for preventing metastasis in a patient with cancer, by administering to a patient a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof.

[00019] Still another method provided by the present disclosure is a method for preventing metastasis in a patient with cancer, by administering to a patient a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

[00020] In the methods of the present disclosure, HPTP β -ECD binding agents include, but are not limited to antibodies, proteins, peptides, aptamers, peptibodies, adnectins, or nucleic acids, that binds to the extracellular portion of HPTP β .

BRIEF DESCRIPTION OF THE FIGURES

[00021] **Fig. 1.** The monoclonal antibody R15E6 recognizes endogenous HPTP β on endothelial Cells. (Panel A) Endothelial cell lysates are immunoprecipitated with a control antibody (Lane 1), with R15E6 (Lane 2), or with a mixture of anti-Tie2 and anti-VEGFR2 antibodies (Lane 3). Immunoprecipitates are resolved by SDS-PAGE, transferred to a PVDF membrane and probed by western blot with a mixture of R15E6, anti-Tie2 and anti-VEGFR2

antibodies. A single major high molecular weight band consistent with HPTP β is seen with R15E6 (Lane 2), and not with the control antibody (Lane 1), or the mixture of anti-Tie2 and anti-VEGFR2 (Lane 3). (Panel B) Endothelial cells are subjected to FACS analysis with R15E6 (white peak) or a no primary antibody control (black peak). The robust shift in fluorescence indicates that R15E6 binds to HPTP β on the surface of intact endothelial cells.

[00022] Fig. 2 The monoclonal antibody R15E6 enhances Tie2 Receptor Activation in HUVECs. Tie2 activation is measured in human endothelial cells as described in Example 4. R15E6 dose dependently enhances both basal and Ang1-induced Tie2 activation.

[00023] Fig. 3. Is a graphical representation of the mean area of choroidal neovascularization in C57BL/6 mice 14 days post laser treatment in eyes treated with intravitreal injection of 1 μ g or 2 μ g of an anti-VE-PTP extracellular domain antibody in one eye versus similar treatment of the fellow eye with vehicle.

[00024] Fig. 4. Shows the mean area (mm²) of retinal neovascularization in C57BL/6 mice on day P17 after containment in a 75% oxygen atmosphere from P5 to P12 and intravitreal injection of an anti-VE-PTP extracellular domain antibody at P12 when the mice were returned to room air.

[00025] Fig. 5. Show representative fluorescent micrographs of mouse retinas in the oxygen-induced retinopathy model after intravitreal injection of vehicle or 2 μ g of an anti-VE-PTP extracellular domain antibody.

[00026] Fig. 6. Shows the mean area (mm²) of retinal neovascularization in C57BL/6 mice on day P17 after containment in a 75% oxygen atmosphere from P5 to P12 followed by return to room air on P12 with subcutaneous administration of 1 mg/kg of an anti-VE-PTP extracellular domain antibody on days P12, 14 and 16.

[00027] Fig. 7. Shows the mean area (mm²) of retinal neovascularization in C57BL/6 mice on day P17 after containment in a 75% oxygen atmosphere from P5 to P12 follow by return to room air on P12 with subcutaneous administration of 2 mg/kg of an anti-VE-PTP extracellular domain antibody on days P12, 14 and 16.

DETAILED DESCRIPTION

General Definitions

[00028] In this specification and in the claims that follow, reference will be made to a number of terms, which shall be defined to have the following meanings:

[00029] The term "HPTP β -ECD binding agent" and "specific binding agent" are used interchangeably herein and refer to a molecule that specifically binds to the extracellular portion of HPTP β , and variants and derivatives thereof, as defined herein, that inhibits the Tie2 dephosphorylase activity of HPTP β .

[00030] "Agent" as used herein refers to an "HPTP β binding agent" or unless otherwise noted.

[00031] "Specifically binds HPTP β -ECD" refers to the ability of a specific binding agent of the present invention to recognize and bind to an epitope of the extracellular domain of HPTP β with higher affinity than to other related and/or unrelated molecules. Specific binding agents preferentially bind to HPTP β in a complex mixture of proteins and/or macromolecules. The specific binding agent is preferably selective for HPTP β . "Selective" means that the agent has significantly greater activity toward HPTP β compared with other related and/or unrelated molecules, not that it is completely inactive with regard to other molecules. For example, a selective agent may show 10-fold, 100-fold, or 1000-fold selectivity toward HPTP β than to other related or unrelated molecules.

[00032] The term "anti-HPTP β -ECD antibodies" refers to antibodies or antibody fragments that bind to the extracellular domain of HPTP β . Anti-HPTP β -ECD antibodies are a type of HPTP β -ECD binding agent as defined herein.

[00033] The term "VE-PTP" refers to the mouse ortholog of HPTP β .

[00034] All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius ($^{\circ}\text{C}$) unless otherwise specified.

[00035] Ranges may be expressed herein as from one particular value to another particular value, the endpoints are included in the range. For example for the range from "1mg to 50mg" includes the specific values 1mg and 50mg. The antecedent "about" indicates that the values are approximate. For example for the range from "about 1mg to about 50mg" indicates that the

values are approximate values. Additionally, when such a range is expressed, the range includes the range “from 1mg to 50mg”. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint, and independently of the other endpoint. For example the range “from 1mg to 50mg”, includes the range “from 30mg to 40mg.”

[00036] As used herein, the term “in combination” refers to the use of more than one prophylactic and/or therapeutic agent. The use of the term “in combination” does not restrict the order in which prophylactic and/or therapeutic agents are administered to a patient. A first prophylactic or therapeutic agent can be administered prior to (e.g., 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 1 minute, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second prophylactic or therapeutic agent to a patient which had, has, or is susceptible to a disorder. The prophylactic or therapeutic agents are administered to a patient in a sequence and within a time interval such that the agent of the present disclosure can act together with the other agent to provide an increased benefit than if they were administered otherwise. Any additional prophylactic or therapeutic agent can be administered in any order with the other additional prophylactic or therapeutic agents

[00037] “Effective amount” means an amount of an active agent or combination of agents effective to ameliorate or prevent the symptoms, or prolong the survival of the patient being treated. An effective amount may vary according to factors known in the art, such as the disease state, age, sex, and weight of the human or animal being treated. Although particular dosage regimes may be described in examples herein, a person skilled in the art would appreciate that the dosage regime may be altered to provide optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. In addition, the compositions of this disclosure can be administered as frequently as necessary to achieve a therapeutic amount. Determination of a therapeutically effective amount is well within the capabilities of those skilled in the art, especially in light of the detailed disclosure provided herein.

[00038] As used herein the term “inhibit” or “inhibiting” refers to a statistically significant and measurable reduction in activity, preferably a reduction of at least about 10% versus control, more preferably a reduction of about 50% or more, still more preferably a reduction of about 80% or more.

[00039] As used herein the term “increase” or “increasing” refers to a statistically significant and measurable increase in activity, preferably an increase of at least about 10% versus control, more preferably an increase of about 50% or more, still more preferably an increase of about 80% or more.

[00040] “HPTP beta” or “HPTP β ” are used interchangeably herein and are abbreviations for human protein tyrosine phosphatase beta.

[00041] As used herein, “subject” means an individual. Thus, the “subject” can include domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), laboratory animals (e.g., mouse, rabbit, rat, guinea pig, etc.), and birds. “Patient” can also include a mammal, such as a primate or a human. “Subject” and “patient” are used interchangeably herein. Preferably the subject is a human.

[00042] By “reduce” or other forms of the word, such as “reducing” or “reduction,” is meant lowering of an event or characteristic (e.g., vascular leakage). It is understood that this is typically in relation to some standard or expected value, in other words it is relative, but that it is not always necessary for the standard or relative value to be referred to.

[00043] The terms “treatment”, “treating”, “treat” and the like, refer to obtaining a desired pharmacologic and/or physiologic effect such as mitigating a disease or a disorder in a host and/or reducing, inhibiting, or eliminating a particular characteristic or event associated with a disorder (e.g., vascular leak). Thus, the term "treatment" includes, preventing a disorder from occurring in a host, particularly when the host is predisposed to acquiring the disease, but has not yet been diagnosed with the disease; inhibiting the disorder; and/or alleviating or reversing the disorder. Insofar as the methods of the present invention are directed to preventing disorders, it is understood that the term "prevent" does not require that the disease state be completely thwarted. Rather, as used herein, the term preventing refers to the ability of the skilled artisan to identify a population that is susceptible to disorders, such that administration of the HPTP β -ECD binding agents of the disclosure may occur prior to onset of a disease. The term does not imply

that the disease state is completely avoided.

[00044] As used herein, the term “cancer treatment” means any treatment for cancer known in the art including, but not limited to, chemotherapy and radiation therapy.

[00045] As used herein, the term “cancer treatment” means any treatment for cancer known in the art including, but not limited to, chemotherapy and radiation therapy.

[00046] Throughout the description and claims of this specification the word “comprise” and other forms of the word, such as “comprising” and “comprises,” means including but not limited to, and is not intended to exclude, for example, other additives, components, integers, or steps.

[00047] As used in the description and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a composition” includes mixtures of two or more such compositions.

[00048] “Optional” or “optionally” means that the subsequently described event or circumstance can or cannot occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

[00049] “Specifically binds HPTP β ” refers to the ability of an agent of the present invention to recognize and bind to an epitope of the extracellular domain of HPTP β with higher affinity than to the other related and/or unrelated molecules. The agent is preferably selective for HPTP β . “Specific” means that the agent has significantly greater activity toward HPTP β compared with other related and/or unrelated molecules, not that it is completely inactive with regard to other molecules. For example, a selective agent may show 10-fold, 100-fold, or 1000-fold selectivity toward HPTP β than to other related or unrelated molecules.

[00050] The term “epitope” refers to any portion of any molecule capable of being recognized by and bound by an agent at one or more of the agent’s antigen binding regions. Epitopes usually consist of distinct surface groupings such as amino acids, sugars, lipids, phosphoryl, or sulfonyl, and, in certain embodiments, may have specific three dimensional structural characteristics, and/or specific charge characteristics. Epitopes as used herein may be conformational or linear.

[00051] “Peptibody” is a molecule comprising an antibody Fc domain attached to at least one peptide. The production of peptibodies is generally described in WO2002/24782.

[00052] “Fragment” refers to a portion of an agent. A fragment may retain the desired biological activity of the agent and may be considered to be an agent itself. For example a truncated protein in which the amino terminus and/or carboxy terminus and/or an internal amino acid residue is deleted is a fragment of the protein and an Fab of an immunoglobulin molecule is a fragment of the immunoglobulin. Such fragments may also be connected to another molecule by way of a direct connection (e.g. a peptide or disulfide bond) or by way of a linker.

[00053] “Protein” is used herein interchangeably with peptide and polypeptide.

[00054] Peptides of the present invention include, but are not limited to amino acid sequences having from about 3 to about 75 amino acids, or from about 5 to about 50 amino acids, or from about 10 to about 25 amino acids. Peptides may be naturally occurring or artificial amino acid sequences.

[00055] A protein of the invention may be obtained by methods well known in the art, for example, using standard direct peptide synthesizing techniques such as via solid-phase synthesis. If the gene sequence is known or can be deduced then the protein may be produced by standard recombinant methods. The proteins may be isolated or purified in a variety of ways known to one skilled in the art. Standard purification methods include precipitation with salts, electrophoretic, chromatographic techniques and the like.

[00056] “Derivatives” include those binding agents that have been chemically modified in some manner distinct from insertion, deletion, or substitution variants. For example, wherein the binding agent is a protein, the carboxyl terminus may be capped with an amino group, such as NH₂.

[00057] In some embodiments one or more molecules are linked together to form the agent. For example antibody fragments may be connected by a linker. In general the chemical structure of the linker is not critical as it serves primarily as a space. In one embodiment the linker is made of amino acids linked together by way of peptide bonds. In another embodiment the linker is a non-peptide linker such as a non-sterically hindering C₁-C₆ alkyl group. In another

embodiment the linker is a PEG linker. It will further be appreciated that the linker can be inserted in a number of locations on the molecule.

[00058] Variants of an agent are included within the scope of the present invention. “Variant” or “Variants” as used herein means an agent having a protein or nucleotide sequence which is substantially similar to the protein or nucleotide sequence of the non-variant agent and which shares a similar activity of the non-variant agent. A protein or nucleotide sequence may be altered in various ways to yield a variant encompassed by the present invention, including substitutions, deletions, truncations, insertions and other modifications. Methods for such manipulations are well known in the art. See, for example, Current Protocols in Molecular Biology (and updates) Ausubel et al., Eds (1996), John Wiley and Sons, New York: Methods in Molecular Biology, Vol. 182, In vitro Mutagenesis Protocols, 2nd Edition, Barman Ed. (2002), Humana Press), and the references cited therein. For example, variants include peptides and polypeptides wherein amino acid residues are inserted into, deleted from and/or substituted into the known amino acid sequence for the binding agent. In one embodiment, the substitution of the amino acid is conservative in that it minimally alters the biochemical properties of the variant. In other embodiments, the variant may be an active fragment of a full-length protein, a chemically modified protein, a protein modified by addition of affinity or epitope tags, or fluorescent or other labeling moieties, whether accomplished by *in vivo* or *in vitro* enzymatic treatment of the protein, by chemical modification, or by the synthesis of the protein using modified amino acids.

[00059] Fusions proteins are also contemplated herein. Using known methods, one of skill in the art would be able to make fusion proteins of the proteins of the invention; that, while different from native form, may be useful. For example, the fusion partner may be a signal (or leader) polypeptide sequence that co-translationally or post-translationally directs transfer of the protein from its site of synthesis to another site (e.g., the yeast alpha-factor leader). Alternatively, it may be added to facilitate purification or identification of the protein of the invention (e.g., poly-His, Flag peptide, or fluorescent proteins).

[00060] Standard techniques may be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques may be performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The techniques and procedures are generally performed according to conventional methods known in the art and as described in

various general and more specific references that are cited and discussed throughout the present specification. Unless specific definitions are provided, the nomenclature utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those known and commonly used in the art. Standard techniques may be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, delivery, and treatment of patients.

Sequence Listing

[00061] Table 1.

SEQ ID NO:1	Full length Human HPTP β nucleotide sequence (X54131)
SEQ ID NO:2	Full length Human HPTP β amino acid sequence (P23467)
SEQ ID NO:3	Extracellular Portion of Human HPTP β with (His) ₆ Gly Tag
SEQ ID NO:4	Extracellular Portion of Human HPTP β
SEQ ID NO:5	Full length mouse VE-PTP nucleotide sequence (AY077755)
SEQ ID NO:6	Full length mouse VE-PTP amino acid sequence (AAL75813)
SEQ ID NO:7	Extracellular portion of mouse VE-PTP amino acid sequence

HPTP β -ECD binding agents

[00062] Agents useful in the present invention include, but are not limited to, antibodies, proteins, darpins, peptides, aptamers, adnectins, peptibodies, or nucleic acids that bind specifically to the extracellular portion of HPTP β and inhibit at least one phosphatase activity of HPTP β . As used herein, “phosphatase activity” includes enzymatic activity and biologic activity where biological activity is measured by assessing Tie2 phosphorylation.

[00063] Agents useful in the present invention further include: antibodies, or antigen binding fragments thereof which bind to the extracellular portion of HPTP β wherein the antibody or antigen-binding fragment inhibits at least one phosphatase activity of HPTP β . These agents include monoclonal and polyclonal antibodies. An agent may be a fragment of an antibody, wherein the fragment comprises the heavy and light chain variable regions, or the fragment is an F(ab')₂, or the fragment is a dimer or trimer of an Fab, Fv, scFv, or a dia-, tria-, or tetrabody derived from the antibody.

[00064] For example, the agent may be, without limitation, an antibody or antibody fragment that binds the extracellular portion of HPTP β ; or in particular an antibody that binds an FN3 repeat of HPTP β , or more specifically an antibody that binds the first FN3 repeat of HPTP β .

[00065] Agents further include: the monoclonal antibody R15E6 which is described in U.S. Pat. No. 7,973,142, which is hereby incorporated in its entirety. (The mouse hybridoma, Balbc spleen cells (B cells) which may be used to produce the antibody are deposited with American Type Culture Collection (ATCC), P.O. Box 1549, Manassas, Va. 20108 USA on 4 May 2006, assigned ATCC No. PTA-7580) (Referred to herein as R15E6)), antibodies having the same or substantially the same biological characteristics of R15E6; antibody fragments of R15E6, wherein the fragment comprises the heavy and light chain variable regions; an F(ab')₂ of R15E6; dimers or trimers of an Fab, Fv, scFv; and dia-, tria-, or tetrabodies derived from R15E6.

[00066] In particular, an agent suitable for use in the present invention is an antibody, antibody fragment, variant or derivatives thereof, either alone or in combination with other amino acid sequences, provided by known techniques. Such techniques include, but are not limited to enzymatic cleavage, chemical cleavage, peptide synthesis or recombinant techniques. The invention further embraces derivative agents, e.g. peptibodies.

[00067] Thus, one embodiment of an HPTP β -ECD binding agent is an antibody, another embodiment is a protein, yet another embodiment is a peptide, and another embodiment is a darpin, another embodiment is an aptamer, another embodiment is a peptibody, still another embodiment is an adnectin, another embodiment is a nucleic acid. In some embodiments the HPTP β -ECD binding agent is an monoclonal antibody, or is a polyclonal antibody. In particular embodiments, the HPTP β -ECD binding agent is an antibody fragment that is capable of binding to HPTP β -ECD. Preferably the HPTP β -ECD binding agent is an antibody, or an antibody fragment, including but not limited to, an F(ab')₂, an Fab, a dimer of an Fab, an Fv, a dimer of an Fv, a scFv, a dimer of a scFv, a dimer an Fab, an Fv, a dimer of an Fv, a scFv, a dimer of a scFv, a trimer of an Fab, a trimer of an Fv, a trimer of a scFv, minibodies, a diabody, a triabody, a tetrabody, a linear antibody, a protein, a peptide, an aptamer, a peptibody, an adnectin, or a nucleic acid, that binds to the extracellular portion of HPTP β . In certain embodiments the HPTP β -ECD binding agent is and F(ab')₂ of a monoclonal antibody. In some embodiments the HPTP β -ECD binding agent comprises a plurality of HPTP β -ECD binding sites, for example where the HPTP β -ECD binding agent is an intact antibody or an F(ab')₂, or a dimer of an Fab, or

a trimer of an Fab. For example, in some embodiments an HPTP β -ECD binding agent is able to bind to two HPTP β molecules simultaneously at the same or different epitope, thereby bringing the two HPTP β molecules into close proximity with one and other. In other embodiments the HPTP β -ECD binding agent is able to bind to three HPTP β molecules simultaneously at the same or different epitope, thereby bringing the three HPTP β molecules into close proximity with one and other. In another embodiment, the HPTP β -ECD binding agent is the monoclonal antibody produced by hybridoma cell line ATCC No. PTA-7680. In yet another embodiment, the HPTP β -ECD binding agent is an antigen binding fragment of the monoclonal antibody produced by hybridoma cell line ATCC No. PTA-7680. In still another embodiment, the HPTP β -ECD binding agent is an antibody having the same or substantially the same biological characteristics the monoclonal antibody produced by hybridoma cell line ATCC No. PTA-7680 or an antigen binding fragment thereof.

[00068] Any of the embodiments of HPTP β -ECD binding agents disclosed in the present application, may be covalently or non-covalently conjugated to a vehicle. The term “vehicle” refers to a molecule that affects a biological property of an agent. For example, a vehicle may prevent degradation, and/or increase half-life, absorption, reduce toxicity, reduce immunogenicity, or increase biological activity of the agent. Exemplary vehicles include, but are not limited to, Fc domains of immunoglobulins; polymers, for example: polyethylene glycol (PEG), polylysine, dextran; lipids; cholesterol groups (such as a steroid); carbohydrates, dendrimers, oligosaccharides, or peptides that binds to a salvage receptor. In some embodiments the vehicle is polyethylene glycol (PEG), in other embodiments the vehicle is polylysine, in yet other embodiments the vehicle is dextran, in still other embodiments the vehicle is a lipid

[00069] Water soluble polymer attachments, such as polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol, as described U.S. Pat. Nos. 4,640,835, 4,496,689, 4,301,144, 4,670,417, 4,791,192, and 4,179,337, which are incorporated herein in their entirety. Still other useful polymers known in the art include monomethoxy-polyethylene glycol, dextran, cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone)-polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol) and polyvinyl alcohol, as well as mixtures of these polymers. Particularly preferred are peptibodies covalently modified with polyethylene glycol (PEG) subunits. Water soluble polymers may be bonded at specific positions, for example at the amino terminus of the peptibodies, or randomly attached to one or more side chains of the

polypeptide. The use of PEG for improving the therapeutic capacity for agents, e.g. peptibodies, and for humanized antibodies in particular, is described in U.S. Pat. No. 6,133,426. The invention also contemplates derivatizing the peptide and/or vehicle portion of the agents. Such derivatives may improve the solubility, absorption, biological half-life, and the like of the agents. The moieties may alternatively eliminate or attenuate any undesirable side-effect of the agents and the like.

[00070] The term "antibody" (Ab) as used herein includes monoclonal antibodies, polyclonal antibodies, multi-specific antibodies (e.g. bispecific antibodies), single chain antibodies, e.g., antibodies from llama and camel, antibody fragments, e.g., variable regions and/or constant region fragments, so long as they exhibit a desired biological activity, e.g., antigen-binding activity. The term "immunoglobulin" (Ig) is used interchangeably with "antibody" herein.

[00071] An "antigen binding fragment" as used herein is a fragment of an agent that binds to a portion of HPTP β and inhibits at least one phosphatase activity of HPTP β .

[00072] The basic four-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains (an IgM antibody consists of 5 of the basic heterotetramer units along with an additional polypeptide called J chain, and therefore contain 10 antigen binding sites, while secreted IgA antibodies may polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain). In the case of IgGs, the four-chain unit is generally about 150 kilo Daltons (kDa). Each L chain is linked to an H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (V_H) followed by three constant domains (C_H) for each of the alpha and gamma chains and four C_H domains for mu and epsilon isotypes. Each L chain has at the N-terminus, a variable domain (V_L) followed by a constant domain (C_L) at its other end. The V_L is aligned with the V_H and the C_L is aligned with the first constant domain of the heavy chain (C_{H1}). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, e.g., Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, 1994, page 71 and Chapter 6.

[00073] The L chain from any vertebrate species may be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (C_H), immunoglobulins may be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, having heavy chains designated alpha, delta, epsilon, gamma and mu, respectively. The gamma and alpha classes are further divided into subclasses on the basis of relatively minor differences in C_H sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2.

[00074] Members of the Camelidae family, e.g., llama, camel, and dromedaries, contain a unique type of antibody, that are devoid of light chains, and further lack the C_{H1} domain (Muyldermans, S., Rev. Mol. Biotechnol., 74, 277-302 (2001)). The variable region of these heavy chain antibodies are termed V_{HH} or VHH, and constitute the smallest available intact antigen binding fragment (15 kDa) derived from a functional immunoglobulin.

[00075] The term "variable" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and defines specificity of a particular antibody for its antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of relatively invariant stretches called framework regions (FR) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies. The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

[00076] The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g. around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the V_L , and around about 1-35

(H1), 50-65 (H2) and 95-102 (H3) in the V_H; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)) and/or those residues from a "hypervariable loop".

[00077] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. In contrast to polyclonal antibody preparations which include different antibodies directed against different epitopes, each monoclonal antibody is directed against a single epitope, i.e., a single antigenic determinant. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. The modifier "monoclonal" is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies useful in the present invention may be prepared by the hybridoma methodology or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells (see, e.g., U.S. Pat. No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries, using the available techniques, e.g., Clackson et al., Nature, Vol. 352, pp. 624-628 (1991).

[00078] The monoclonal antibodies herein include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (see U.S. Pat. No. 4,816,567; and Morrison et al., Proc. Natl. Acad. Sci. USA, 81, 6851-6855 (1984)).

[00079] An "antibody fragment" comprises a portion of a multimeric antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, dimers and trimers of Fabs, Fv, scFv, minibodies; dia-, tria-, and tetrabodies; linear antibodies (See Hudson et al., Nature Med. 9, 129-134 (2003)).

[00080] "Fv" is the minimum antibody fragment which contains a complete antigen binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six

hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, and are therefore included in the definition of Fv.

[00081] A single-chain variable fragment (scFv) is a fusion protein of the variable regions of the heavy (V_H) and light chains (V_L) of immunoglobulins, connected with a short linker peptide of ten to about 25 amino acids. The linker is usually rich in glycine for flexibility, as well as serine or threonine for solubility, and can either connect the N-terminus of the V_H with the C-terminus of the V_L , or vice versa. This protein retains the specificity of the original immunoglobulin, despite removal of the constant regions and the introduction of the linker.

[00082] Divalent (or bivalent) single-chain variable fragments (di-scFvs, bi-scFvs) can be engineered by linking two scFvs. This can be done by producing a single peptide chain with two V_H and two V_L regions, yielding tandem scFvs. Another possibility is the creation of scFvs with linker peptides that are too short for the two variable regions to fold together (about five amino acids), forcing scFvs to dimerize. This type is known as diabodies. Diabodies have been shown to have dissociation constants up to 40-fold lower than corresponding scFvs, meaning that they have a much higher affinity to their target. Consequently, diabody drugs could be dosed much lower than other therapeutic antibodies and are capable of highly specific targeting of tumors *in vivo*. Still shorter linkers (one or two amino acids) lead to the formation of trimers, so-called triabodies or tribodies. Tetrabodies are known and have been shown to exhibit an even higher affinity to their targets than diabodies.

[00083] The term "humanized antibody" or "human antibody" refers to antibodies which comprise heavy and light chain variable region sequences from a non-human species (e.g., a mouse) but in which at least a portion of the V_H and/or V_L sequence has been altered to be more "human-like", i.e., more similar to human germline variable sequences. One type of humanized antibody is a CDR-grafted antibody, in which human CDR sequences are introduced into non-human V_H and V_L sequences to replace the corresponding nonhuman CDR sequences. Means for making chimeric, CDR-grafted and humanized antibodies are known to those of ordinary skill in the art (see, e.g., U.S. Pat. Nos. 4,816,567 and 5,225,539). One method for making human antibodies employs the use of transgenic animals, such as a transgenic mouse. These transgenic

animals contain a substantial portion of the human antibody producing genome inserted into their own genome and the animal's own endogenous antibody production is rendered deficient in the production of antibodies. Methods for making such transgenic animals are known in the art. Such transgenic animals may be made using XenoMouse.RTM. technology or by using a "minilocus" approach. Methods for making XenoMice.RTM. are described in U.S. Pat. Nos. 6,162,963, 6,150,584, 6,114,598 and 6,075,181. Methods for making transgenic animals using the "minilocus" approach are described in U.S. Pat. Nos. 5,545,807, 5,545,806, 5,625,825, and WO 93/12227.

[00084] Humanization of a non-human antibody has become routine in recent years, and is now within the knowledge of one skilled in the art. Several companies provide services to make a humanized antibody, e.g., Xoma, Aries, Medarex, PDL, and Cambridge Antibody Technologies. Humanization protocols are extensively described in technical literature, e.g., Kipriyanov and Le Gall, *Molecular Biotechnol.*, Vol. 26, pp. 39-60 (2004), Humana Press, Totowa, N.J.; Lo, *Methods Mol. Biol.*, Vol. 248, pp. 135-159 (2004), Humana Press, Totowa, N.J.; Wu et al., *J. Mol. Biol.*, 294, pp. 151-162 (1999).

[00085] In certain embodiments, antibodies useful in the present invention may be expressed in cell lines other than hybridoma cell lines. Sequences encoding particular antibodies may be used for transformation of a suitable mammalian host cell by known methods for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector), or by transfection procedures known in the art, as exemplified by U.S. Pat. Nos. 4,399,216, 4,912,040, 4,740,461 and 4,959,455. The transformation procedure used may depend upon the host to be transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are known in the art and include; but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, mixing nucleic acid with positively-charged lipids, and direct microinjection of the DNA into nuclei.

[00086] A nucleic acid molecule encoding the amino acid sequence of a heavy chain constant region, a heavy chain variable region, a light chain constant region, or a light chain variable region of an antibody, or a fragment thereof in a suitable combination if desired, is/are inserted into an appropriate expression vector using standard ligation techniques. The antibody heavy

chain or light chain constant region may be appended to the C-terminus of the appropriate variable region and is ligated into an expression vector. The vector is typically selected to be functional in the particular host cell employed (i.e., the vector is compatible with the host cell machinery such that amplification of the gene and/or expression of the gene may occur). For a review of expression vectors, see Methods Enzymol. Vol. 185 (Goeddel, ed.), 1990, Academic Press.

Identification of specific binding agents

[00087] Suitable selective binding agents may be identified using a variety of techniques known in the art. For example candidate agents can be screened for binding to HPTP β , and screened for activity. Generally the candidate agents will first be screened for binding and those that show selective binding will then be screened to determine ability to inhibit the HPTP β -mediated dephosphorylation of Tie2. In some cases however the candidate agents may be first screened *in vitro* for activity.

Determination of binding activity

[00088] The selection of a suitable assay for use in identification of a specific binding agent depends on the nature of the candidate agent to be screened. One of skill in the art would be able to choose the appropriate assays for the particular candidate agent.

[00089] For example, where the candidates are antibodies or peptibodies which comprises an Fc moiety, FACS analysis as described in Example 3 B allows the candidate agent to be selected based on its ability to bind to cells which express HPTP β . The cell may endogenously express HPTP β or may be genetically engineered to express HPTP β .

[00090] For other candidate agents such as aptamers, other techniques are known in the art. For example, aptamers which specifically bind to HPTP β can be selected using a technique known as SELEX (systematic evolution of ligands by exponential enrichment) which selects specific aptamers through repeated rounds of *in vitro* selection.

Determination of inhibitor activity by Western blot

[00091] As exemplified in Example 4, in one suitable assay HUVECs are cultured in serum-free media in the presence or absence of various concentrations of candidate agent and lysates of the cells are prepared, immunoprecipitated with a Tie2 antibody, resolved by polyacrylamide gel

electrophoresis and transferred to a PVDF membrane. Membrane-bound immunoprecipitated proteins are then serially western blotted with an antiphosphotyrosine antibody to quantify Tie2 phosphorylation followed by a Tie2 antibody to quantify total Tie2. Tie2 phosphorylation is expressed as the ratio of the anti-phosphotyrosine signal over the total Tie2 signal. Greater levels of the anti-phosphotyrosine signal indicate greater HPTP β inhibition by the candidate agent.

[00092] Candidate agents that can be screened include, but are not limited to, libraries of known agents, including natural products, such as plant or animal extracts, biologically active molecules including proteins, peptides including but not limited to members of random peptide libraries and combinatorial chemistry derived molecular library made of D- or L-configuration amino acids, antibodies including, but not limited to, polyclonal, monoclonal, chimeric, human, single chain antibodies, Fab, F(ab)₂ and Fab expression library fragments and eptiope-binding fragments thereof).

[00093] As used herein “antibody fragments” include, but are not limited, to an F(ab')₂, a dimer or trimer of an Fab, Fv, scFv, or a dia-, tria-, or tetrabody derived from an antibody.

[00094] Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art.

[00095] The vascular endothelium lines the inside of all blood vessels, forming a non-thrombogenic surface that controls the entry and exit of plasma and white blood cells to and from the bloodstream. The quiescent endothelium has turnover rates of months to years, and proliferates only following angiogenic activation. The loss of endothelial quiescence is a common feature of conditions such as inflammation, atherosclerosis, restenosis, angiogenesis and various types of vasculopathies.

[00096] Vasculogenesis and angiogenesis are down-regulated in the healthy adult and are, except for the organs of the female reproductive system, almost exclusively associated with pathology when angiogenesis is induced by microenvironmental factors such as hypoxia or inflammation. These pathological processes associated with, or induced by, angiogenesis include diseases as diverse as cancer, psoriasis, macular degeneration, diabetic retinopathy, thrombosis, and inflammatory disorders including arthritis and atherosclerosis. However, in certain instances insufficient angiogenesis can lead to diseases such as ischemic heart disease and pre-eclampsia.

[00097] The quiescent vascular endothelium forms a tight barrier that controls the passage of plasma and cells from the bloodstream to the underlying tissues. Endothelial cells adhere to each other through junctional transmembrane proteins that are linked to specific intracellular structural and signaling complexes. The endothelial layer can undergo a transition from the resting state to the active state wherein activation of the endothelium results in the expression of adhesion molecules. This endothelium activation is a prerequisite for initiating angiogenesis, inflammation and inflammation associated diseases.

[00098] Tie-2, a receptor-like tyrosine kinase exclusively expressed in endothelial cells that controls endothelial differentiation. Tie-2 binds and is activated by the stimulatory ligand angiopoietin-1 (Ang-1) which promotes autophosphorylation of the Tie-2 receptor leading to a cascade of events that results in stabilization of vascular structures by promoting endothelial cell viability and preventing basement membrane dissolution. As such, Tie-2 activation is a method for attenuating leaking vasculature by maintaining a quiescent, intact vascular endothelium. Tie-2 activation is inhibited by Ang-2, which exhibits Ang-1 antagonism by competitively binding to Tie-2 and thus blocking phosphorylation of Tie-2. Elevated levels of Ang-2 have been found to be associated with inflammatory diseases, *inter alia*, sepsis, lupus, inflammatory bowel disease and metastatic diseases such as cancer.

[00099] During periods of high Ang-2 levels, fissures or breaks in the endothelium form which results in vascular leak syndrome. Vascular leak syndrome results in life-threatening effects such as tissue and pulmonary edema. For many disease states elevated Ang-2 levels are clear markers that a disease state or condition exists. Once a disease state has been resolved, the Ang-1/Ang-2 balance returns and the vascular endothelium is stabilized. In conditions wherein the normal balance between Ang-1 and Ang-2 has been disrupted, the disclosed agents have been found to amplify Tie-2 signaling by inhibiting dephosphorylation of phosphorylated Tie-2 via inhibition of Human Protein Tyrosine Phosphatase- β (HPTP- β). In addition, the disclosed agents can be used in varying amounts to increase the Tie-2 signaling in a very controlled manner, and to therefore titrate the level of Tie-2 amplification.

[000100] The present disclosure provides methods for treating a patient having vascular leak syndrome comprising administering to the patient a composition comprising effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof. The compositions of the present disclosure may also comprise one or more pharmaceutically acceptable excipients.

[000101] Disclosed herein, are compositions comprising an HPTP β -ECD binding agent wherein the compositions are useful for treatment of the disclosed conditions, illness, injuries, courses of treatment, cellular treatments and the like.

[000102] In one embodiment, the method comprises treating vascular leak in a patient wherein the patient suffers from an inflammatory disease or condition which comprises administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Another embodiment is a method of treating a patient suffering from a physical trauma comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. In a particular embodiment the trauma is surgical trauma. In one embodiment the method is a method of treating a patient suffering from shock comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent.

[000103] Particular embodiments include post-hemorrhagic shock, or post-traumatic shock or septic shock. The present disclosure also provides for a method of treating a patient suffering from adult respiratory distress syndrome by administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Another embodiment is a method of treating a patient with an acute lung injury comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Cancer metastasis and bacterial and viral infections are covered below.

[000104] In some embodiments an HPTP β -ECD binding agent is administered prophylactically to stabilize the patient's vasculature prior to an event that places the patient at risk for vascular leak. In one embodiment the HPTP β -ECD binding agent is administered prophylactically to stabilize the patient's vasculature prior to surgery. Still another embodiment is a method of preventing vascular leak syndrome in a patient wherein an effective amount of an HPTP β -ECD binding agent is administered to the patient prior to undergoing chemotherapy. Another embodiment is a method of treating a patient at risk of shock comprising administering to the patient an effective amount of an HPTP β -ECD binding agent.

[000105] The disclosed HPTP β -ECD binding agents can be used to prevent, abate, minimize, control, and/or lessen tumor metastasis in humans and animals. The disclosed HPTP β -ECD binding agents can also be used to slow the rate of primary tumor growth. As such, the agents disclosed herein can be administered as part of a combination therapy with one or more drugs or

other pharmaceutical agents. When used as part of the combination therapy, the decrease in metastasis and reduction in primary tumor growth afforded by the disclosed agents allows for a more effective and efficient use of any pharmaceutical or drug therapy being used to treat the patient. In addition, control of metastasis by the disclosed agent affords the subject a greater ability to concentrate the disease in one location.

[000106] Thus, one embodiment of the present disclosure is a method of treating cancer in a patient comprising administering a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof. Another embodiment is a method of preventing metastasis in a patient suffering from cancer comprising administering a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof. Yet another embodiment is a method of minimizing tumor metastasis in a patient suffering from cancer comprising administering a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof. Disclosed herein are methods for preventing metastasis of malignant tumors or to reduce the rate of tumor growth. Thus, another embodiment is a method of treating a patient diagnosed with a malignant tumor comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof. Another embodiment is a method of preventing metastasis in a patient diagnosed with a malignant tumor comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof. Yet another embodiment is a method of reducing the rate of tumor growth in a patient diagnosed with a tumor comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent or a pharmaceutically acceptable salt thereof.

[000107] The following are non-limiting examples of cancers that can be treated by the disclosed methods and compositions: leukemia, for example, chronic myelogenous leukemia; acute lymphoblastic leukemia, acute childhood myeloid leukemia; adult acute myeloid leukemia, hairy cell leukemia; lymphoma, for example, Burkitt's lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous t-cell lymphoma, central nervous system lymphoma; astrocytomas, for example, cerebellar astrocytoma, childhood astrocytoma, pilocytic astrocytoma, diffuse astrocytoma, anaplastic astrocytoma, gliomas, oligodendroglioma, cerebral astrocytoma visual pathway glioma and hypothalamic glioma, brain stem glioma, visual pathway,

hypothalamic glioma, cerebral astrocytoma/malignant glioma; carcinoma, for example, thymoma carcinoma, thymic carcinoma, squamous cell carcinoma, skin carcinoma, Merkel cell carcinoma, adrenocortical carcinoma, basal cell carcinoma; sarcoma, for example, rhabdomyosarcoma sarcoma, Ewing sarcoma, Kaposi sarcoma, soft tissue sarcoma, uterine sarcoma, osteosarcoma, malignant fibrous histiocytoma of the bone; appendix cancer; extrahepatic bile duct cancer; bladder cancer; bone cancer; salivary gland cancer; brain tumor; childhood central nervous system atypical teratoid/rhabdoid tumor; central nervous system embryonal tumors; craniopharyngioma; ependymoblastoma; ependymoma; medulloblastoma; medulloepithelioma; pineal parenchymal tumors of intermediate differentiation; supratentorial primitive neuroectodermal tumors and pineoblastoma; brain and spinal cord tumors; breast cancer; bronchial tumors; carcinoid tumor; gastrointestinal carcinoid tumor; central nervous system embryonal tumors; cervical cancer; chordoma, childhood; chronic myeloproliferative disorders; colon cancer; colorectal cancer; craniopharyngioma; extragonadal germ cell tumor; testicular germ cell tumor; retinoblastoma; gallbladder cancer; gastric (stomach) cancer; gastrointestinal carcinoid tumor; gastrointestinal stromal tumor (gist); extracranial germ cell tumor; gestational trophoblastic tumor; glioblastoma; head and neck cancer; hepatocellular (liver) cancer; Langerhans cell histiocytosis; hypopharyngeal cancer; islet cell tumors; kidney (renal cell) cancer; laryngeal cancer; lip and oral cavity cancer; liver cancer; non-small cell lung cancer; small-cell lung cancer; mesothelioma; metastatic squamous neck cancer with occult primary; mouth cancer; childhood multiple endocrine neoplasia syndrome; multiple myeloma/plasma cell neoplasm; mycosis fungoides; myelodysplastic syndromes; multiple myeloma; myeloproliferative disorders, chronic; nasal cavity and paranasal sinus cancer; neuroblastoma; oral cancer; oropharyngeal cancer; ovarian cancer, for example, ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor; pancreatic cancer; islet cell tumors; papillomatosis; thyroid cancer; parathyroid cancer; penile cancer; esophageal cancer; pharyngeal cancer; nasopharyngeal cancer; pheochromocytoma; pineal parenchymal tumors; pituitary tumor; plasma cell neoplasm/multiple myeloma; pleuropulmonary blastoma; prostate cancer; rectal cancer; renal cell (kidney) cancer; renal pelvis and ureter cancer; Sézary syndrome; skin cancer (nonmelanoma); skin cancer (melanoma); intraocular melanoma; malignant melanoma, small intestine cancer; metastatic squamous neck cancer; stomach (gastric) cancer; testicular cancer; throat cancer; transitional cell cancer of the renal pelvis and ureter; gestational trophoblastic tumor; urethral cancer; uterine cancer, endometrial; vaginal cancer; vulvar cancer; Waldenström macroglobulinemia; and Wilms tumor.

[000108] The HPTP β -ECD binding agents can be administered in combination with one or more chemotherapeutic agent.

[000109] A “chemotherapeutic agent” or “chemotherapeutic compound” is a chemical compound useful in the treatment of cancer. Chemotherapeutic cancer agents that can be used in combination with an HPTP β -ECD binding agent disclosed herein, include but are not limited to, mitotic inhibitors (vinca alkaloids). These include vincristine, vinblastine, vindesine and NavelbineTM (vinorelbine-5'-noranhydroblastine). In yet other embodiments, chemotherapeutic cancer agents include topoisomerase I inhibitors, such as camptothecin compounds. As used herein, “camptothecin compounds” include CamptosarTM (irinotecan HCL), HycamtinTM (topotecan HCL) and other compounds derived from camptothecin and its analogues. Another category of chemotherapeutic cancer agents that may be used in the methods and compositions of the present disclosure are podophyllotoxin derivatives, such as etoposide, teniposide and mitopodozide. The present disclosure further encompasses other chemotherapeutic cancer agents known as alkylating agents, which alkylate the genetic material in tumor cells. These include without limitation cisplatin, cyclophosphamide, nitrogen mustard, trimethylene thiophosphoramidate, carmustine, busulfan, chlorambucil, belustine, uracil mustard, chlormaphazin and dacarbazine. The present disclosure encompasses antimetabolites as chemotherapeutic agents. Examples of these types of agents include cytosine arabinoside, fluorouracil, methotrexate, mercaptopurine, azathioprine and procarbazine. An additional category of chemotherapeutic cancer agents that may be used in the methods and compositions of the present disclosure include antibiotics. Examples include without limitation doxorubicin, bleomycin, dactinomycin, daunorubicin, mithramycin, mitomycin, mytomycin C and daunomycin. There are numerous liposomal formulations commercially available for these compounds. The present disclosure further encompasses other chemotherapeutic cancer agents including without limitation anti-tumor antibodies, dacarbazine, azacytidine, amsacrine, melphalan, VM-26, ifosfamide, taxol and its derivatives, L-asparaginase, mitoxantrone, IF-2, gemcitabine, erlotinib, doxil, irinotecan and bevacizumab.

[000110] Other anti-cancer agents that can be used in combination with the disclosed HPTP β -ECD binding agent include, but are not limited to: acivicin, aclarubicin, acodazole hydrochloride, acronine, adozelesin, aldesleukin, altretamine, ambomycin, ametantrone acetate, aminoglutethimide, anastrozole, anthramycin, asperlin, azacitidine, azetepa, azotomycin, batimastat, benzodepa, bicalutamide, bisantrene hydrochloride, bisnafide dimesylate, bizelesin,

bleomycin sulfate, brequinar sodium, broprimine, cactinomycin, calusterone, caracemide, carbetimer, carboplatin, carubicin hydrochloride, carzelesin, cedefingol, cirolemycin, cladribine, crisnatol mesylate, cytarabine, daunorubicin hydrochloride, decitabine, dexormaplatin, dezaguanine, dezaguanine mesylate, diaziquone, docetaxel, doxorubicin hydrochloride, droloxifene, droloxifene citrate, dromostanolone propionate, duazomycin, edatrexate, eflornithine hydrochloride, elsamitrucin, enloplatin, enpromate, epipropidine, epirubicin hydrochloride, erbulozole, esorubicin hydrochloride, estramustine, estramustine phosphate sodium, etanidazole, etoposide phosphate, etoprine, fadrozole hydrochloride, fazarabine, fenretinide, floxuridine, fludarabine phosphate, flurocitabine, fosquidone, fostriecin sodium, gemcitabine hydrochloride, hydroxyurea, idarubicin hydrochloride, ilmofofosine, interleukin 2 (including recombinant interleukin 2, or rIL2), interferon alfa-2a, interferon alfa-2b, interferon alfa-n1, interferon alfa-n3, interferon beta-1a, interferon gamma-1b, iproplatin, irinotecan hydrochloride, lanreotide acetate, letrozole, leuprolide acetate, liarozole hydrochloride, lometrexol sodium, lomustine, losoxantrone hydrochloride, masoprocol, maytansine, mechlorethamine hydrochloride, megestrol acetate, melengestrol acetate, menogaril, methotrexate sodium, metoprine, meturedopa, mitindomide, mitocarcin, mitocromin, mitogillin, mitomalcin, mitosper, mitotane, mitoxantrone hydrochloride, mycophenolic acid, nocodazole, nogalamycin, ormaplatin, oxisuran, paclitaxel, pegaspargase, peliomycin, pentamustine, peplomycin sulfate, perfosfamide, pipobroman, pipsulfan, piroxantrone hydrochloride, plicamycin, plomestane, porfimer sodium, porfiromycin, prednimustine, procarbazine hydrochloride, puromycin, puromycin hydrochloride, pyrazofurin, riboprine, rogletimide, safinol, safinol hydrochloride, semustine, simtrazene, sparfosate sodium, sparsomycin, spirogermanium hydrochloride, spiromustine, spiroplatin, streptonigrin, streptozocin, sulofenur, talisomycin, tecogalan sodium, tegafur, teloxantrone hydrochloride, temoporfin, teroxirone, testolactone, thiamiprine, thioguanine, thiotepa, tiazofurin, tirapazamine, toremifene citrate, trestolone acetate, triciribine phosphate, trimetrexate, trimetrexate glucuronate, triptorelin, tubulozole hydrochloride, uredepa, vaporeotide, verteporfin, vinblastine sulfate, vincristine sulfate, vindesine sulfate, vinepidine sulfate, vinglycinat sulfate, vinleurosine sulfate, vinorelbine tartrate, vinrosidine sulfate, vinzolidine sulfate, vorozole, zeniplatin, zinostatin, zorubicin hydrochloride. Other anti-cancer drugs include, but are not limited to: 20-epi-1,25 dihydroxyvitamin D3, 5-ethynyluracil, abiraterone, aclarubicin, acylfulvene, adecypenol, adozelesin, aldesleukin, ALL-TK antagonists, altretamine, ambamustine, amidox, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, andrographolide, angiogenesis inhibitors, antagonist D, antagonist G, antarelix, anti-dorsalizing morphogenetic

protein-1, antiandrogen, prostatic carcinoma, antiestrogen, antineoplaston, aphidicolin glycinate, apoptosis gene modulators, apoptosis regulators, apurinic acid, ara-CDP-DL-PTBA, arginine deaminase, asulacrine, atamestane, atrimustine, axinastatin 1, axinastatin 2, axinastatin 3, azasetron, azatoxin, azatyrosine, baccatin III derivatives, balanol, batimastat, BCR/ABL antagonists, benzochlorins, benzoylstauroporine, beta lactam derivatives, beta-alethine, betaclamycin B, betulinic acid, bFGF inhibitor, bicalutamide, bisantrene, bisaziridinylspermine, bisnafide, bistratene A, bizelesin, breflate, bropirimine, budotitane, buthionine sulfoximine, calcipotriol, calphostin C, canarypox IL-2, capecitabine, carboxamide-amino-triazole, carboxyamidotriazole, CaRest M3, CARN 700, cartilage derived inhibitor, carzelesin, casein kinase inhibitors (ICOS), castanospermine, cecropin B, cetorelix, chlorlins, chloroquinoxaline sulfonamide, cicaprost, cis-porphyrin, cladribine, clomifene analogues, clotrimazole, collismycin A, collismycin B, combretastatin A4, combretastatin analogue, conagenin, crambescidin 816, crisnatol, cryptophycin 8, cryptophycin A derivatives, curacin A, cyclopentantraquinones, cycloplatan, cypemycin, cytarabine ocfosfate, cytolytic factor, cytostatin, dacliciximab, decitabine, dehydroidemnin B, deslorelin, dexamethasone, dexifosfamide, dexrazoxane, dexverapamil, diaziqune, didemnin B, didox, diethylnorspermine, dihydro-5-azacytidine, dihydrotaxol, 9-, dioxamycin, diphenyl spiromustine, docetaxel, docosanol, dolasetron, doxifluridine, droloxifene, dronabinol, duocarmycin SA, ebselen, ecomustine, edelfosine, edrecolomab, eflornithine, elemene, emitefur, epirubicin, epristeride, estramustine analogue, estrogen agonists, estrogen antagonists, etanidazole, etoposide phosphate, exemestane, fadrozole, fazarabine, fenretinide, filgrastim, finasteride, flavopiridol, flezelastine, fluasterone, fludarabine, fluorodaunorubicin hydrochloride, forfenimex, formestane, fostriecin, fotemustine, gadolinium texaphyrin, gallium nitrate, galocitabine, ganirelix, gelatinase inhibitors, gemcitabine, glutathione inhibitors, hepsulfam, heregulin, hexamethylene bisacetamide, hypericin, ibandronic acid, idarubicin, idoxifene, idramantone, ilmofofine, ilomastat, imidazoacridones, imiquimod, immunostimulant peptides, insulin-like growth factor-1 receptor inhibitor, interferon agonists, iobenguane, iododoxorubicin, ipomeanol, 4-, iroplact, irsogladine, isobengazole, isohomohalicondrin B, itasetron, jasplakinolide, kahalalide F, lamellarin-N triacetate, lanreotide, leinamycin, lenograstim, lentinan sulfate, leptolstatin, letrozole, leukemia inhibiting factor, leukocyte alpha interferon, leuprolide+estrogen+progesterone, leuprorelin, levamisole, liarazole, linear polyamine analogue, lipophilic disaccharide peptide, lipophilic platinum compounds, lissoclinamide 7, lobaplatin, lombricine, lometrexol, lonidamine, losoxantrone, lovastatin, loxoribine, lurtotecan, lutetium texaphyrin, lysofylline, lytic peptides, maitansine, mannostatin A,

marimastat, masoprocol, maspin, matrilysin inhibitors, matrix metalloproteinase inhibitors, menogaril, merbarone, meterelin, methioninase, metoclopramide, MIF inhibitor, mifepristone, miltefosine, mirimostim, mismatched double stranded RNA, mitoguazone, mitolactol, mitomycin analogues, mitonafide, mitotoxin fibroblast growth factor-saporin, mofarotene, molgramostim, monoclonal antibody, human chorionic gonadotrophin, monophosphoryl lipid A+myobacterium cell wall sk, mopidamol, multiple drug resistance gene inhibitor, multiple tumor suppressor 1-based therapy, mustard anticancer agent, mycaperoxide B, mycobacterial cell wall extract, myriaporone, N-acetyldinaline, N-substituted benzamides, nafarelin, nagrestip, naloxone+pentazocine, napavin, naphterpin, nartograstim, nedaplatin, nemorubicin, neridronic acid, neutral endopeptidase, nilutamide, nisamycin, nitric oxide modulators, nitroxide antioxidant, nitrullyn, O6-benzylguanine, octreotide, okicenone, oligonucleotides, onapristone, ondansetron, ondansetron, oracin, oral cytokine inducer, ormaplatin, osaterone, oxaliplatin, oxaunomycin, paclitaxel, paclitaxel analogues, paclitaxel derivatives, palauamine, palmitoylrhizoxin, pamidronic acid, panaxytriol, panomifene, parabactin, pazelliptine, pegaspargase, peldesine, pentosan polysulfate sodium, pentostatin, pentozole, perflubron, perfosamide, perillyl alcohol, phenazinomycin, phenylacetate, phosphatase inhibitors, picibanil, pilocarpine hydrochloride, pirarubicin, piritrexim, placetin A, placetin B, plasminogen activator inhibitor, platinum complex, platinum compounds, platinum-triamine complex, porfimer sodium, porfiromycin, prednisone, propyl bis-acridone, prostaglandin J2, proteasome inhibitors, protein A-based immune modulator, protein kinase C inhibitor, protein kinase C inhibitors, microalgal, protein tyrosine phosphatase inhibitors, purine nucleoside phosphorylase inhibitors, purpurins, pyrazoloacridine, pyridoxylated hemoglobin polyoxyethylene conjugate, raf antagonists, raltitrexed, ramosetron, ras farnesyl protein transferase inhibitors, ras inhibitors, ras-GAP inhibitor, retelliptine demethylated, rhenium Re 186 etidronate, rhizoxin, ribozymes, RII retinamide, rogletimide, rohitukine, romurtide, roquinimex, rubiginone B1, ruboxyl, safingol, saintopin, SarCNU, sarcophytol A, sargramostim, Sdi 1 mimetics, semustine, senescence derived inhibitor 1, sense oligonucleotides, signal transduction inhibitors, signal transduction modulators, single chain antigen binding protein, sizofiran, sobuzoxane, sodium borocaptate, sodium phenylacetate, solverol, somatomedin binding protein, sonermin, sparfosic acid, spicamycin D, spiromustine, splenopentin, spongistatin 1, squalamine, stem cell inhibitor, stem-cell division inhibitors, stipiamide, stromelysin inhibitors, sulfinosine, superactive vasoactive intestinal peptide antagonist, suradista, suramin, swainsonine, synthetic glycosaminoglycans, tallimustine, tamoxifen methiodide, tauromustine, tazarotene, tecogalan sodium, tegafur, tellurapyrylium,

telomerase inhibitors, temoporfin, temozolomide, tetrachlorodecaoxide, tetrazomine, thaliblastine, thiocoraline, thrombopoietin, thrombopoietin mimetic, thymalfasin, thymopoietin receptor agonist, thymotrinan, thyroid stimulating hormone, tin ethyl etiopurpurin, tirapazamine, titanocene bichloride, topsentin, toremifene, totipotent stem cell factor, translation inhibitors, tretinoin, triacetyluridine, tricyriline, trimetrexate, triptorelin, tropisetron, turosteride, tyrosine kinase inhibitors, tyrphostins, UBC inhibitors, ubenimex, urogenital sinus-derived growth inhibitory factor, urokinase receptor antagonists, vapreotide, variolin B, vector system, erythrocyte gene therapy, velaresol, veramine, verdins, verteporfin, vinxaltine, vitaxin, vorozole, zanoterone, zeniplatin, zilascorb, and zinostatin stimalamer. In one embodiment, the anti-cancer drug is 5-fluorouracil or leucovorin.

[000111] Anti-angiogenic agents are also useful in the treatment of cancer. Anti-angiogenic agents are well known to those of skill in the art. Suitable anti-angiogenic agents for use in the methods and compositions of the present disclosure include anti-VEGF antibodies, including humanized and chimeric antibodies, anti-VEGF aptamers and antisense oligonucleotides. Other known inhibitors of angiogenesis include angiostatin, endostatin, interferons, interleukin 1 (including α and β) interleukin 12, retinoic acid, and tissue inhibitors of metalloproteinase-1 and metalloproteinase-2. (TIMP-1 and -2). Small molecules, including topoisomerases such as razoxane, a topoisomerase II inhibitor with anti-angiogenic activity, can also be used.

[000112] One embodiment of the disclosure is a method for treating a patient diagnosed with a carcinoma, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Yet another embodiment is a method for treating a patient diagnosed with a carcinoma, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent in combination with an effective amount of a chemotherapeutic agent, wherein the HPTP β -ECD binding agent and chemotherapeutic agent are administered together or in any order.

[000113] One embodiment of the disclosure is a method for preventing or reducing metastasis in a patient diagnosed with a carcinoma, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Yet another embodiment is a method for preventing or reducing metastasis in a patient diagnosed with a carcinoma, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent in combination with an effective amount of a chemotherapeutic

agent, wherein the HPTP β -ECD binding agent and chemotherapeutic agent are administered together or in any order.

[000114] In yet another embodiment of the disclosure is a method for treating a patient diagnosed with a sarcoma, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Yet another embodiment is a method for treating a patient diagnosed with a sarcoma, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent in combination with an effective amount of a chemotherapeutic agent, wherein the HPTP β -ECD binding agent and the chemotherapeutic agent are administered together or in any order.

[000115] Yet another embodiment of the disclosure is a method for preventing or reducing metastasis in a patient diagnosed with a sarcoma, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Yet another embodiment is a method for preventing or reducing metastasis in a patient diagnosed with a sarcoma, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent in combination with an effective amount of one or more chemotherapeutic agent, wherein the HPTP β -ECD binding agent and one or more chemotherapeutic agent are administered together or in any order.

[000116] Yet another embodiment of the disclosure is a method for treating a patient diagnosed with pancreatic cancer, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Still another embodiment is a method for treating a patient diagnosed with pancreatic cancer, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent in combination with an effective amount of one or more chemotherapeutic agents, wherein the HPTP β -ECD binding agent and one or more chemotherapeutic agents are administered together or in any order.

[000117] Yet another embodiment of the disclosure is a method for preventing or reducing metastasis in a patient diagnosed with pancreatic cancer, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Still another embodiment is a method for preventing or reducing metastasis in a patient diagnosed with pancreatic cancer, comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent in combination with an effective amount of one or

more chemotherapeutic agent, wherein the HTPP β -ECD binding agent and one or more chemotherapeutic agents are administered together or in any order.

[000118] In some embodiments the chemotherapeutic agent used in the treatment of pancreatic cancer is gemcitabine, or 5-fluorouracil, or cisplatin or capecitabine, or oxaliplatin, or mitomycin, or any combination thereof.

[000119] Still another embodiment is a method for treating a patient diagnosed with malignant melanoma, comprising administering to the patient a composition comprising an effective amount of an HTPP β -ECD binding agent. Yet another embodiment is a method for treating a patient diagnosed with metastatic melanoma, comprising administering to the patient a composition comprising an effective amount of an HTPP β -ECD binding agent in combination with an effective amount of one or more chemotherapeutic agent, wherein the HTPP β -ECD binding agent and one or more chemotherapeutic agents are administered together or in any order.

[000120] Still another embodiment is a method for preventing or reducing metastasis in a patient diagnosed with malignant melanoma, comprising administering to the patient a composition comprising an effective amount of an HTPP β -ECD binding agent. Yet another embodiment is a method for preventing or reducing metastasis in a patient diagnosed with metastatic melanoma, comprising administering to the patient a composition comprising an effective amount of an HTPP β -ECD binding agent in combination with an effective amount of one or more chemotherapeutic agent, wherein the HTPP β -ECD binding agent and one or more chemotherapeutic agents are administered together or in any order.

[000121] In some embodiments the chemotherapeutic agent is used to treat melanoma is cisplatin, or vinblastine, or dacarbazine, or any combination thereof.

[000122] Still another embodiment is a method for treating a patient diagnosed with breast cancer comprising administering to the patient a composition comprising an effective amount of an HTPP β -ECD binding agent. Yet another embodiment is a method for treating a patient diagnosed with breast cancer comprising administering to the patient a composition comprising an effective amount of an HTPP β -ECD binding agent in combination with an effective amount of one or more chemotherapeutic agent, wherein the HTPP β -ECD binding agent and one or more chemotherapeutic agents are administered together or in any order. Yet another embodiment is a

method for preventing or reducing metastasis in a patient diagnosed with breast cancer comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Yet another embodiment is a method for preventing or reducing metastasis in a patient diagnosed with breast cancer comprising administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent in combination with an effective amount of one or more chemotherapeutic agent, wherein the HPTP β -ECD binding agent and one or more chemotherapeutic agent are administered together or in any order. In some embodiments the chemotherapeutic agent is used in the treatment of breast cancer is taxol or an analog of taxol.

[000123] In particular embodiments the HPTP β -ECD binding agent is administered in combination with IL-2.

IL-2 Induced Vascular Leak: Treatment of Metastatic Cancers

[000124] Immunotherapy is one method of treating cancer. Up-regulation of the body's own immune system is one aspect of immunotherapy. Among the many immune system signaling molecules is interleukin-2 (IL-2) which is instrumental in the body's natural response to microbial infection and in discriminating between foreign (non-self) and self. High-dose interleukin-2 is an FDA approved treatment for patients with metastatic renal cell carcinoma and metastatic melanoma. Although it has been reported that only 23% of those subjects given this therapy show a tumor response, the duration of this response can exceed 10 years (Elias L. et al., "A literature analysis of prognostic factors for response and quality of response of patients with renal cell carcinoma to interleukin-2-based therapy." *Oncology*, (2001), Vol. 61, pp. 91-101). As such, IL-2 therapy is the only available treatment that offers the potential for cure.

[000125] Gallagher (Gallagher, D.C. et al., "Angiopoietin 2 Is a Potential Mediator of High-Dose Interleukin 2-Induced Vascular Leak" *Clin. Cancer Res.*, (2007), Vol. 13, No. 7, pp. 2115-2120) reports that elevated levels of angiopoietin-2 are found in patients treated with high doses of IL-2 and suggests that overcoming Ang-2 blockade of Tie-2 signaling might be curative for vascular leak syndrome which is a side effect of this therapy.

[000126] IL-2 is known to cause endothelial cell activation, however, with loss of proper barrier function. Amplification of Tie-2 signaling during high dose IL-2 immunotherapy would lead to attenuation of vascular leakage since Tie-2 stimulation promotes endothelial cell stability.

As such, by administering an agent that can amplify Tie-2 signaling, vascular stability can be increased and, hence, the side effects of high IL-2 dosing mitigated. The disclosed HPTP β -ECD binding agents can amplify Tie-2 signaling under the conditions of low angiopoietin-1 concentrations or when high concentrations of angiopoietin-2 are present as in IL-2 treated patients.

[000127] By amplifying Tie-2 signaling without affecting Ang-2 levels, the use of elevated levels of Ang-2 as a potential pathology marker is retained. For example, a patient suffering from an inflammatory disease such as sepsis will normally have an elevated Ang-2 level that acts to suppress Ang-1 stimulation of Tie-2. This elevated Ang-2 results in edema which is a symptom of vascular leakage. The present methods, by amplifying Tie-2 signaling without affecting the Ang-2 level, provide a method for alleviating the symptoms that are associated with vascular leak while retaining the ability to use Ang-2 levels as a measure of disease progress and resolution.

[000128] As many as 65% of patients receiving this IL-2 therapy will necessarily interrupt or discontinue treatment due to VLS. The major dose-limiting toxicity of interleukin-2 (IL-2) and of immunotoxin (IT) therapies is vascular leak syndrome (VLS). VLS is characterized by an increase in vascular permeability accompanied by extravasation of fluids and proteins resulting in interstitial edema and organ failure. Manifestations of VLS include fluid retention, hypotension, increase in body weight, peripheral edema, pulmonary edema, pleural and pericardial effusions, ascites, anasarca and, in severe form, signs of pulmonary and cardiovascular failure.

[000129] The disclosed HPTP β -ECD binding agents can be used as an effective therapy to reduce vascular leak caused by treatment with IL-2. Therefore an embodiment of the present invention is a method of treating, reducing or preventing vascular leak in a patient being administered IL-2 wherein the method comprises administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. The HPTP β -ECD binding agent can be co-administered with IL-2 or administered separately. The IL-2 and the HPTP β -ECD binding agent may be administered in any order and by any method, for example, intravenously, orally, by patch, subcutaneous injection and the like.

[000130] One embodiment of the present disclosure is a method for treating renal cell carcinoma comprising administering to a patient a composition comprising: a) an effective amount of interleukin-2 such that an immune response is provided; and b) an effective amount of

an HPTP β -ECD binding agent; wherein the interleukin-2 and the HPTP β -ECD binding agent can be administered together or in any order. Another embodiment disclosed herein is a method for treating renal cell carcinoma comprising administering to a patient a composition comprising: a) a high dose of interleukin-2; and b) an effective amount of an HPTP β -ECD binding agent.

[000131] Further disclosed is a method for treating metastatic melanoma comprising administering to a patient a series of compositions, wherein the compositions can be administered in any order and at any effective amount, a first composition comprising, a high dose of interleukin-2 and the second composition comprising an effective amount of an HPTP β -ECD binding agent.

[000132] Still further disclosed is a method for treating renal cell carcinoma comprising administering to a patient a series of compositions, wherein the compositions can be administered in any order and at any effective amount, a first composition comprising a high dose of interleukin-2 and the second composition comprising an effective amount of an HPTP β -ECD binding agent.

[000133] Disclosed herein is a method for treating metastatic melanoma by administering to a patient in need of treatment a therapy that comprises: a) an effective amount of interleukin-2 such that an immune response is provided; and b) an effective amount of an HPTP β -ECD binding agent; wherein the interleukin-2 and the HPTP β -ECD binding agent can be administered together or in any order.

[000134] Also disclosed herein is a method for treating metastatic melanoma by administering to a patient in need of treatment a therapy that comprises: a) an effective amount of interleukin-2 such that an immune response is provided; and b) an effective amount of an HPTP β -ECD binding agent; wherein the interleukin-2 and the HPTP β -ECD binding agent can be administered together or in any order.

[000135] Disclosed herein are compositions which can be used to treat patients with cancer, wherein the patient having cancer is treated with one or more cancer agents that induce vascular leak syndrome in the patient. As such, disclosed herein are compositions effective in reducing vascular leak resulting from a cancer treatment, the compositions comprising an effective amount of an HPTP β -ECD binding agent.

[000136] Another aspect disclosed herein are compositions effective for treating humans or other mammals having a medical condition or disease state wherein the treatment for the medical condition or disease state induces vascular leak syndrome, the composition comprising: a) an effective amount of an HPTP β -ECD binding agent; and b) one or more pharmaceutical drugs; wherein at least one of the pharmaceutical drugs induces vascular leak syndrome.

[000137] In a further aspect, disclosed herein are compositions comprising: a) an effective amount of an HPTP β -ECD binding agent; and b) one or more chemotherapeutic agent.

[000138] Also disclosed herein are compositions which can be used to control vascular leakage, the compositions comprising an effective amount of one or more of the agents disclosed herein. Still further disclosed herein are compositions which can be used to treat patients with an inflammatory disease, non-limiting examples of which include sepsis, lupus, and inflammatory bowel disease, the compositions comprising an effective amount of an HPTP β -ECD binding agents disclosed herein. The HPTP β -ECD binding agents inhibit the Tie2 dephosphorylase activity of HPTP β acting as Tie-2 signaling amplifiers.

[000139] Tumor growth is often a multi-step process that starts with the loss of control of cell proliferation. The cancerous cell then begins to divide rapidly, resulting in a microscopically small, spheroid tumor: an *in situ* carcinoma. As the tumor mass grows, the cells will find themselves further and further away from the nearest capillary. Finally the tumor stops growing and reaches a steady state, in which the number of proliferating cells counterbalances the number of dying cells. The restriction in size is caused by the lack of nutrients and oxygen. In tissues, the oxygen diffusion limit corresponds to a distance of 100 μ m between the capillary and the cells, which is in the range of 3-5 lines of cells around a single vessel. *In situ* carcinomas may remain dormant and undetected for many years and metastasis are rarely associated with these small (2 to 3 mm²), avascular tumors.

[000140] When a tumor's growth is stopped due to a lack of nutrients and/or oxygen, this reduction in tumor vasculature also limits the ability of anti-tumor drugs to be delivered to the malignant cells. Moreover, if there is a slight increase in tumor vasculature, this will allow delivery of anti-tumor therapies to the malignant cells without initiating metastasis. As such, the disclosed agents when used to slightly amplify Tie-2 signaling can be used to increase blood flow to the tumor cells without setting off metastasis or uncontrolled tumor cell proliferation while providing a method for delivering anti-cancer drugs to malignant cells.

[000141] Disclosed herein, is a method for treating cancer comprising administering to a patient in need an effective amount of an HPTP β -ECD binding agent in conjunction with one or more chemotherapeutic compound or immunotherapeutic compound. To “slightly amplify Tie-2 signaling” means that a sufficient amount of a disclosed compound is administered to a patient such that the amount of tumor cell vasculature is increased such that the increased circulation allows for delivery of the anti-tumor compound or therapy without instigating tumor growth wherein the rate of tumor cell growth is less than the rate of tumor cell death. It is recognized that amplifying Tie2 signaling would stabilize the tumor vasculature making it resistant to angiogenic signals reducing tumor angiogenesis and tumor growth while improving tumor blood flow and the delivery of chemotherapeutic agents.

[000142] Angiopoietin-2 is significantly correlated to Gleason Score, metastasis and to cancer specific survival (Lind A.J. et al., “Angiopoietin-2 expression is related to histological grade, vascular density, metastasis and outcome in prostate cancer” Prostate, (2005), Vol. 62, pp. 394-299). Angiopoietin-2 was found to be expressed in prostate cancer bone, liver and lymph node metastasis, but with little to no angiopoietin-1 expression in prostate cancer tumor cells in bone, liver and lymph nodes (Morrissey C. et al., “Differential expression of angiogenesis associated genes in prostate cancer bone, live and lymph node metastasis” Clin. Exp. Metastasis, (2008), Vol. 25, pp. 377-388). As such, monitoring the level of Ang-2 provides a method for evaluating the presence of prostate cancer and the spread of prostate cancer cells throughout the body due to vascular leakage.

[000143] Thus, another embodiment of the disclosure is a method of evaluating efficacy of treatment comprising monitoring the Ang-2 level of the patient while the patient is undergoing treatment.

Vasculature Stabilization in Diseases Caused by Pathogens

[000144] Disclosed herein is a method for preventing or treating vascular leak syndrome caused by one or more pathogens, comprising administering to a human or other mammal in need of treatment an effective amount of one or more HPTP β -ECD binding agent.

[000145] One embodiment is a method for treating vascular leak syndrome caused by one or more pathogens, comprising administering to a human or other mammal in need of treatment a composition comprising: a) an effective amount of one or more compounds effective against a

pathogen present in the human or mammal; and b) an effective amount of an HPTP β -ECD binding agent; wherein the one or more compounds effective against a pathogen and the HPTP β -ECD binding agent can be administered together or in any order.

[000146] Further disclosed is a method for preventing vascular leak syndrome in a human or other mammal diagnosed with a pathogen infection that can produce vascular leak syndrome in a human or mammal, comprising administering to a human or mammal a composition comprising: a) an effective amount of one or more compounds effective against a pathogen present in the human or mammal; and b) an effective amount of one or more HPTP β -ECD binding agent; wherein the one or more compounds effective against a pathogen and the one or more HPTP β -ECD binding agent can be administered together or in any order.

[000147] The following are non-limiting examples of viruses, bacteria and other pathogens where virulence can be controlled by mitigating the degree of vascular leak that is induced by the organism. *Staphylococcus aureus*, *Bacillus anthracis*, *Pseudomonas*, *Streptococcus pyogenes*, and dengue virus.

[000148] One embodiment is a method for treating vascular leak syndrome in a patient suffering from a bacterial infection by administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Further disclosed is a method for preventing vascular leak syndrome in a human or other mammal diagnosed with a bacterial infection.

[000149] Thus one embodiment of the present disclosure is a method of treating a patient suffering from a bacterial infection by administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. In particular embodiments the bacterial infection is a *Bacillus anthracis* infection. In other embodiments the bacterial infection is a *Pseudomonas* infection. In yet other embodiments the bacterial infection is a *Streptococcus pyogenes* infection.

[000150] One embodiment is a method for treating vascular leak syndrome in a patient suffering from a viral infection by administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. Further disclosed is a method for preventing vascular leak syndrome in a human or other mammal diagnosed with a viral infection.

[000151] Another embodiment is a method of treating a patient suffering from a viral infection by administering to the patient a composition comprising an effective amount of an HPTP β -ECD binding agent. In particular embodiments the viral infection is a dengue virus infection.

[000152] The HPTP β -ECD binding agent may be administered in combination with one or more antibacterial or antiviral agent wherein the HPTP β -ECD binding agent and the antiviral or antibacterial agents can be administered together or in any order. Thus, an embodiment of the present disclosure is a method of treating a patient suffering from a bacterial infection comprising administering: a) an HPTP β -ECD binding agent; and b) one or more antibacterial agents, wherein the HPTP β -ECD binding agent and antibacterial agent can be administered together or in any order. Another embodiment of the present disclosure is a method of treating a patient suffering from a viral infection comprising administering: a) an HPTP β -ECD binding agent; and b) one or more antiviral agents wherein the HPTP β -ECD binding agent and antiviral agent can be administered together or in any order.

[000153] Another method provided by the present disclosure, is a method for determining the course of treatment for a patient suffering from vascular leak syndrome, comprising:
a) administering to a patient a composition comprising an effective amount of an HPTP β -ECD binding agent; b) monitoring the level of angiotensin-2 present in the patient during the course of treatment; and c) discontinuing treatment when the angiotensin-2 level returns to within a normal range.

[000154] A further aspect relates to methods of treating vascular leak in a patient infected with anthrax comprising administering a composition comprising an effective amount of an HPTP β -ECD binding agent in combination with an effective amount of one or more antibacterial agents effective against anthrax, wherein the HPTP β -ECD binding agent and the antibacterial agents effective against anthrax are administered together or in any order.

[000155] Yet another aspect relates to methods of treating vascular leak in a patient infected with a virus comprising administering a composition comprising an effective amount of an HPTP β -ECD binding agent in combination with an effective amount of one or more antiviral agents, wherein the HPTP β -ECD binding agent and the antiviral agent are administered together or in any order.

[000156] Increased amplification of Tie-2 signaling using the disclosed agents provides a method for stabilizing vasculature without the need to affect Ang-1 and/or Ang-2 levels.

Disclosed herein are methods for stabilizing vasculature, comprising administering to a patient an effective amount of an HPTP β -ECD binding agents.

[000157] Because the disclosed agents can amplify Tie-2 signaling without increasing the amount of Ang-2, monitoring the amount of Ang-2 in blood serum of a patient while administering to a patient an HPTP β -ECD binding agent, serves as a method for determining the course of various illnesses or disease states associated with vascular leak syndrome, for example, sepsis as a result of infection. As such, disclosed is a method for stabilizing vasculature in a patient suffering from an inflammatory disease wherein the level of angiopoietin-2 is elevated, comprising: a) administering to a patient an effective amount of an HPTP β -ECD binding agent; b) monitoring the level of angiopoietin-2 present in the patient; and c) discontinuing treatment when the angiopoietin-2 level returns to a normal range.

[000158] What is meant herein by “normal angiopoietin-2 level” is an amount of Ang-2 in blood serum of from about 1 ng/mL to about 2 ng/mL. Alternatively, the level of Ang-2 can be determined for an individual suffering from a disease state, for example, severe sepsis and the level of Ang-2 can be monitored until the amount of Ang-2 in the patient’s serum drop to a level that is nearer the normal range. In this case, the co-administration of a drug can be continued or discontinued.

[000159] Therefore, disclosed herein is a method for stabilizing the vasculature of a patient during a course of treatment, comprising: a) co-administering to a patient an effective amount of an HPTP β -ECD binding agent and one or more drugs as a treatment; b) monitoring the level of angiopoietin-2 present in the patient; and c) discontinuing the administration of the one or more drugs, and selecting one or more other drugs for use as a treatment if the level of serum angiopoietin-2 does not decrease.

[000160] The HPTP β -ECD binding agent, while stabilizing the vasculature of a patient such that a course of treatment against a pathogen can be sustained, can also be used to stabilize a patient during a period wherein an effective treatment against a pathogen is being determined. That is, the HPTP β -ECD binding agents by themselves can have a beneficial effect on the outcome of diseases caused by pathogens by reducing vascular leak and its complications.

[000161] Any of the foregoing compositions comprising an HPTP β -ECD binding agent are suitable for use in the manufacture of a medicament for treatment of any of the diseases or disorder described above. In addition, any of the foregoing compositions comprising an HPTP β -ECD binding agent are suitable for use in treating any of the diseases or disorder described above.

In Vivo Vascular Leak

[000162] The Miles assay (Miles, A. A. and E. M. Miles (1952) Vascular reactions to histamine, histamine-liberator and leukotaxine in the skin of guinea-pigs. J. Physiol., Vol. 118, pp. 228-257 incorporated herein by reference in its entirety) can be used to directly investigate and quantify lethal toxin, as well as edema toxin (ET [PA plus EF])-mediated vascular leakage in the mouse model. The following is a modified Miles assay as described by Gozes Y. et al., Anthrax Lethal Toxin Induces Ketotifen-Sensitive Intradermal Vascular Leakage in Certain Inbred Mice Infect. Immun., 2006 February, Vol. 74, No. 2, pp. 1266–1272 incorporated herein by reference in its entirety, that can be used to evaluate the disclosed HPTP β -ECD binding agents for their ability to prevent vascular leakage in humans and animals exposed to anthrax.

[000163] Highly pure PA, LF, and mutant LF E687C are purified as previously described (Varughese M. et al., (1998) Internalization of a *Bacillus anthracis* protective antigen-c-Myc fusion protein mediated by cell surface anti-c-Myc antibodies. Mol. Med. 4:87-95 included herein by reference in its entirety). Doses of ET or LT refer to the amount of each component (i.e., 100 μ g LT is 100 μ g PA plus 100 μ g of LF). All drugs except for azelastine can be purchased from Sigma Aldrich (St. Louis, MO); azelastine can be purchased from LKT Laboratories (St. Paul, MN). LT is an abbreviation for lethal toxin; PA is an abbreviation for protective antigen; LF is an abbreviation for lethal factor; and EP is an abbreviation for edema factor.

Animals.

[000164] BALB/cJ, DBA/2J, C3H/HeJ, C3H/HeOuJ, WBB6F1/J-Kit^W/Kit^{W-v}, and colony-matched wild-type homozygous control mice can be purchased from The Jackson Laboratory (Bar Harbor, ME). BALB/c nude, C57BL/6J nude, and C3H hairless (C3.Cg/TifBomTac-hr) mice can be purchased from Taconic Farms (Germantown, NY). C3H nude mice can be purchased from The National Cancer Institute Animal Production Area (Frederick, MD). Mice are used when they are 8 to 12 weeks old. Except for C3H hairless and nude animals, all mice are shaved

24 hours prior to intradermal (i.d.) injections. In order to assess the susceptibility to systemic LT, mice are injected intraperitoneally (i.p.) with 100 µg LT and observed over 5 days for signs of malaise or death. Fischer 344 rats can be purchased from Taconic Farms (Germantown, NY) and used at weights of 150 to 180 g. Rats are injected intravenously (i.v.) in the tail vein with 12 µg LT, with or without 250 µg of the mast cell stabilizer drug ketotifen and monitored for the exact time to death.

Miles Assay.

[000165] The Miles assay uses i.v. injection of Evans blue dye (which binds to endogenous serum albumin) as a tracer to assay macromolecular leakage from peripheral vessels after i.d. injection of test substances. Nude mice and normal shaved mice are injected i.v. with 200 µl of 0.1% Evans blue dye (Sigma Chemical Co., St. Louis, MO). After 10 min, 30 µl of test toxin or control samples (PA only, LF only, EF only, or phosphate-buffered saline) are injected i.d. in both left and right flanks, as well as at single or dual dorsal sites. To quantify the extents of leakage, equally sized (1.0- to 1.5-cm diameter) skin regions surrounding i.d. injection sites are removed 60 min after injection and placed in formamide (1 ml) at 41°C for 48 h, allowing for dye extraction. The A_{620} of samples is read, and the extent of leakage is calculated by comparison with phosphate-buffered saline-, PA-, or LF-treated controls.

[000166] In experiments wherein the effectiveness of the HPTPβ-ECD binding agents are tested for LT-mediated leakage, mice are injected i.v. with Evans blue as described above, and the test agent introduced systemically through i.p. injection 10 min after dye injection. LT was introduced by i.d. injection 30 min after the injection of Evans blue. In another embodiment, the agent to be tested can be introduced locally by i.d. injection and LT injected in the same site after 10 min.

Cytotoxicity Experiments.

[000167] MC/9 mast cells can be obtained from ATCC (Manassas, VA) and grown in Dulbecco's modified Eagle's medium supplemented with l-glutamine (2 mM), 2-mercaptoethanol (0.05 mM), Rat T-STIM (BD Biosciences-Discovery Labware, Bedford, MA) (10%), and fetal bovine serum (FBS, 10% final concentration; Invitrogen-GIBCO BRL, Gaithersburg, MD). Cells are then seeded at a density of 10^4 /well in 96-well plates prior to treatment with various LT concentrations or PA-only controls. After 6, 12, and 24 hours, viability is assessed using Promega's CellTiter 96 AQueous One Solution cell proliferation assay (Promega, Madison, WI)

per the manufacturer's protocol. Alternatively, toxicity assays can be performed in medium provided with all supplements except FBS (serum-free medium). In other embodiments, pooled human umbilical vein endothelial cells (HUVECs) at third to fifth passage can be obtained from Cambrex Corp. (Cambrex, Walkersville, MD) and grown in an EGM-MV Bulletkit (Cambrex, Walkersville, MD) in flasks pretreated with endothelial cell attachment factor (Sigma, St. Louis, MO). For cytotoxicity experiments, cells are typically seeded in 96-well plates in an EGM-MV Bulletkit. On the day of assays, this medium is then replaced with M199 medium (Sigma, St. Louis, MO) supplemented with 10% FBS or human serum (Sigma, St. Louis, MO), and cells are reseeded in 96-well plates at a density of 2×10^3 /0.1 ml/well and treated with various concentrations of LT in triplicate. Cell viability is typically assessed as for MC/9 cells at 24, 48 and 72 hour time points.

HUVEC Permeability Assay

[000168] HUVEC monolayers can be effectively cultured on Transwell-Clear cell culture inserts (6.5-mm diameter, 0.4- μ m pore size; Corning-Costar, Acton, MA) in 24-well plates, creating a two-chamber culturing system consisting of a luminal compartment (inside the insert) and a subluminal compartment (the tissue culture plate well). Prior to seeding cells, the inserts are coated with endothelial cell attachment factor (Sigma, St. Louis, MO). Pre-warmed CS-C medium (Sigma, St. Louis, MO) containing 10% iron-supplemented calf serum and 1% endothelial cell growth factor (Sigma, St. Louis, MO) is added to wells prior to insert placement. A HUVEC cell suspension (200 μ L of 5×10^5 cells/ml) is then added to each insert. Cells are cultured at 37 °C in 5% CO₂ for up to 21 days to ensure proper formation of a monolayer. For testing barrier function, medium can be changed to RPMI supplemented with 10% FBS or to RPMI without serum. To assess barrier function, horseradish peroxidase enzyme (Sigma, St. Louis, MO) is added to the inserts (10 μ g/well). LT (1 μ g/mL) or control treatments of PA alone (1 μ g/mL) or LF alone (1 μ g/mL) are added to duplicate wells, and every hour (for 12 hours), a sample of 10 μ L was taken from the subluminal compartment and tested for the enzymatic activity of horseradish peroxidase by adding 100 μ L substrate [2',2'-azino-bis(3-ethylbenzthiazolin 6-sulfonic acid)] (A-3219; Sigma, St. Louis, MO) and reading at 405 nm.

Anthrax Combination Therapy

[000169] Increased stabilization of vascular tissue can increase the effectiveness of known antimicrobials against anthrax infection. As such, HPTP β -ECD binding agents can be evaluated

as a combination therapy for the treatment of anthrax. The following describes a series of assays that can be used to determine the effectiveness of an HPTP β -ECD binding agent as one part of a combination therapy useful for treating anthrax infections.

[000170] LF has been found to cleave mitogen-activated protein kinase kinases (MAPKK), disrupts signal transduction, and leads to macrophage lysis. As such, in addition to the Miles Assay, the following cell-based and peptide cleavage assay can be used to confirm the potency of the HPTP β -ECD binding agents to inhibit the effect of LT activity. For the following assay, MAPKKide can be purchased from List Biological Laboratories (Campbell, CA. Fluorinated peptide substrate is available from Anaspec (San Jose, CA).

In Vivo Assays

[000171] One week before beginning an evaluation of a combination course of treatment for anthrax, test agents (200 mg each) are dissolved in 800 μ L of DMSO and stored at -20 °C. Immediately before injection, each test agent is diluted in PBS, resulting in a final concentration of 0.5 mg/mL in 2% DMSO. Test animal are challenged on day 0 with 2×10^7 spores per mouse in PBS through i.p. injection. Treatment was started 24 hours after challenge. One example of a suitable treatment regimen is the combination of ciprofloxacin (50 mg/kg) and an HPTP β -ECD binding agent (5 mg/kg). A control sample of untreated animals, ciprofloxacin alone, a disclosed agent alone and ciprofloxacin in combination with a disclosed agent are given to the animals and they are monitored twice per day until day 14 after injection.

[000172] Ciprofloxacin and the agent to be tested can be conveniently administered through parenteral injection with a volume of 200 μ L for each once per day for 10 days. All surviving animals are sacrificed on day 14. Sick animals that appear moribund (i.e., exhibiting a severely reduced or absent activity or locomotion level, an unresponsiveness to external stimuli, or an inability to obtain readily available food or water, along with any of the following accompanying signs: ruffled haircoat, hunched posture, inability to maintain normal body temperature, signs of hypothermia, respiratory distress, or other severely debilitating condition) should be sacrificed on the same day these symptoms are manifested.

Modulation of Bacterium-Induced Vascular Leak

[000173] Pathogenic bacteria are known to cause vascular leak. This induced vascular leakage inhibits the ability of antimicrobials and other pharmaceuticals from targeting the invading

microorganism. As such, HPTP β -ECD binding agents can be used alone or in combination with other pharmaceutical ingredients to boost the host immune system by preventing excess vascular leakage that occurs as a result of a bacterial infection.

[000174] The following describe tests and assays that can be used to determine the effectiveness of an HPTP β -ECD binding agent, either alone, or a combination therapy.

[000175] *Staphylococcus aureus* (*S. aureus*) is a major pathogen of gram-positive septic shock and is associated with consumption of plasma kininogen. The effect of an HPTP β -ECD binding agent on *S. aureus* induced vascular leakage activity can be determined by measuring the activity of these agents with respect to two cysteine proteinases that are secreted by *S. aureus*.

Proteolytically active staphopain A (ScpA) induces vascular leakage in a bradykinin (BK) B₂-receptor-dependent manner in guinea pig skin. This effect is augmented by staphopain B (SspB), which, by itself, had no vascular leakage activity. ScpA also produces vascular leakage activity from human plasma.

[000176] An important pathophysiologic mechanism of septic shock is hypovolemic hypotension that is caused by plasma leakage into the extravascular space. It has been found that ScpA induced vascular leakage at a concentration as low as 20 nM within 5 minute after injection into the guinea pig skin—with the reaction being augmented by coexisting SspB indicating that vascular leakage induction by these proteinases occurs efficiently *in vivo* (Imamura T. et al., Induction of vascular leakage through release of bradykinin and a novel kinin by cysteine proteinases from *Staphylococcus aureus* (2005) J. Experimental Medicine, Vol. 201, No. 10, pp. 1669-1676).

Vascular Leakage Assay.

[000177] Animals can be evaluated for vascular leakage using the following procedure. 100 μ L of a 1% solution of Evans blue dye (Sigma Aldrich) in saline is injected into the tail vein. Thirty minutes later, mice are sacrificed and perfused with saline via the right ventricle to remove intravascular Evans blue. Lungs are excised and extracted in 1 mL of formamide at 55 °C overnight. Evans blue content is determined as OD₆₂₀ minus OD₅₀₀ of the formamide extract.

[000178] The agents disclosed herein can be used as a single pharmaceutical therapy to reduce the severity of influenza by mediating the effects of vascular leak caused by viruses, and, hence, allowing the body's own immune system to affect greater resistance to these pathogens. The

following assays can be used to determine the effect of an HPTP β -ECD binding agent to inhibit viral severity because of improved vascular integrity.

[000179] The disclosed assays can use inhibition of viral plaques, viral cytopathic effect (CPE), and viral hemagglutinin.

Proteolytic Sensitivity Assay

[000180] An HPTP β -ECD binding agent can be determined to bind to hemagglutinin and thereby destabilize the protein assembly. The following procedure can be used to determine the increase in destabilization and therefore the increased sensitivity of hemagglutinin to proteolytic attack caused by an HPTP β -ECD binding agent. At the fusion conformation, HA becomes more sensitive to protease digestion. This property can be used to verify if a fusion inhibitor interacts with HA (Luo G. et al., "Molecular mechanism underlying the action of a novel fusion inhibitor of influenza A virus." J. Virol., (1997), Vol. 71, No. 5, pp. 4062-4070). Thus, an HPTP β -ECD binding agent, due to the control of vascular leakage, can be evaluated for its ability to indirectly effect HA digestion by enhancing the body's immune response.

[000181] The purified trimer of hemagglutinin ectodomain is incubated with the agent to be tested at a concentration of 5 μ M. The trimers are subjected to trypsin digestion at pH 7.0 and pH 5.0 with controls of untreated HA and HA treated with DMSO which is the solvent used to dissolve the test agent. For the pH 5.0 sample, the HA trimers are treated with a pH 5.0 buffer for 15 minutes and neutralized to pH 7.0. Trypsin (20 ng) is added to the sample in 10 μ L and the digestion allowed to proceed for 1 hour at 37 °C. The amount of HA present is assessed by a western blot gel electrophoresis using anti-HA (H3) antisera. Samples containing effective inhibitors will provide an increase in digestion of HA by trypsin.

[000182] In addition, combination therapies can provide a method for treating influenza by providing an antiviral medication together with an agent that prevents the severity of vascular leakage due to influenza viruses.

[000183] An antiviral compound, for example, oseltamivir, can be used for an *in vivo* evaluation of the disclosed combination therapy and to evaluate the effectiveness of an HPTP β -ECD binding agent. The drug combination is administered in a single dose to mice infected with the influenza A/NWS/ (H1N1) virus. In some instances, infection of the animals will include multiple passage of the virus through their lungs. One convenient protocol involves

administering 20 mg/kg per day twice daily for 5 days beginning 4 hours prior to virus exposure. The animals are then challenged with different concentrations of virus, ranging 10-fold from 10^{-2} ($10^{5.75}$ cell culture 50 % infectious doses (CCID₅₀) per mL). Four mice in each group are sacrificed on day 6 and their lungs removed, assigned a consolidation score ranging from 0 (normal) to 4 (maximal plum coloration), weighted, homogenized, the homogenates centrifuged at 2000 x g for 10 minutes, and varying 10-fold dilutions of the supernatant assayed for virus titer in MDCK cells using CPE produced after a 96-hour incubation at 37 °C as endpoint.

[000184] The serum taken from mice on day 6 is assayed for α_1 -AG using single radial immunodiffusion kites. Eight additional mice in each group are continually observed daily for death for 21 days, and their arterial oxygen saturation (SaO₂) values determined by pulse oximetry (Sidwell R. et al., (1992) Utilization of pulse oximetry for the study of the inhibitory effects of antiviral agents on influenza virus in mice. *Antimicrob. Agents Chemother.* **36**, 473-476) on day 3, when SaO₂ decline usually begins to occur, through day 11, when the values are seen to decline to the maximum degree of the animals otherwise die.

Inhibition of Protein Tyrosine Phosphatase beta in a Cell

[000185] Disclosed herein are methods for inhibiting protein tyrosine phosphatase beta (HPTP- β) activity in a cell, comprising contacting a cell with an effective amount of an HPTP β -ECD binding agents. The cell can be contacted *in vivo*, *ex vivo*, or *in vitro*.

Administration

[000186] Depending on the nature of the particular agent, agents of the present disclosure can be administered to humans and other animal, parenterally, (e.g., by intravenous or intraperitoneal injection), subcutaneously, orally, topically, rectally, buccally, as an oral or nasal spray.

[000187] The HPTP β -ECD binding agents of the disclosure are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression “dose” or “dosage unit form” as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the HPTP β -ECD binding agents and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment.

Dosing

[000188] Effective dosages and schedules for administering the HPTP β -ECD binding agent may be determined empirically, and making such determinations is within the skill in the art. Those skilled in the art will understand that the dosage of the agent that must be administered will vary depending on, for example, the subject which will receive the agent, the route of administration, the particular type of agent used and other drugs being administered to the subject. For example, guidance in selecting appropriate doses for antibodies is found in the literature on therapeutic uses of antibodies, e.g., Handbook of Monoclonal Antibodies, Ferrone et al., eds., Noyes Publications, Park Ridge, N.J., (1985) ch. 22 and pp. 303-357; Smith et al., Antibodies in Human Diagnosis and Therapy, Haber et al., eds., Raven Press, New York (1977) pp. 365-389. A typical dose of the agent used alone might range from about 0.01 mg/kg to up to 500 mg/kg of body weight or more per day, or from about 0.01 mg/kg to about 50 mg/kg, or from 0.1 mg/kg to about 50 mg/kg, or from about 0.1 mg/kg to up to about 10 mg/kg, or from about 0.2 mg/kg to about 1 mg/kg, or from about 1mg/kg to about depending on the factors mentioned above.

[000189] The dosing schedules for administration of an HPTP β -ECD binding agent include, but are not limited to, once daily, three-times weekly, twice weekly, once weekly, three times, twice monthly, once monthly and once every other month.

Formulations

[000190] In one aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the agents as described herein, and a pharmaceutically acceptable carrier and, in addition, can include other pharmaceutical agents, adjuvants or diluents. For example, pharmaceutical compositions can also include one or more additional active ingredients such as antimicrobial agents, anti-inflammatory agents, anesthetics and the like.

[000191] The formulation may vary depending on the mode of administration. The pharmaceutical compositions can be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, lotions, creams, gels, or the like, preferably in unit dosage form suitable for single administration of a precise dosage.

[000192] For the purposes of the present disclosure the term “excipient” and “carrier” are used interchangeably throughout the description of the present disclosure and said terms are defined herein as, “ingredients which are used in the practice of formulating a safe and effective pharmaceutical composition.” The formulator will understand that excipients are used primarily to serve in delivering a safe, stable and functional pharmaceutical, serving not only as part of the overall vehicle for delivery but also as a means for achieving effective absorption by the recipient of the active ingredient. An excipient may fill a role as simple and direct as being an inert filler, or an excipient as used herein may be part of a pH stabilizing system or coating to insure delivery of the ingredients.

[000193] “Pharmaceutically acceptable” means a material that is not biologically or otherwise undesirable, i.e., the material may be administered to a patient without causing any undesirable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical formulation in which it is contained. The carrier would naturally be selected to minimize any degradation of the active ingredient and to minimize any adverse side effects in the patient, as would be well known to one of skill in the art. See Remington's Pharmaceutical Sciences, 18th ed., Gennaro, AR. Ed., Mack Publishing, Easton Pa. (1990), which discloses typical carriers and conventional methods of preparing pharmaceutical compositions that can be used in conjunction with the preparation of formulations of the agents described herein. It will be apparent to those persons skilled in the art that certain carriers can be more preferable depending upon, for instance, the route of administration and concentration of composition being administered.

[000194] For solid compositions, conventional nontoxic solid carriers include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate and the like. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., an active agent as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered can also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art.

[000195] The disclosed agents can also be present in liquids, emulsions, or suspensions for delivery of active therapeutic agents. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, etc., an active agent as described herein and optional pharmaceutical adjuvants in an excipient, such as, for example, water, saline aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered can also contain minor amounts of nontoxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, etc. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example see Remington's Pharmaceutical Sciences, 18th ed., Gennaro, AR. Ed., Mack Publishing, Easton Pa. (1990).

[000196] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[000197] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[000198] The disclosed agents can also be present in liquids, emulsions, or suspensions for delivery of active therapeutic agents in aerosol form to cavities of the body such as the nose, throat, or bronchial passages. The ratio of agents to the other compounding agents in these preparations will vary as the dosage form requires.

[000199] Depending on the intended mode of administration, the pharmaceutical compositions can be in the form of solid, semi-solid or liquid dosage forms, such as, for example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, lotions, creams, gels, or the like,

preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include, as noted above, an effective amount of the agents in combination with a pharmaceutically acceptable carrier and, in addition, can include other medicinal agents, pharmaceutical agents, carriers, adjuvants, diluents, etc.

[000200] When the agents are to be delivered into a mammal other than a human, the mammal can be a non-human primate, horse, pig, rabbit, dog, sheep, goat, cow, cat, guinea pig, or rodent. The terms human and mammal do not denote a particular age or sex. Thus, adult and newborn subjects, as well as fetuses, whether male or female, are intended to be covered. A patient, subject, human or mammal refers to a subject afflicted with a disease or disorder. The term “patient” includes human and veterinary subjects.

KITS

[000201] Also disclosed are kits comprising the agents be delivered into a human, mammal, or cell. The kits can comprise one or more packaged unit doses of a composition comprising an HPTP β -ECD binding agent to be delivered into a human, mammal, or cell. The kit optionally includes directions for using the components of the kit. The agents can be packaged as a sterile formulation, and the hermetically sealed container is designed to preserve sterility of the formulation until use.

EXAMPLES

EXAMPLE 1

Production of the HPTP β Extracellular Domain Protein

[000202] Full length HPTP β cDNA (SEQ ID NO:1) is cloned from a human placental library according to the manufacturer's (Origene) instructions. A cDNA encoding the entire soluble extracellular domain (ECD) of HPTP β is cloned by PCR from the full length cDNA coding for amino acids 1-1621 with an added c-terminal His-His-His-His-His-His-Gly (6His-Gly) (SEQ ID NO:3). The resulting cDNA is cloned into mammalian expression vectors for transient (pShuttle-CMV) or stable (pcDNA3.1(-)) expression in HEK293 cells. To obtain purified HPTP β ECD (β ED), HEK293 cells transfected with a β ED expression vector are incubated in OptiMEM-serum free (Gibco) for 24 hours under normal growth conditions. The conditioned media is then recovered, centrifuged to remove debris, and 1 mL of washed Ni-NTA agarose (Qiagen) (500 μ L packed material) is added to each 10 μ L of cleared media and allowed to rock overnight at 4° C.

On the following day, the mixture is loaded into a column and washed with 20 bed volumes of 50 mM NaH₂PO₄, 300 mM NaCl, 20 mM imidazole, pH 8. The purified HPTP β extracellular domain protein (SEQ ID NO:4) is then eluted with 200 μ L/elution in 50 mM NaH₂PO₄, 300 mM NaCl, 250 mM Imidazole, pH 8. Fractions are analyzed for protein content using reducing-denaturing SDS-polyacrylimide gel electrophoresis and detected by silver stain (Invitrogen) and confirmed by mass spectrometry.

EXAMPLE 2

[000203] Purified HPTP β extracellular domain protein is produced, for example by the procedure described in Example 1. For production of the HPTP β extracellular domain immunogen, the purified HPTP β extracellular domain-6-His protein is conjugated to porcine thyroglobulin (Sigma) using EDC coupling chemistry (Hockfield, S. et al., (1993) Cold Spring Harbor Laboratory Press., Vol. 1 pp. 111-201, Immunocytochemistry). The resulting HPTP β extracellular domain-thyroglobulin conjugate is dialyzed against PBS, pH 7.4. Adult Balb/c mice are then immunized subcutaneously with the conjugate (100-200 μ g) and complete Freund's adjuvant in a 1:1 mixture. After 2-3 weeks, the mice are injected intraperitoneally or subcutaneously with incomplete Freund's adjuvant and the conjugate in a 1:1 mixture. The injection is repeated at 4-6 weeks. Sera are collected from mice 7 days post-third-injection and assayed for immunoreactivity to HPTP β extracellular domain antigen by ELISA and western blotting. Mice that display a good response to the antigen are boosted by a single intra-spleen injection with 50 μ l of purified HPTP β extracellular domain protein mixed 1:1 with Alum hydroxide using a 31 gauge extra long needle (Goding, J. W., (1996) Monoclonal Antibodies: Principles and Practices. Third Edition, Academic Press Limited. p.145). Briefly, mice are anesthetized with 2.5% avertin, and a 1 centimeter incision is created on the skin and left oblique body wall. The antigen mixture is administered by inserting the needle from the posterior portion to the anterior portion of the spleen in a longitudinal injection. The body wall is sutured and the skin is sealed with two small metal clips. Mice are monitored for safe recovery. Four days after surgery the mouse spleen is removed and single cell suspensions are made for fusion with mouse myeloma cells for the creation of hybridoma cell lines (Spitz, M., (1986) Methods In Enzymology, Vol. 121. Eds. John J, Lagone and Helen Van Vunakis. pp. 33-41 (Academic Press, New York, NY)). Resulting hybridomas are cultured in Dulbeccos modified media (Gibco)

supplemented with 15 % fetal calf serum (Hyclone) and hypoxanthine, aminopterin and thymidine.

[000204] Screening for positive hybridomas begins 8 days after the fusion and continues for 15 days. Hybridomas producing anti-HPTP β extracellular domain antibodies are identified by ELISA on two sets of 96-well plates: one coated with the histidine tagged-HPTP β extracellular domain and another one coated with a histidine-tagged bacterial MurA protein as a negative control. The secondary antibody is a donkey anti-mouse IgG labeled with horseradish peroxidase (HRP) (Jackson ImmunoResearch). Immunoreactivity is monitored in wells using color development initiated by ABTS tablets dissolved in TBS buffer, pH 7.5. The individual HRP reaction mixtures are terminated by adding 100 microliters of 1% SDS and reading absorbance at 405 nm with a spectrophotometer. Hybridomas producing antibodies that interact with HPTP β extracellular domain-6His, and not with the murA-6His protein are used for further analysis. Limiting dilutions (0.8 cells per well) are performed twice on positive clones in 96 well plates, with clonality defined as having greater than 99% of the wells with positive reactivity. Isotypes of antibodies are determined using the iso-strip technology (Roche). To obtain purified antibody for further evaluation, tissue culture supernatants are affinity purified using a protein A or a protein G column.

[000205] Five monoclonal antibodies immunoreactive to HPTP β -ECD protein were isolated and given the following nomenclature, R15E6, R12A7, R3A2, R11C3, R15G2 and R5A8. Based on its reaction with the HPTP β -ECD protein in ELISA and in western blots, R15E6 was selected for further study.

EXAMPLE 3

The monoclonal antibody R15E6

[000206] The monoclonal antibody R15E6 was identified and characterized as described in Example 2 of the present application and in U.S. Pat. No. 7,973,142; the procedure and results are summarized below.

A. R15E6 binds endogenous HPTP β as demonstrated by immunoprecipitation.

[000207] Materials: Human umbilical vein endothelial cells (HUVECs), EGM media, and trypsin neutralizing solution from Cambrex; OPTIMEM I (Gibco), bovine serum albumin (BSA; Santa Cruz), phosphate buffered saline (PBS; Gibco), Growth Factors including Angiopoietin 1 (Ang1), vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) (R&D Systems), Tie2 monoclonal antibody (Duke University/P&GP), VEGF receptor 2 (VEGFR2) polyclonal antibody (Whitaker et. al), protein A/G agarose (Santa Cruz), Tris-Glycine pre-cast gel electrophoresis/transfer system (6-8%) (Invitrogen), PVDF membranes (Invitrogen), lysis buffer (20 mM Tris-HCl, 137 mM NaCl, 10% glycerol, 1% triton-X-100, 2 mM EDTA, 1 mM NaOH, 1 mM NaF, 1 mM PMSF, 1 µg/ml leupeptin, 1 µg/ml pepstatin).

[000208] Method: HUVECs are pre-treated for 30 min with antibody (in OPTIMEM) or OPTIMEM I alone. After removal of pre-treatment, cells are treated with Ang1 (100 ng/ml) for 6 minutes in PBS+0.2% BSA and lysed in lysis buffer. Lysates are run directly on a Tris-Glycine gel or immunoprecipitated with 2-5 µg/ml Tie-2 antibody or 10 µg/ml R15E6 antibody and protein A/G agarose. Immunoprecipitated samples are rinsed once with lysis buffer and boiled for 5 min in 1 x times sample buffer. Samples are resolved on a Tris-Glycine gel, transferred to a PVDF membrane, and detected by western blot using the indicated antibodies (pTYR Ab (PY99, Santa Cruz), Tie-2, VEGFR2 and/or R15E6).

[000209] Results: By IP/western blotting, R15E6 recognizes a major, high molecular weight band consistent with the size of HPTPβ (**Figure 1**, Panel A, Lane 2). The less intense, lower molecular weight bands likely represent less glycosylated precursor forms of HPTPβ. An immunoprecipitation (IP) with control, non-immune IgG shows no bands in the molecular weight range of HPTPβ (**Fig. 1**, Panel A, Lane 1), and a combined Tie2/VEGFR2 IP shows bands of the expected molecular weight (**Fig. 1**, Panel A, Lane 3). This result demonstrates that R15E6 recognizes and is specific for HPTPβ.

B. R15E6 Binds Endogenous HPTPβ as Demonstrated by FACS Analysis

[000210] Materials: HUVECs, EGM media, and trypsin neutralizing solution from Cambrex; Secondary Alexfluor 488-tagged antibody from Molecular Probes; Hanks balanced salt solution (Gibco); FACSCAN flow cytometer and CellQuest software from Becton Dickinson.

[000211] Method: HUVECs are trypsinized, treated with trypsin neutralizing solution and rinsed with HBSS. R15E6 antibody (0.6 µg) is added to 250,000 cells in 50µl of HBSS and

incubated on ice for 20 minutes. Cells are rinsed with 1 ml HBSS followed by adding 2 μ g of fluorescent-conjugated secondary antibody for 20 minutes on ice. Cells are rinsed and resuspended in 1 ml HBSS then analyzed on the FACSCAN flow cytometer with CellQuest software. Control cells are treated with fluorescent-conjugated secondary antibody only.

[000212] Results: By FACS analysis, intact HUVECs, R15E6 causes a robust shift (>90% of cells) in the fluorescence signal compared to the secondary antibody alone (**Fig. 1, Panel B**). This result indicates that R15E6 binds to endogenous HPTP β presented on the surface of intact endothelial cells.

EXAMPLE 4

R15E6 Enhances Tie2 Activation

[000213] R15E6 enhances Tie2 phosphorylation in the absence and presence of the angiopoietin 1 (Ang1), the Tie2 ligand.

[000214] Methods: HUVECs are cultured in serum free media as described above in the presence or absence of various concentrations of R15E6 and with or without added Ang1. Lysates are prepared, immunoprecipitated with a Tie2 antibody, resolved by polyacrylamide gel electrophoresis and transferred to a PVDF membrane. Membrane-bound immunoprecipitated proteins are then serially western blotted with an antiphosphotyrosine antibody to quantify Tie2 phosphorylation followed by a Tie2 antibody to quantify total Tie2. Tie2 phosphorylation is expressed as the ratio of the antiphosphotyrosine signal over the total Tie2 signal.

[000215] Results: R15E6 enhances Tie2 phosphorylation both in the absence and presence of Ang1 (**Fig. 2**). This result indicates that binding of R15E6 to HPTP β on the surface of endothelial cells modulates its biological function resulting in enhanced activation of Tie2 in the absence or presence of ligand.

EXAMPLE 5

Generation of anti-VE-PTP extracellular domain antibodies

A. Production of mouse VE-PTP extracellular domain protein (VE-PTP-ECD)

[000216] VE-PTP –ECD may be produced by any suitable method. Such methods are well known in the art. For example, VE-PTP –ECD can be produced using a method similar to

Example 1 of the present disclosure where VE-PTP-ECD cDNA is used in place of cDNA encoding HPTP β -ECD. SEQ ID NO:7 provides a nucleotide sequence that encodes VE-PTP-ECD. SEQ ID NO:8 provides the amino acid sequence of VE-PTP-ECD.

B. Generation of antibodies to VE-PTP ECD

[000217] Anti-VE-PTP antibodies are readily generated by methods that are well known in the art. For example, anti VE-PTP antibodies can be generated using the method of Example 2 of the present disclosure by substituting VE-PTP-ECD for the HPTP β extracellular domain and immunizing rats with the resulting protein. The rat anti-mouse VE-PTP antibody used in the present studies was kindly provided by Dr. D. Vestweber (mAb 109). The antibody was generated as described in Baumer S. et al., Blood, 2006, Vol. 107, pp. 4754-4762. Briefly, the antibody was generated by immunizing rats with a VE-PTP-Fc fusion protein. Immunization, hybridoma-fusion, and screening were conducted as described in Gotsch U., et al., J Cell Sci., 1997, Vol. 110, pp. 583-588 and Bosse R. and Vestweber D., Eur J Immunol., 1994, Vol. 24, pp. 3019-3024.

[000218] The fusion protein was constructed such that the first 8 fibronectin type III-like repeats ending with the amino acid proline at position 732 of VE-PTP were fused in frame with the Fc part of human IgG1 (starting with amino acid proline at position 239). This construct cloned into pcDNA3 (Invitrogen) was stably transfected into CHO cells, and the fusion protein was purified by protein A Sepharose affinity purification.

EXAMPLE 6

Intravitreal injections of an anti- VE-PTP ECD antibody

[000219] Laser-induced Choroidal Neovascularization Model: The choroidal neovascularization model is considered to represent a model of neovascular age-related macular degeneration. Choroidal NV was generated as previously described. See Tobe T, et al., Am. J. Pathol., 1998, Vol. 153, pp. 1641-1646. Adult C57BL/6 mice had laser-induced rupture of Bruch's membrane in three locations in each eye and were then given 1 μ L intravitreal injections of 1 or 2 μ g of a rat anti-mouse VE-PTP-ECD antibody (IgG2a), in one eye and vehicle (5% dextrose) in the fellow eye. These treatments were repeated on day 7. Fourteen days after laser, the mice were perfused with fluorescein-labeled dextran (2×10^6 average MW, Sigma, St. Louis, MO) and the extent of neovascularization was assessed in choroidal flat mounts by fluorescence

microscopy. The area of CNV at each Bruch's membrane rupture site was measured by image analysis by an observer masked with respect to treatment group. The area of CNV is the average of the three rupture sites in one eye. As shown in Fig. 3, treatment with the VE-PTP-ECD antibody significantly reduced choroidal neovascularization at both 1 and 2 μg doses versus treatment with vehicle control.

Example 7

Oxygen-Induced Ischemic Retinopathy

[000220] The oxygen-induced ischemic retinopathy model is considered to represent a model of proliferative diabetic retinopathy. Ischemic retinopathy was produced in C57BL/6 mice by a method described by Smith, L.E.H., et al. Oxygen-induced retinopathy in the mouse. *Invest. Ophthalmol. Vis. Sci.* 35, 101-111 (1994).

[000221] C57BL/6 mice at postnatal day 7 (P7) and their mothers were placed in an airtight chamber and exposed to hyperoxia ($75 \pm 3\%$ oxygen) for five days. Oxygen was continuously monitored with a PROOX model 110 oxygen controller (Reming Bioinstruments Co., Redfield, NY). On P12, mice were returned to room air and under a dissecting microscope, a Harvard Pump Microinjection System and pulled glass pipettes were used to deliver a 1 μl intravitreal injection of 1 or 2 μg of a VE-PTP-ECD antibody was made in one eye and vehicle was injected in the fellow eye. At P17, the area of NV on the surface of the retina was measured at P17 as previously described. See Shen J, et al., *Invest. Ophthalmol. Vis. Sci.*, 2007, Vol. 48, pp. 4335-4341. Briefly, mice were given an intraocular injection of 1 μl containing 0.5 μg rat anti-mouse PECAM antibody (PharMingen, San Jose, CA). Twelve hours later, the mice were euthanized, the eyes fixed in 10% formalin. The retinas were dissected, incubated for 40 minutes in 1:500 goat anti-rat IgG conjugated with Alexa488 (Invitrogen, Carlsbad, CA), washed, and whole mounted. An observer masked with respect to treatment group examined the slides with a Nikon Fluorescence microscope and measured the area of NV per retina by computerized image analysis using ImagePro Plus software (Media Cybernetics, Silver Spring, MD). Fig. 4 shows that treatment with the VE-PTP-ECD antibody significantly reduced retinal neovascularization at both 1 and 2 μg doses versus treatment with vehicle control. Fig. 5 shows representative retinal whole mounts from a mouse treated with vehicle versus a mouse treated with 2 μg of the VE-PTP-ECD antibody.

Example 8**Subcutaneous injection of a VE-PTP-ECD antibody**

[000222] The oxygen-induced ischemic retinopathy model was conducted as described in Example 7 (containment in a 75% oxygen atmosphere from P5 to P12) for intravitreal dosing except that the VE-PTP-ECD antibody (1 mg/kg) was dosed subcutaneously at P12 when the mice were returned to room air and again on days P14 and P16 (three total doses). Neovascularization was assessed as described above on day (P17). Fig. 6 shows that subcutaneous dosing of the VE-PTP-ECD antibody reduces the area of retinal neovascularization.

Example 9

[000223] The experiment described in Example 8 was repeated at a subcutaneous dose of 2 mg/kg. (Fig. 7)

[000224] While a number of embodiments of this disclosure are described, it is apparent that the basic examples may be altered to provide other embodiments that utilize or encompass the HPTP β -ECD binding agent, methods and processes of this invention. The embodiments and examples are for illustrative purposes and are not to be interpreted as limiting the disclosure, but rather, the appended claims define the scope of this invention.

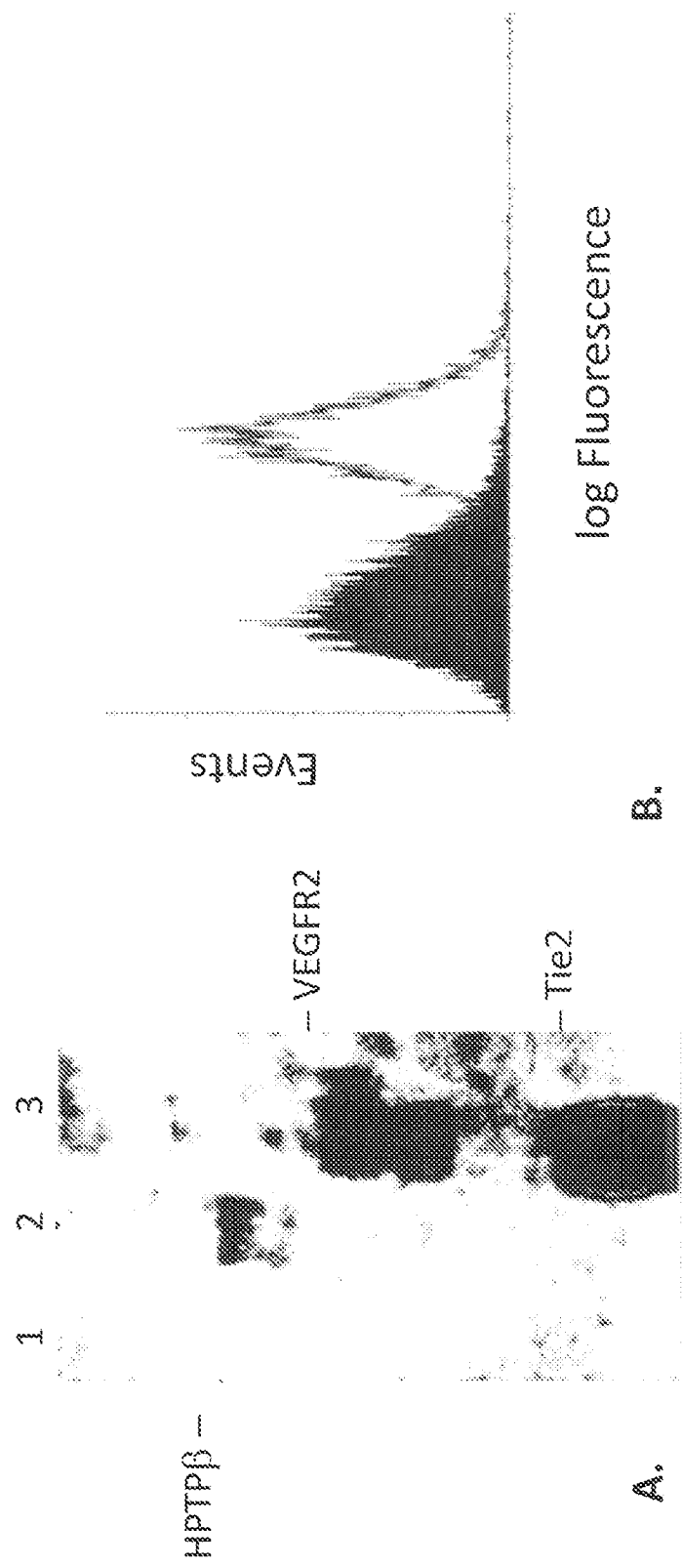
CLAIMS

1. A method for alleviating vascular leak syndrome, the method comprising administering to a subject in need thereof a therapeutically-effective amount of a human protein tyrosine phosphatase beta-extracellular domain (HPTP β -ECD) binding agent, wherein the HPTP β -ECD binding agent is a monoclonal antibody or an antigen-binding fragment thereof.
2. The method of claim 1, wherein the subject has an inflammatory disease.
3. The method of claim 1, wherein the subject has cancer.
4. The method of any one of claims 1-3, wherein the monoclonal antibody is produced by hybridoma cell line ATCC No. PTA 7580.
5. The method of any one of claims 1-3, wherein the HPTP β -ECD binding agent comprises an F(ab')₂, dimer of an Fab, dimer of an Fv, or dimer of a scFv.
6. The method of any one of claims 1-5, wherein a dose of the HPTP β -ECD binding agent is from about 0.01 mg/kg to about 500 mg/kg by weight of the subject.
7. The method of any one of claims 1-6, wherein a dose of the HPTP β -ECD binding agent is from about 0.1 mg/kg to about 10 mg/kg by weight of the subject.
8. The method of any one of claims 1-7, wherein the HPTP β -ECD binding agent is administered in combination with an additional therapeutic agent.
9. The method of claim 8, wherein the additional therapeutic agent is IL-2.
10. The method of any one of claims 1-9, wherein the administration is intraocular.

11. The method of any one of claims 1-9, wherein the administration is subcutaneous.
12. The method of any one of claims 1-9, wherein the administration is intravenous.
13. The method of any one of claims 1-12, wherein the HPTP β -ECD binding agent is R15E6.
14. The method of any one of claims 1-13, wherein the HPTP β -ECD binding agent is humanized.
15. A use of a HPTP β -ECD binding agent for the manufacture of a medicament for alleviating vascular leak syndrome in a subject in need thereof, wherein the HPTP β -ECD binding agent is a monoclonal antibody or an antigen-binding fragment thereof.
16. The use of claim 15, wherein the subject has an inflammatory disease.
17. The use of claim 15, wherein the subject has cancer.
18. The use of any one of claims 15-17, wherein the monoclonal antibody is produced by hybridoma cell line ATCC No. PTA 7580.
19. The use of any one of claims 15-18, wherein the HPTP β -ECD binding agent comprises an F(ab')₂, dimer of an Fab, dimer of an Fv, or dimer of a scFv.
20. The use of any one of claims 15-19, wherein a dose of the HPTP β -ECD binding agent is from about 0.01 mg/kg to about 500 mg/kg by weight of the subject.
21. The use of any one of claims 15-20, wherein a dose of the HPTP β -ECD binding agent is from about 0.1 mg/kg to about 10 mg/kg by weight of the subject.

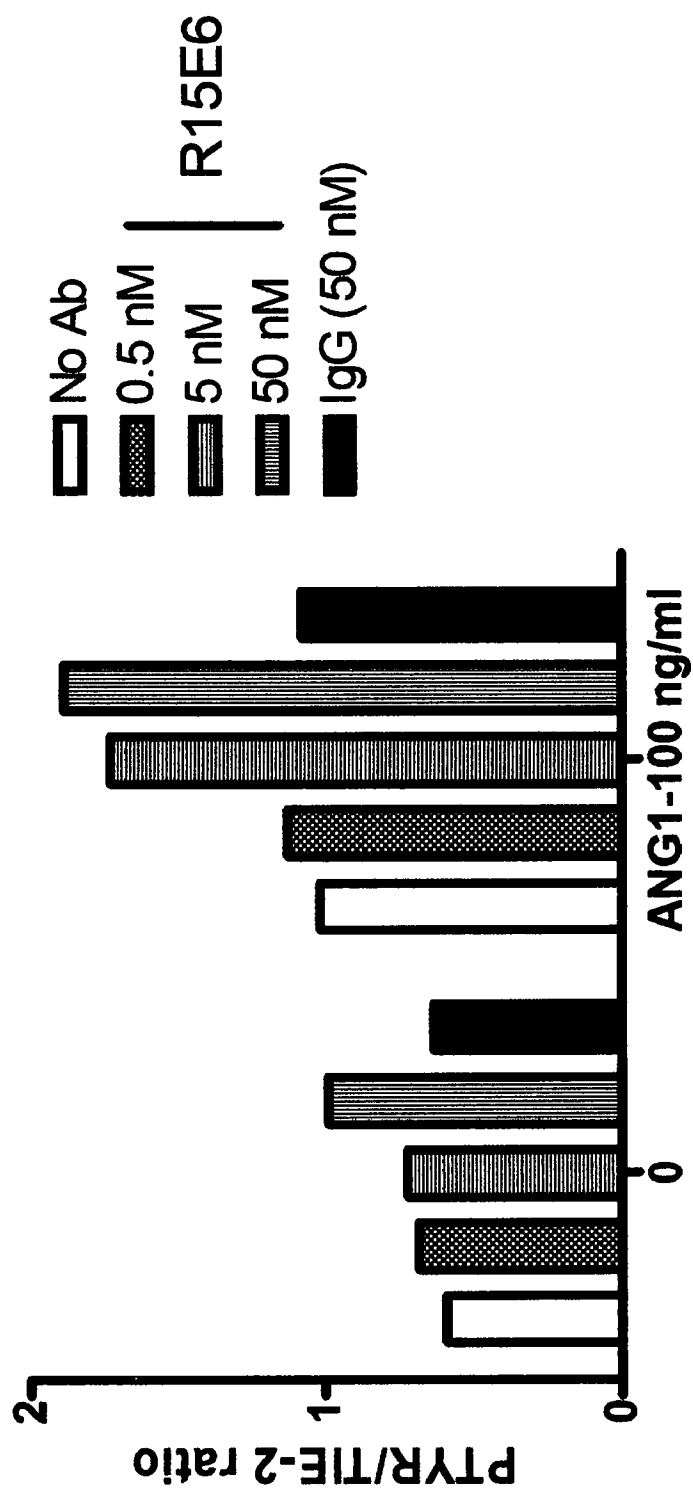
22. The use of any one of claims 15-21, wherein the HPTP β -ECD binding agent is administered in combination with an additional therapeutic agent.
23. The use of claim 22, wherein the additional therapeutic agent is IL-2.
24. The use of any one of claims 15-23, wherein the medicament is formulated for administration by intraocular injection.
25. The use of any one of claims 15-23, wherein the medicament is formulated for administration by subcutaneous injection.
26. The use of any one of claims 15-23, wherein the medicament is formulated for administration by intravenous injection.
27. The use of any one of claims 15-26, wherein the HPTP β -ECD binding agent is R15E6.
28. The use of any one of claims 15-27, wherein the HPTP β -ECD binding agent is humanized.

Fig. 1



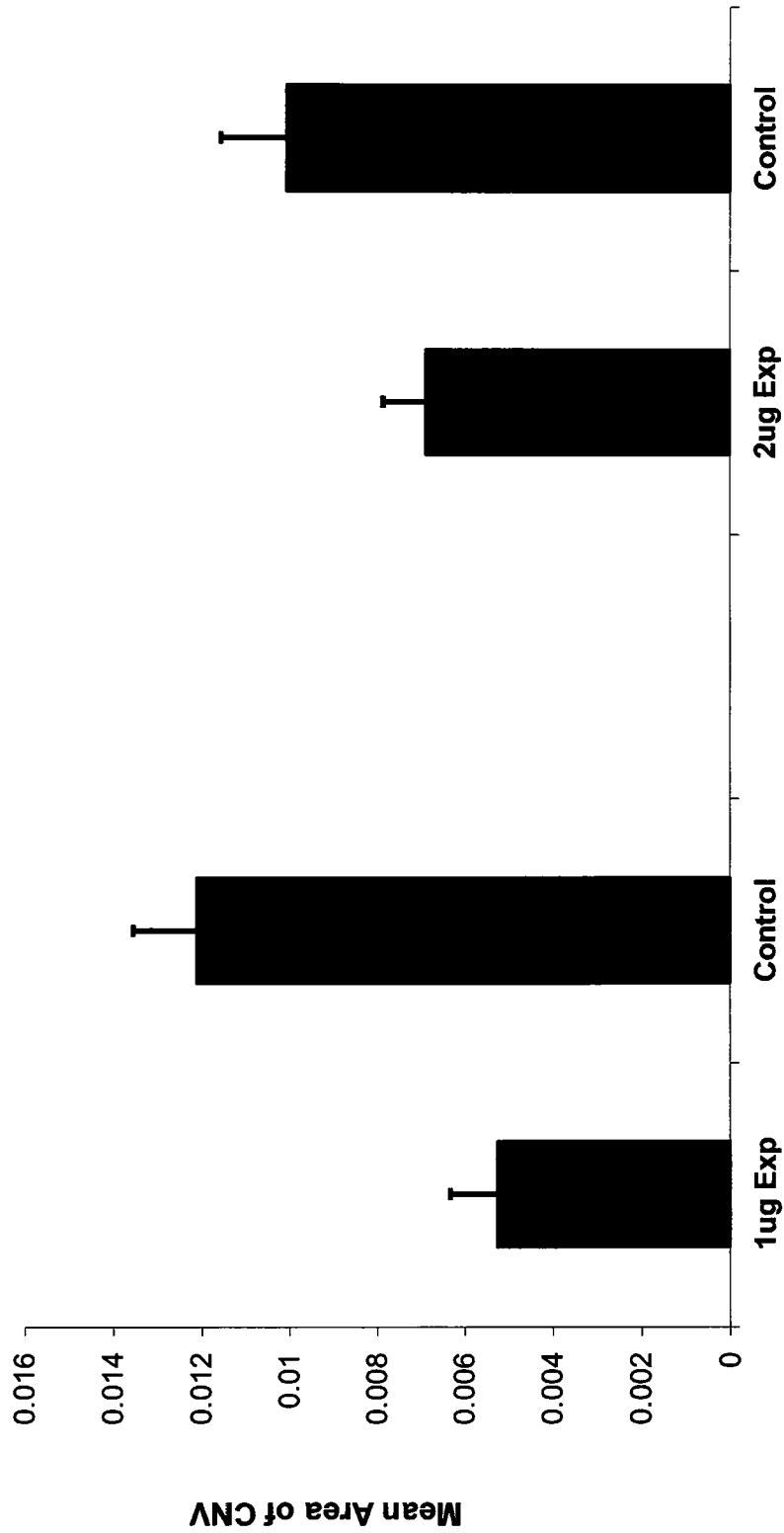
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Fig. 2



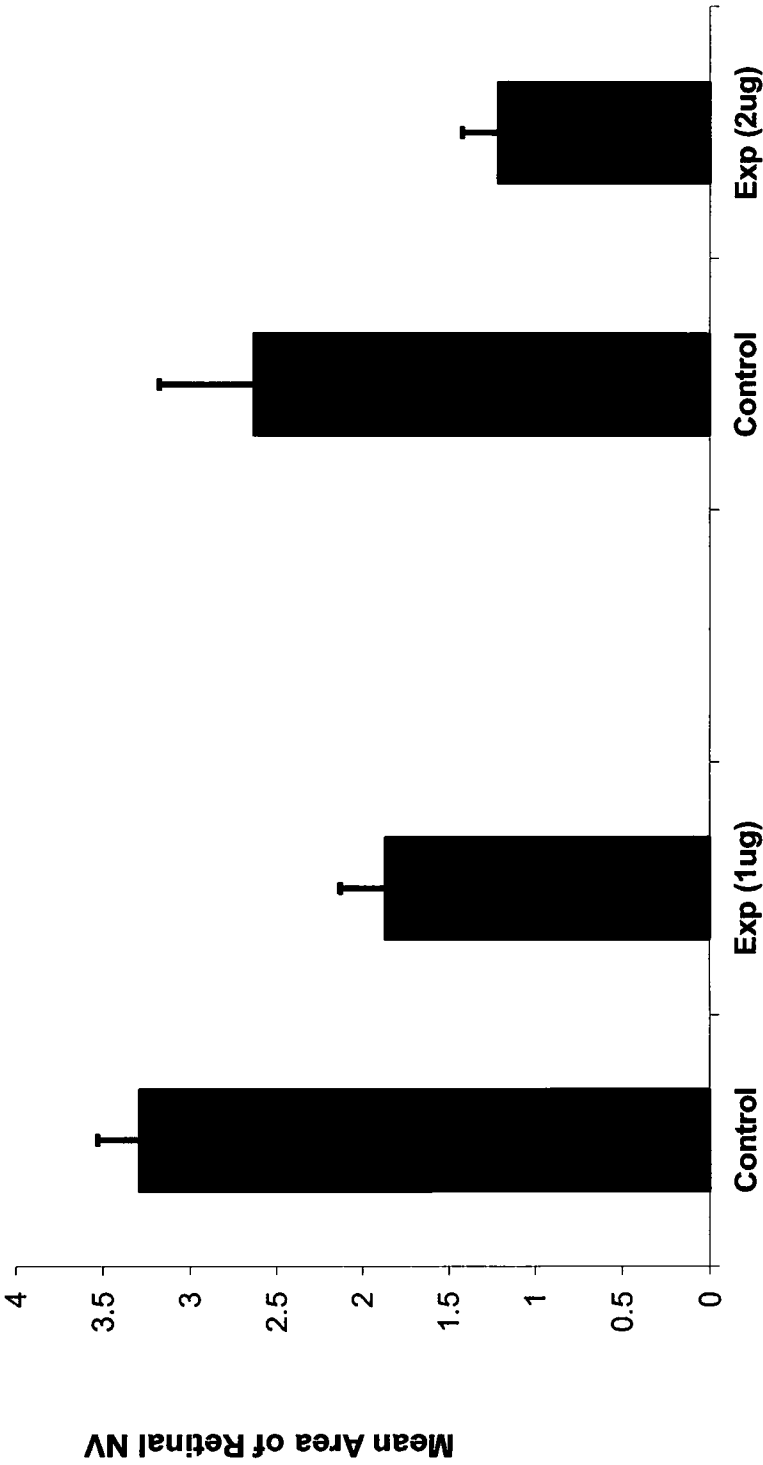
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Fig. 3



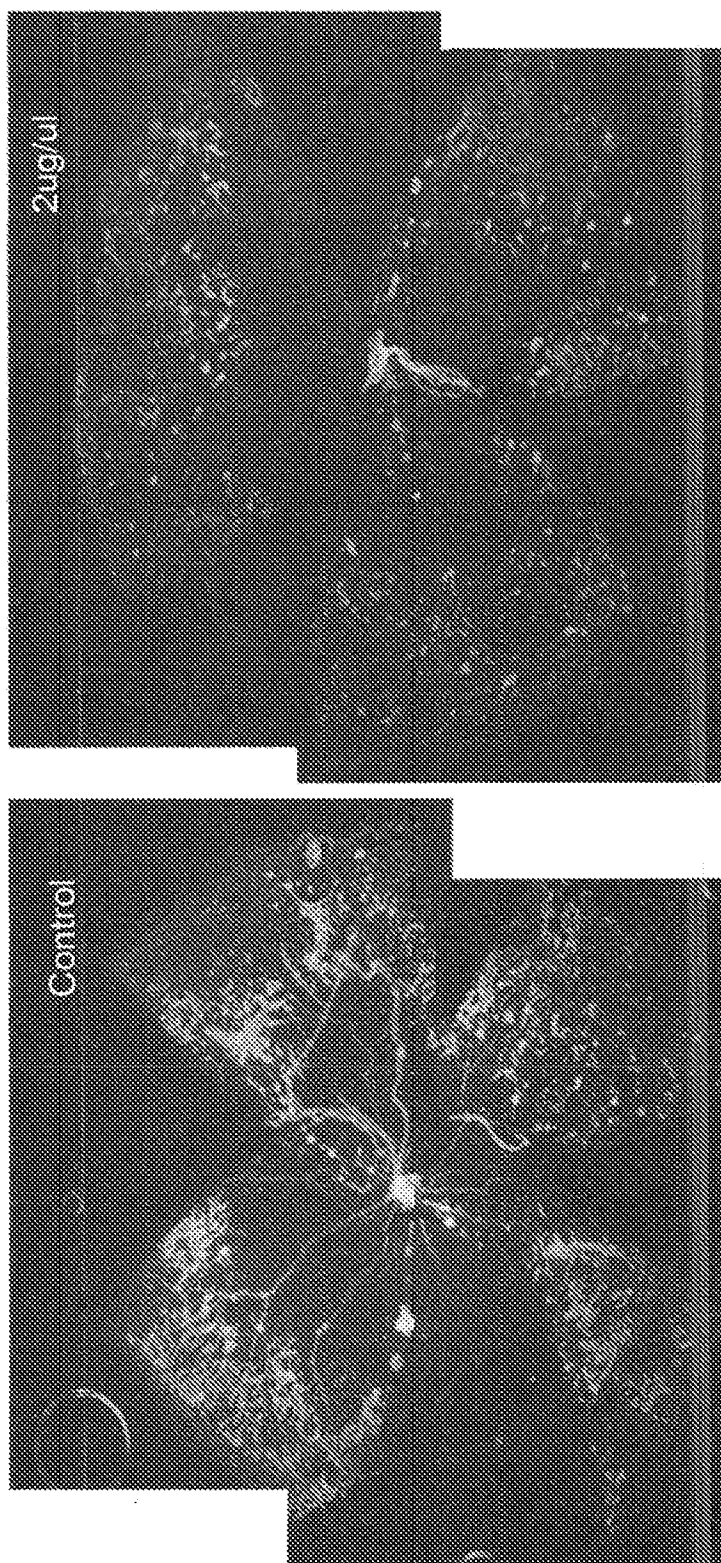
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Fig. 4



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Fig. 5



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Fig. 6

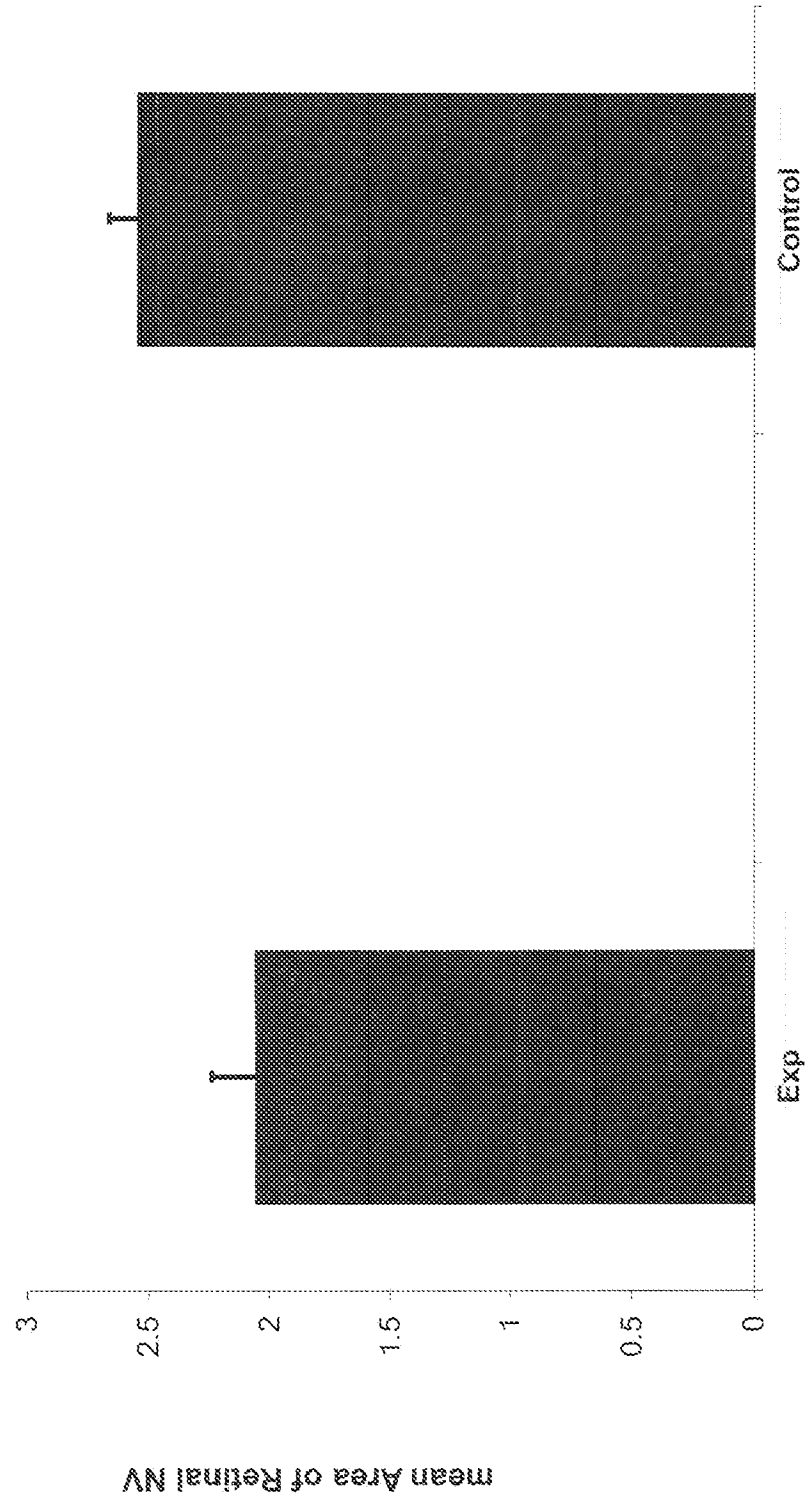
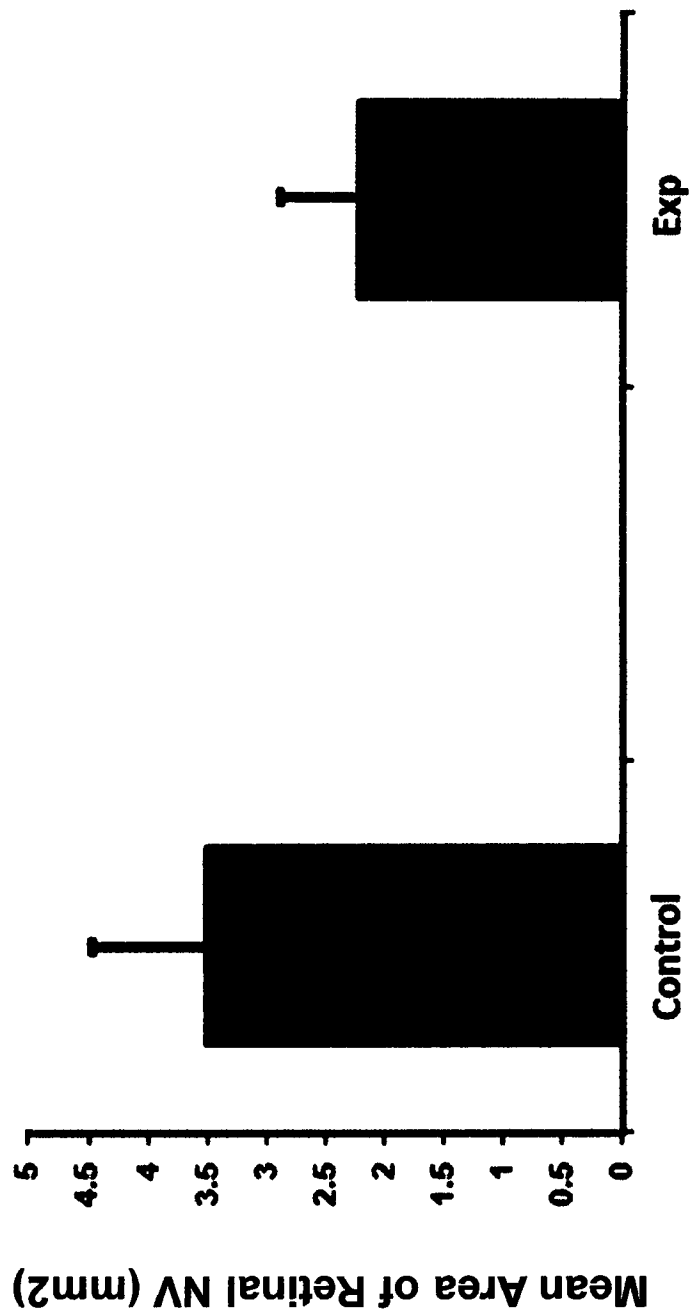


Fig. 7



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233106-331560_Seq_Li sti ng_ST25. txt

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233106-331560_Seq_Li sti ng_ST25. txt

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Glu Ser Lys Ala Ser Ser His Ser Val Ser Ile Gln Trp Arg Ile Leu
35          40          45

Gly Ser Pro Cys Asn Phe Ser Leu Ile Tyr Ser Ser Asp Thr Leu Gly
50          55          60

Ala Ala Leu Cys Pro Thr Phe Arg Ile Asp Asn Thr Thr Tyr Gly Cys
65          70          75          80

Asn Leu Gln Asp Leu Gln Ala Gly Thr Ile Tyr Asn Phe Arg Ile Ile
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Ser Leu Asp Glu Glu Arg Thr Val Val Leu Gln Thr Asp Pro Leu Pro
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Pro Ala Arg Phe Gly Val Ser Lys Glu Lys Thr Thr Ser Thr Ser Leu
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His Val Trp Trp Thr Pro Ser Ser Gly Lys Val Thr Ser Tyr Glu Val
130         135         140

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233106-331560_Seq_Listing_ST25.txt

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Glu Ser Thr Ser Trp Asn Glu Tyr Thr Phe Phe Asn Leu Thr Ala Gly
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Ser Lys Tyr Asn Ile Ala Ile Thr Ala Val Ser Gly Gly Lys Arg Ser
180 185 190

Phe Ser Val Tyr Thr Asn Gly Ser Thr Val Pro Ser Pro Val Lys Asp
195 200 205

Ile Gly Ile Ser Thr Lys Ala Asn Ser Leu Leu Ile Ser Trp Ser His
210 215 220

Gly Ser Gly Asn Val Glu Arg Tyr Arg Leu Met Leu Met Asp Lys Gly
225 230 235 240

Ile Leu Val His Gly Gly Val Val Asp Lys His Ala Thr Ser Tyr Ala
245 250 255

Phe His Gly Leu Thr Pro Gly Tyr Leu Tyr Asn Leu Thr Val Met Thr
260 265 270

Glu Ala Ala Gly Leu Gln Asn Tyr Arg Trp Lys Leu Val Arg Thr Ala
275 280 285

Pro Met Glu Val Ser Asn Leu Lys Val Thr Asn Asp Gly Ser Leu Thr
290 295 300

Ser Leu Lys Val Lys Trp Gln Arg Pro Pro Gly Asn Val Asp Ser Tyr
305 310 315 320

Asn Ile Thr Leu Ser His Lys Gly Thr Ile Lys Glu Ser Arg Val Leu
325 330 335

Ala Pro Trp Ile Thr Glu Thr His Phe Lys Glu Leu Val Pro Gly Arg
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Leu Tyr Gln Val Thr Val Ser Cys Val Ser Gly Glu Leu Ser Ala Gln
355 360 365

Lys Met Ala Val Gly Arg Thr Phe Pro Asp Lys Val Ala Asn Leu Glu
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Ala Asn Asn Asn Gly Arg Met Arg Ser Leu Val Val Ser Trp Ser Pro
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233106-331560_Seq_Listing_ST25.txt

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Thr Val Pro Leu Ala Val Leu Gln Leu Arg Val Lys His Ala Asn Glu
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Thr Ser Leu Ser Ile Met Trp Gln Thr Pro Val Ala Glu Trp Glu Lys
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Tyr Ile Ile Ser Leu Ala Asp Arg Asp Leu Leu Leu Ile His Lys Ser
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Leu Ser Lys Asp Ala Lys Glu Phe Thr Phe Thr Asp Leu Val Pro Gly
515 520 525

Arg Lys Tyr Met Ala Thr Val Thr Ser Ile Ser Gly Asp Leu Lys Asn
530 535 540

Ser Ser Ser Val Lys Gly Arg Thr Val Pro Ala Gln Val Thr Asp Leu
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His Val Ala Asn Gln Gly Met Thr Ser Ser Leu Phe Thr Asn Trp Thr
565 570 575

Gln Ala Gln Gly Asp Val Glu Phe Tyr Gln Val Leu Leu Ile His Glu
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Asn Val Val Ile Lys Asn Glu Ser Ile Ser Ser Glu Thr Ser Arg Tyr
595 600 605

Ser Phe His Ser Leu Lys Ser Gly Ser Leu Tyr Ser Val Val Val Thr
610 615 620

Thr Val Ser Gly Gly Ile Ser Ser Arg Gln Val Val Val Glu Gly Arg
625 630 635 640

Thr Val Pro Ser Ser Val Ser Gly Val Thr Val Asn Asn Ser Gly Arg
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Asn Asp Tyr Leu Ser Val Ser Trp Leu Leu Ala Pro Gly Asp Val Asp
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Asn Tyr Glu Val Thr Leu Ser His Asp Gly Lys Val Val Gln Ser Leu
675 680 685

233106-331560_Seq_Listing_ST25.txt

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Asn	His	Ser	Phe	Ser 725	Gln	Glu	Arg	Thr	Val 730	Pro	Asp	Lys	Val	Gln 735	Gly
Val	Ser	Val	Ser 740	Asn	Ser	Ala	Arg	Ser 745	Asp	Tyr	Leu	Arg	Val 750	Ser	Trp
Val	His	Ala 755	Thr	Gly	Asp	Phe	Asp 760	His	Tyr	Glu	Val	Thr 765	Ile	Lys	Asn
Lys	Asn 770	Asn	Phe	Ile	Gln	Thr 775	Lys	Ser	Ile	Pro	Lys 780	Ser	Glu	Asn	Glu
Cys 785	Val	Phe	Val	Gln	Leu 790	Val	Pro	Gly	Arg	Leu 795	Tyr	Ser	Val	Thr	Val 800
Thr	Thr	Lys	Ser	Gly 805	Gln	Tyr	Glu	Ala	Asn 810	Glu	Gln	Gly	Asn	Gly 815	Arg
Thr	Ile	Pro	Glu 820	Pro	Val	Lys	Asp	Leu 825	Thr	Leu	Arg	Asn	Arg 830	Ser	Thr
Glu	Asp	Leu 835	His	Val	Thr	Trp	Ser 840	Gly	Ala	Asn	Gly	Asp 845	Val	Asp	Gln
Tyr	Glu 850	Ile	Gln	Leu	Leu	Phe 855	Asn	Asp	Met	Lys	Val 860	Phe	Pro	Pro	Phe
His 865	Leu	Val	Asn	Thr	Ala 870	Thr	Glu	Tyr	Arg	Phe 875	Thr	Ser	Leu	Thr	Pro 880
Gly	Arg	Gln	Tyr	Lys 885	Ile	Leu	Val	Leu	Thr 890	Ile	Ser	Gly	Asp	Val 895	Gln
Gln	Ser	Ala	Phe 900	Ile	Glu	Gly	Phe	Thr 905	Val	Pro	Ser	Ala	Val 910	Lys	Asn
Ile	His	Ile 915	Ser	Pro	Asn	Gly	Ala 920	Thr	Asp	Ser	Leu	Thr 925	Val	Asn	Trp
Thr	Pro 930	Gly	Gly	Gly	Asp	Val 935	Asp	Ser	Tyr	Thr	Val 940	Ser	Ala	Phe	Arg
His 945	Ser	Gln	Lys	Val	Asp 950	Ser	Gln	Thr	Ile	Pro 955	Lys	His	Val	Phe	Glu 960

233106-331560_Seq_Listing_ST25.txt

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 Ala Ser Val Ser Gly Ser Leu Lys Asn Gln Ile Asn Val Val Gly Arg
 980 985 990

 Thr Val Pro Ala Ser Val Gln Gly Val Ile Ala Asp Asn Ala Tyr Ser
 995 1000 1005

 Ser Tyr Ser Leu Ile Val Ser Trp Gln Lys Ala Ala Gly Val Ala
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 Glu Arg Tyr Asp Ile Leu Leu Leu Thr Glu Asn Gly Ile Leu Leu
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 Arg Asn Thr Ser Glu Pro Ala Thr Thr Lys Gln His Lys Phe Glu
 1040 1045 1050

 Asp Leu Thr Pro Gly Lys Lys Tyr Lys Ile Gln Ile Leu Thr Val
 1055 1060 1065

 Ser Gly Gly Leu Phe Ser Lys Glu Ala Gln Thr Glu Gly Arg Thr
 1070 1075 1080

 Val Pro Ala Ala Val Thr Asp Leu Arg Ile Thr Glu Asn Ser Thr
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 Arg His Leu Ser Phe Arg Trp Thr Ala Ser Glu Gly Glu Leu Ser
 1100 1105 1110

 Trp Tyr Asn Ile Phe Leu Tyr Asn Pro Asp Gly Asn Leu Gln Glu
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 Arg Ala Gln Val Asp Pro Leu Val Gln Ser Phe Ser Phe Gln Asn
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 Leu Leu Gln Gly Arg Met Tyr Lys Met Val Ile Val Thr His Ser
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 Gly Glu Leu Ser Asn Glu Ser Phe Ile Phe Gly Arg Thr Val Pro
 1160 1165 1170

 Ala Ser Val Ser His Leu Arg Gly Ser Asn Arg Asn Thr Thr Asp
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 Ser Leu Trp Phe Asn Trp Ser Pro Ala Ser Gly Asp Phe Asp Phe
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 Tyr Glu Leu Ile Leu Tyr Asn Pro Asn Gly Thr Lys Lys Glu Asn
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233106-331560_Seq_Listing_ST25.txt

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Tyr	Asn	Asn	Arg	Lys	Ser	Glu	Gly	Arg	Ile	Val	Tyr	Gly	Leu	Arg
	1310					1315					1320			
Pro	Gly	Arg	Ser	Tyr	Gln	Phe	Asn	Val	Lys	Thr	Val	Ser	Gly	Asp
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Ser	Trp	Lys	Thr	Tyr	Ser	Lys	Pro	Ile	Phe	Gly	Ser	Val	Arg	Thr
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Lys	Pro	Asp	Lys	Ile	Gln	Asn	Leu	His	Cys	Arg	Pro	Gln	Asn	Ser
	1355					1360					1365			
Thr	Ala	Ile	Ala	Cys	Ser	Trp	Ile	Pro	Pro	Asp	Ser	Asp	Phe	Asp
	1370					1375					1380			
Gly	Tyr	Ser	Ile	Glu	Cys	Arg	Lys	Met	Asp	Thr	Gln	Glu	Val	Glu
	1385					1390					1395			
Phe	Ser	Arg	Lys	Leu	Glu	Lys	Glu	Lys	Ser	Leu	Leu	Asn	Ile	Met
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Met	Leu	Val	Pro	His	Lys	Arg	Tyr	Leu	Val	Ser	Ile	Lys	Val	Gln
	1415					1420					1425			
Ser	Ala	Gly	Met	Thr	Ser	Glu	Val	Val	Glu	Asp	Ser	Thr	Ile	Thr
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Met	Ile	Asp	Arg	Pro	Pro	Pro	Pro	Pro	Pro	His	Ile	Arg	Val	Asn
	1445					1450					1455			
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233106-331560_Seq_Listing_ST25. txt

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233106-331560_Seq_Listing_ST25.txt

Gly	Lys	Asn	Arg	Tyr	Asn	Asn	Ile	Leu	Pro	Tyr	Asp	Ala	Thr	Arg
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	1760					1765					1770			
Val	Thr	Gln	Gly	Pro	Leu	Pro	Gly	Thr	Lys	Asp	Asp	Phe	Trp	Lys
	1775					1780					1785			
Met	Val	Trp	Glu	Gln	Asn	Val	His	Asn	Ile	Val	Met	Val	Thr	Gln
	1790					1795					1800			
Cys	Val	Glu	Lys	Gly	Arg	Val	Lys	Cys	Asp	His	Tyr	Trp	Pro	Ala
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Ser	Glu	Ser	Val	Leu	Pro	Glu	Trp	Thr	Ile	Arg	Glu	Phe	Lys	Ile
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Cys	Gly	Glu	Glu	Gln	Leu	Asp	Ala	His	Arg	Leu	Ile	Arg	His	Phe
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His	Tyr	Thr	Val	Trp	Pro	Asp	His	Gly	Val	Pro	Glu	Thr	Thr	Gln
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Ser	Leu	Ile	Gln	Phe	Val	Arg	Thr	Val	Arg	Asp	Tyr	Ile	Asn	Arg
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Ser	Pro	Gly	Ala	Gly	Pro	Thr	Val	Val	His	Cys	Ser	Ala	Gly	Val
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Leu	Asp	Ser	Lys	Asp	Ser	Val	Asp	Ile	Tyr	Gly	Ala	Val	His	Asp
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Val	Tyr	Leu	His	Gln	Cys	Val	Arg	Asp	Val	Leu	Arg	Ala	Arg	Lys
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<400> 3

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Gly Ser Pro Cys Asn Phe Ser Leu Ile Tyr Ser Ser Asp Thr Leu Gly
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Asn Leu Gln Asp Leu Gln Ala Gly Thr Ile Tyr Asn Phe Arg Ile Ile
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Ser Leu Asp Glu Glu Arg Thr Val Val Leu Gln Thr Asp Pro Leu Pro
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Pro Ala Arg Phe Gly Val Ser Lys Glu Lys Thr Thr Ser Thr Ser Leu
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Gln Leu Phe Asp Glu Asn Asn Gln Lys Ile Gln Gly Val Gln Ile Gln
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Glu Ser Thr Ser Trp Asn Glu Tyr Thr Phe Phe Asn Leu Thr Ala Gly
165 170 175

Ser Lys Tyr Asn Ile Ala Ile Thr Ala Val Ser Gly Gly Lys Arg Ser
180 185 190

Phe Ser Val Tyr Thr Asn Gly Ser Thr Val Pro Ser Pro Val Lys Asp
195 200 205

Ile Gly Ile Ser Thr Lys Ala Asn Ser Leu Leu Ile Ser Trp Ser His
210 215 220

Gly Ser Gly Asn Val Glu Arg Tyr Arg Leu Met Leu Met Asp Lys Gly

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Phe	His	Gly	Leu 260	Thr	Pro	Gly	Tyr	Leu 265	Tyr	Asn	Leu	Thr	Val 270	Met	Thr
Glu	Ala	Ala 275	Gly	Leu	Gln	Asn	Tyr 280	Arg	Trp	Lys	Leu	Val 285	Arg	Thr	Ala
Pro	Met 290	Glu	Val	Ser	Asn	Leu 295	Lys	Val	Thr	Asn	Asp 300	Gly	Ser	Leu	Thr
Ser 305	Leu	Lys	Val	Lys	Trp 310	Gln	Arg	Pro	Pro	Gly 315	Asn	Val	Asp	Ser	Tyr 320
Asn	Ile	Thr	Leu	Ser 325	His	Lys	Gly	Thr	Ile 330	Lys	Glu	Ser	Arg	Val 335	Leu
Ala	Pro	Trp	Ile 340	Thr	Glu	Thr	His	Phe 345	Lys	Glu	Leu	Val	Pro 350	Gly	Arg
Leu	Tyr	Gln 355	Val	Thr	Val	Ser	Cys 360	Val	Ser	Gly	Glu	Leu 365	Ser	Ala	Gln
Lys	Met 370	Ala	Val	Gly	Arg	Thr 375	Phe	Pro	Asp	Lys	Val 380	Ala	Asn	Leu	Glu
Ala 385	Asn	Asn	Asn	Gly	Arg 390	Met	Arg	Ser	Leu	Val 395	Val	Ser	Trp	Ser	Pro 400
Pro	Ala	Gly	Asp	Trp 405	Glu	Gln	Tyr	Arg	Ile 410	Leu	Leu	Phe	Asn	Asp 415	Ser
Val	Val	Leu 420	Leu	Asn	Ile	Thr	Val	Gly 425	Lys	Glu	Glu	Thr	Gln 430	Tyr	Val
Met	Asp	Asp 435	Thr	Gly	Leu	Val	Pro 440	Gly	Arg	Gln	Tyr	Glu 445	Val	Glu	Val
Ile	Val 450	Glu	Ser	Gly	Asn	Leu 455	Lys	Asn	Ser	Glu	Arg 460	Cys	Gln	Gly	Arg
Thr 465	Val	Pro	Leu	Ala	Val 470	Leu	Gln	Leu	Arg	Val 475	Lys	His	Ala	Asn	Glu 480
Thr	Ser	Leu	Ser	Ile 485	Met	Trp	Gln	Thr	Pro 490	Val	Ala	Glu	Trp	Glu 495	Lys
Tyr	Ile	Ile	Ser	Leu	Ala	Asp	Arg	Asp	Leu	Leu	Leu	Ile	His	Lys	Ser

500

505

510

Leu Ser Lys₅₁₅ Asp Ala Lys Glu Phe₅₂₀ Thr Phe Thr Asp Leu₅₂₅ Val Pro Gly

Arg Lys₅₃₀ Tyr Met Ala Thr Val₅₃₅ Thr Ser Ile Ser Gly₅₄₀ Asp Leu Lys Asn

Ser₅₄₅ Ser Ser Val Lys Gly₅₅₀ Arg Thr Val Pro Ala₅₅₅ Gln Val Thr Asp Leu₅₆₀

His Val Ala Asn Gln₅₆₅ Gly Met Thr Ser Ser₅₇₀ Leu Phe Thr Asn Trp₅₇₅ Thr

Gln Ala Gln Gly₅₈₀ Asp Val Glu Phe Tyr₅₈₅ Gln Val Leu Leu Ile₅₉₀ His Glu

Asn Val Val₅₉₅ Ile Lys Asn Glu Ser₆₀₀ Ile Ser Ser Glu Thr₆₀₅ Ser Arg Tyr

Ser Phe₆₁₀ His Ser Leu Lys Ser₆₁₅ Gly Ser Leu Tyr Ser₆₂₀ Val Val Val Thr

Thr₆₂₅ Val Ser Gly Gly₆₃₀ Ile Ser Ser Arg Gln Val₆₃₅ Val Val Glu Gly Arg₆₄₀

Thr Val Pro Ser Ser₆₄₅ Val Ser Gly Val Thr₆₅₀ Val Asn Asn Ser Gly₆₅₅ Arg

Asn Asp Tyr Leu₆₆₀ Ser Val Ser Trp Leu₆₆₅ Leu Ala Pro Gly Asp₆₇₀ Val Asp

Asn Tyr Glu₆₇₅ Val Thr Leu Ser His₆₈₀ Asp Gly Lys Val Val₆₈₅ Gln Ser Leu

Val Ile₆₉₀ Ala Lys Ser Val Arg₆₉₅ Glu Cys Ser Phe Ser₇₀₀ Ser Leu Thr Pro

Gly₇₀₅ Arg Leu Tyr Thr Val₇₁₀ Thr Ile Thr Thr Arg₇₁₅ Ser Gly Lys Tyr Glu₇₂₀

Asn His Ser Phe Ser₇₂₅ Gln Glu Arg Thr Val₇₃₀ Pro Asp Lys Val Gln₇₃₅ Gly

Val Ser Val Ser₇₄₀ Asn Ser Ala Arg Ser₇₄₅ Asp Tyr Leu Arg Val₇₅₀ Ser Trp

Val His Ala₇₅₅ Thr Gly Asp Phe Asp₇₆₀ His Tyr Glu Val Thr₇₆₅ Ile Lys Asn

Lys Asn Asn Phe Ile Gln Thr Lys Ser Ile Pro Lys Ser Glu Asn Glu

770

775

780

Cys Val Phe Val Gln Leu Val Pro Gly Arg Leu Tyr Ser Val Thr Val
785 790 795 800

Thr Thr Lys Ser Gly Gln Tyr Glu Ala Asn Glu Gln Gly Asn Gly Arg
805 810 815

Thr Ile Pro Glu Pro Val Lys Asp Leu Thr Leu Arg Asn Arg Ser Thr
820 825 830

Glu Asp Leu His Val Thr Trp Ser Gly Ala Asn Gly Asp Val Asp Gln
835 840 845

Tyr Glu Ile Gln Leu Leu Phe Asn Asp Met Lys Val Phe Pro Pro Phe
850 855 860

His Leu Val Asn Thr Ala Thr Glu Tyr Arg Phe Thr Ser Leu Thr Pro
865 870 875 880

Gly Arg Gln Tyr Lys Ile Leu Val Leu Thr Ile Ser Gly Asp Val Gln
885 890 895

Gln Ser Ala Phe Ile Glu Gly Phe Thr Val Pro Ser Ala Val Lys Asn
900 905 910

Ile His Ile Ser Pro Asn Gly Ala Thr Asp Ser Leu Thr Val Asn Trp
915 920 925

Thr Pro Gly Gly Gly Asp Val Asp Ser Tyr Thr Val Ser Ala Phe Arg
930 935 940

His Ser Gln Lys Val Asp Ser Gln Thr Ile Pro Lys His Val Phe Glu
945 950 955 960

His Thr Phe His Arg Leu Glu Ala Gly Glu Gln Tyr Gln Ile Met Ile
965 970 975

Ala Ser Val Ser Gly Ser Leu Lys Asn Gln Ile Asn Val Val Gly Arg
980 985 990

Thr Val Pro Ala Ser Val Gln Gly Val Ile Ala Asp Asn Ala Tyr Ser
995 1000 1005

Ser Tyr Ser Leu Ile Val Ser Trp Gln Lys Ala Ala Gly Val Ala
1010 1015 1020

Glu Arg Tyr Asp Ile Leu Leu Leu Thr Glu Asn Gly Ile Leu Leu
1025 1030 1035

Arg Asn Thr Ser Glu Pro Ala Thr Thr Lys Gln His Lys Phe Glu

1040

1045

1050

Asp	Leu	Thr	Pro	Gly	Lys	Lys	Tyr	Lys	Ile	Gln	Ile	Leu	Thr	Val
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Ser	Gly	Gly	Leu	Phe	Ser	Lys	Glu	Ala	Gln	Thr	Glu	Gly	Arg	Thr
	1070					1075					1080			
Val	Pro	Ala	Ala	Val	Thr	Asp	Leu	Arg	Ile	Thr	Glu	Asn	Ser	Thr
	1085					1090					1095			
Arg	His	Leu	Ser	Phe	Arg	Trp	Thr	Ala	Ser	Glu	Gly	Glu	Leu	Ser
	1100					1105					1110			
Trp	Tyr	Asn	Ile	Phe	Leu	Tyr	Asn	Pro	Asp	Gly	Asn	Leu	Gln	Glu
	1115					1120					1125			
Arg	Ala	Gln	Val	Asp	Pro	Leu	Val	Gln	Ser	Phe	Ser	Phe	Gln	Asn
	1130					1135					1140			
Leu	Leu	Gln	Gly	Arg	Met	Tyr	Lys	Met	Val	Ile	Val	Thr	His	Ser
	1145					1150					1155			
Gly	Glu	Leu	Ser	Asn	Glu	Ser	Phe	Ile	Phe	Gly	Arg	Thr	Val	Pro
	1160					1165					1170			
Ala	Ser	Val	Ser	His	Leu	Arg	Gly	Ser	Asn	Arg	Asn	Thr	Thr	Asp
	1175					1180					1185			
Ser	Leu	Trp	Phe	Asn	Trp	Ser	Pro	Ala	Ser	Gly	Asp	Phe	Asp	Phe
	1190					1195					1200			
Tyr	Glu	Leu	Ile	Leu	Tyr	Asn	Pro	Asn	Gly	Thr	Lys	Lys	Glu	Asn
	1205					1210					1215			
Trp	Lys	Asp	Lys	Asp	Leu	Thr	Glu	Trp	Arg	Phe	Gln	Gly	Leu	Val
	1220					1225					1230			
Pro	Gly	Arg	Lys	Tyr	Val	Leu	Trp	Val	Val	Thr	His	Ser	Gly	Asp
	1235					1240					1245			
Leu	Ser	Asn	Lys	Val	Thr	Ala	Glu	Ser	Arg	Thr	Ala	Pro	Ser	Pro
	1250					1255					1260			
Pro	Ser	Leu	Met	Ser	Phe	Ala	Asp	Ile	Ala	Asn	Thr	Ser	Leu	Ala
	1265					1270					1275			
Ile	Thr	Trp	Lys	Gly	Pro	Pro	Asp	Trp	Thr	Asp	Tyr	Asn	Asp	Phe
	1280					1285					1290			
Glu	Leu	Gln	Trp	Leu	Pro	Arg	Asp	Ala	Leu	Thr	Val	Phe	Asn	Pro

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1295

1300

1305

Tyr	Asn	Asn	Arg	Lys	Ser	Glu	Gly	Arg	Ile	Val	Tyr	Gly	Leu	Arg
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Pro	Gly	Arg	Ser	Tyr	Gln	Phe	Asn	Val	Lys	Thr	Val	Ser	Gly	Asp
	1325					1330					1335			
Ser	Trp	Lys	Thr	Tyr	Ser	Lys	Pro	Ile	Phe	Gly	Ser	Val	Arg	Thr
	1340					1345					1350			
Lys	Pro	Asp	Lys	Ile	Gln	Asn	Leu	His	Cys	Arg	Pro	Gln	Asn	Ser
	1355					1360					1365			
Thr	Ala	Ile	Ala	Cys	Ser	Trp	Ile	Pro	Pro	Asp	Ser	Asp	Phe	Asp
	1370					1375					1380			
Gly	Tyr	Ser	Ile	Glu	Cys	Arg	Lys	Met	Asp	Thr	Gln	Glu	Val	Glu
	1385					1390					1395			
Phe	Ser	Arg	Lys	Leu	Glu	Lys	Glu	Lys	Ser	Leu	Leu	Asn	Ile	Met
	1400					1405					1410			
Met	Leu	Val	Pro	His	Lys	Arg	Tyr	Leu	Val	Ser	Ile	Lys	Val	Gln
	1415					1420					1425			
Ser	Ala	Gly	Met	Thr	Ser	Glu	Val	Val	Glu	Asp	Ser	Thr	Ile	Thr
	1430					1435					1440			
Met	Ile	Asp	Arg	Pro	Pro	Pro	Pro	Pro	Pro	His	Ile	Arg	Val	Asn
	1445					1450					1455			
Glu	Lys	Asp	Val	Leu	Ile	Ser	Lys	Ser	Ser	Ile	Asn	Phe	Thr	Val
	1460					1465					1470			
Asn	Cys	Ser	Trp	Phe	Ser	Asp	Thr	Asn	Gly	Ala	Val	Lys	Tyr	Phe
	1475					1480					1485			
Thr	Val	Val	Val	Arg	Glu	Ala	Asp	Gly	Asn	Asp	Glu	Leu	Lys	Pro
	1490					1495					1500			
Glu	Gln	Gln	His	Pro	Leu	Pro	Ser	Tyr	Leu	Glu	Tyr	Arg	His	Asn
	1505					1510					1515			
Ala	Ser	Ile	Arg	Val	Tyr	Gln	Thr	Asn	Tyr	Phe	Ala	Ser	Lys	Cys
	1520					1525					1530			
Ala	Glu	Asn	Pro	Asn	Ser	Asn	Ser	Lys	Ser	Phe	Asn	Ile	Lys	Leu
	1535					1540					1545			
Gly	Ala	Glu	Met	Glu	Ser	Leu	Gly	Gly	Lys	Cys	Asp	Pro	Thr	Gln

1550

1555

1560

Gln Lys Phe Cys Asp Gly Pro Leu Lys Pro His Thr Ala Tyr Arg
 1565 1570 1575

Ile Ser Ile Arg Ala Phe Thr Gln Leu Phe Asp Glu Asp Leu Lys
 1580 1585 1590

Glu Phe Thr Lys Pro Leu Tyr Ser Asp Thr Phe Phe Ser Leu Pro
 1595 1600 1605

Ile Thr Thr Glu Ser Glu Pro Leu Phe Gly Ala Ile Glu Arg Gly
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Arg His His His His His Gly
 1625 1630

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 <212> PRT
 <213> Homo sapiens

<400> 4

Met Leu Ser His Gly Ala Gly Leu Ala Leu Trp Ile Thr Leu Ser Leu
 1 5 10 15

Leu Gln Thr Gly Leu Ala Glu Pro Glu Arg Cys Asn Phe Thr Leu Ala
 20 25 30

Glu Ser Lys Ala Ser Ser His Ser Val Ser Ile Gln Trp Arg Ile Leu
 35 40 45

Gly Ser Pro Cys Asn Phe Ser Leu Ile Tyr Ser Ser Asp Thr Leu Gly
 50 55 60

Ala Ala Leu Cys Pro Thr Phe Arg Ile Asp Asn Thr Thr Tyr Gly Cys
 65 70 75 80

Asn Leu Gln Asp Leu Gln Ala Gly Thr Ile Tyr Asn Phe Arg Ile Ile
 85 90 95

Ser Leu Asp Glu Glu Arg Thr Val Val Leu Gln Thr Asp Pro Leu Pro
 100 105 110

Pro Ala Arg Phe Gly Val Ser Lys Glu Lys Thr Thr Ser Thr Ser Leu
 115 120 125

His Val Trp Trp Thr Pro Ser Ser Gly Lys Val Thr Ser Tyr Glu Val
 130 135 140

Gln Leu Phe Asp Glu Asn Asn Gln Lys Ile Gln Gly Val Gln Ile Gln
 145 150 155 160

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Glu Ser Thr Ser Trp Asn Glu Tyr Thr Phe Phe Asn Leu Thr Ala Gly
 165 170 175
 Ser Lys Tyr Asn Ile Ala Ile Thr Ala Val Ser Gly Gly Lys Arg Ser
 180 185 190
 Phe Ser Val Tyr Thr Asn Gly Ser Thr Val Pro Ser Pro Val Lys Asp
 195 200 205
 Ile Gly Ile Ser Thr Lys Ala Asn Ser Leu Leu Ile Ser Trp Ser His
 210 215 220
 Gly Ser Gly Asn Val Glu Arg Tyr Arg Leu Met Leu Met Asp Lys Gly
 225 230 235 240
 Ile Leu Val His Gly Gly Val Val Asp Lys His Ala Thr Ser Tyr Ala
 245 250 255
 Phe His Gly Leu Thr Pro Gly Tyr Leu Tyr Asn Leu Thr Val Met Thr
 260 265 270
 Glu Ala Ala Gly Leu Gln Asn Tyr Arg Trp Lys Leu Val Arg Thr Ala
 275 280 285
 Pro Met Glu Val Ser Asn Leu Lys Val Thr Asn Asp Gly Ser Leu Thr
 290 295 300
 Ser Leu Lys Val Lys Trp Gln Arg Pro Pro Gly Asn Val Asp Ser Tyr
 305 310 315 320
 Asn Ile Thr Leu Ser His Lys Gly Thr Ile Lys Glu Ser Arg Val Leu
 325 330 335
 Ala Pro Trp Ile Thr Glu Thr His Phe Lys Glu Leu Val Pro Gly Arg
 340 345 350
 Leu Tyr Gln Val Thr Val Ser Cys Val Ser Gly Glu Leu Ser Ala Gln
 355 360 365
 Lys Met Ala Val Gly Arg Thr Phe Pro Asp Lys Val Ala Asn Leu Glu
 370 375 380
 Ala Asn Asn Asn Gly Arg Met Arg Ser Leu Val Val Ser Trp Ser Pro
 385 390 395 400
 Pro Ala Gly Asp Trp Glu Gln Tyr Arg Ile Leu Leu Phe Asn Asp Ser
 405 410 415
 Val Val Leu Leu Asn Ile Thr Val Gly Lys Glu Glu Thr Gln Tyr Val
 420 425 430

233106-331560_Seq_Listing_ST25. txt

Met Asp Asp Thr Gly Leu Val Pro Gly Arg Gl n Tyr Gl u Val Gl u Val
435 440 445

I l e Val Gl u Ser Gly Asn Leu Lys Asn Ser Gl u Arg Cys Gl n Gly Arg
450 455 460

Thr Val Pro Leu Ala Val Leu Gl n Leu Arg Val Lys Hi s Ala Asn Gl u
465 470 475 480

Thr Ser Leu Ser I l e Met Trp Gl n Thr Pro Val Ala Gl u Trp Gl u Lys
485 490 495

Tyr I l e I l e Ser Leu Ala Asp Arg Asp Leu Leu Leu I l e Hi s Lys Ser
500 505 510

Leu Ser Lys Asp Ala Lys Gl u Phe Thr Phe Thr Asp Leu Val Pro Gly
515 520 525

Arg Lys Tyr Met Ala Thr Val Thr Ser I l e Ser Gly Asp Leu Lys Asn
530 535 540

Ser Ser Ser Val Lys Gly Arg Thr Val Pro Ala Gl n Val Thr Asp Leu
545 550 560

Hi s Val Ala Asn Gl n Gly Met Thr Ser Ser Leu Phe Thr Asn Trp Thr
565 570 575

Gl n Ala Gl n Gly Asp Val Gl u Phe Tyr Gl n Val Leu Leu I l e Hi s Gl u
580 585 590

Asn Val Val I l e Lys Asn Gl u Ser I l e Ser Ser Gl u Thr Ser Arg Tyr
595 600 605

Ser Phe Hi s Ser Leu Lys Ser Gly Ser Leu Tyr Ser Val Val Val Thr
610 615 620

Thr Val Ser Gly Gly I l e Ser Ser Arg Gl n Val Val Val Gl u Gly Arg
625 630 635 640

Thr Val Pro Ser Ser Val Ser Gly Val Thr Val Asn Asn Ser Gly Arg
645 650 655

Asn Asp Tyr Leu Ser Val Ser Trp Leu Leu Ala Pro Gly Asp Val Asp
660 665 670

Asn Tyr Gl u Val Thr Leu Ser Hi s Asp Gly Lys Val Val Gl n Ser Leu
675 680 685

Val I l e Ala Lys Ser Val Arg Gl u Cys Ser Phe Ser Ser Leu Thr Pro
690 695 700

233106-331560_Seq_Listing_ST25. txt

Gly Arg Leu Tyr Thr Val Thr Ile Thr Thr Arg Ser Gly Lys Tyr Glu
 705 710 715 720
 Asn His Ser Phe Ser Gln Glu Arg Thr Val Pro Asp Lys Val Gln Gly
 725 730 735
 Val Ser Val Ser Asn Ser Ala Arg Ser Asp Tyr Leu Arg Val Ser Trp
 740 745 750
 Val His Ala Thr Gly Asp Phe Asp His Tyr Glu Val Thr Ile Lys Asn
 755 760 765
 Lys Asn Asn Phe Ile Gln Thr Lys Ser Ile Pro Lys Ser Glu Asn Glu
 770 775 780
 Cys Val Phe Val Gln Leu Val Pro Gly Arg Leu Tyr Ser Val Thr Val
 785 790 795 800
 Thr Thr Lys Ser Gly Gln Tyr Glu Ala Asn Glu Gln Gly Asn Gly Arg
 805 810 815
 Thr Ile Pro Glu Pro Val Lys Asp Leu Thr Leu Arg Asn Arg Ser Thr
 820 825 830
 Glu Asp Leu His Val Thr Trp Ser Gly Ala Asn Gly Asp Val Asp Gln
 835 840 845
 Tyr Glu Ile Gln Leu Leu Phe Asn Asp Met Lys Val Phe Pro Pro Phe
 850 855 860
 His Leu Val Asn Thr Ala Thr Glu Tyr Arg Phe Thr Ser Leu Thr Pro
 865 870 875 880
 Gly Arg Gln Tyr Lys Ile Leu Val Leu Thr Ile Ser Gly Asp Val Gln
 885 890 895
 Gln Ser Ala Phe Ile Glu Gly Phe Thr Val Pro Ser Ala Val Lys Asn
 900 905 910
 Ile His Ile Ser Pro Asn Gly Ala Thr Asp Ser Leu Thr Val Asn Trp
 915 920 925
 Thr Pro Gly Gly Gly Asp Val Asp Ser Tyr Thr Val Ser Ala Phe Arg
 930 935 940
 His Ser Gln Lys Val Asp Ser Gln Thr Ile Pro Lys His Val Phe Glu
 945 950 955 960
 His Thr Phe His Arg Leu Glu Ala Gly Glu Gln Tyr Gln Ile Met Ile
 965 970 975

233106-331560_Seq_Listing_ST25. txt

Ala Ser Val Ser Gly Ser Leu Lys Asn Gln Ile Asn Val Val Gly Arg
980 985 990

Thr Val Pro Ala Ser Val Gln Gly Val Ile Ala Asp Asn Ala Tyr Ser
995 1000 1005

Ser Tyr Ser Leu Ile Val Ser Trp Gln Lys Ala Ala Gly Val Ala
1010 1015 1020

Glu Arg Tyr Asp Ile Leu Leu Leu Thr Glu Asn Gly Ile Leu Leu
1025 1030 1035

Arg Asn Thr Ser Glu Pro Ala Thr Thr Lys Gln His Lys Phe Glu
1040 1045 1050

Asp Leu Thr Pro Gly Lys Lys Tyr Lys Ile Gln Ile Leu Thr Val
1055 1060 1065

Ser Gly Gly Leu Phe Ser Lys Glu Ala Gln Thr Glu Gly Arg Thr
1070 1075 1080

Val Pro Ala Ala Val Thr Asp Leu Arg Ile Thr Glu Asn Ser Thr
1085 1090 1095

Arg His Leu Ser Phe Arg Trp Thr Ala Ser Glu Gly Glu Leu Ser
1100 1105 1110

Trp Tyr Asn Ile Phe Leu Tyr Asn Pro Asp Gly Asn Leu Gln Glu
1115 1120 1125

Arg Ala Gln Val Asp Pro Leu Val Gln Ser Phe Ser Phe Gln Asn
1130 1135 1140

Leu Leu Gln Gly Arg Met Tyr Lys Met Val Ile Val Thr His Ser
1145 1150 1155

Gly Glu Leu Ser Asn Glu Ser Phe Ile Phe Gly Arg Thr Val Pro
1160 1165 1170

Ala Ser Val Ser His Leu Arg Gly Ser Asn Arg Asn Thr Thr Asp
1175 1180 1185

Ser Leu Trp Phe Asn Trp Ser Pro Ala Ser Gly Asp Phe Asp Phe
1190 1195 1200

Tyr Glu Leu Ile Leu Tyr Asn Pro Asn Gly Thr Lys Lys Glu Asn
1205 1210 1215

Trp Lys Asp Lys Asp Leu Thr Glu Trp Arg Phe Gln Gly Leu Val
1220 1225 1230

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Pro	Gly	Arg	Lys	Tyr	Val	Leu	Trp	Val	Val	Thr	His	Ser	Gly	Asp
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Leu	Ser	Asn	Lys	Val	Thr	Ala	Glu	Ser	Arg	Thr	Ala	Pro	Ser	Pro
	1250					1255					1260			
Pro	Ser	Leu	Met	Ser	Phe	Ala	Asp	Ile	Ala	Asn	Thr	Ser	Leu	Ala
	1265					1270					1275			
Ile	Thr	Trp	Lys	Gly	Pro	Pro	Asp	Trp	Thr	Asp	Tyr	Asn	Asp	Phe
	1280					1285					1290			
Glu	Leu	Gln	Trp	Leu	Pro	Arg	Asp	Ala	Leu	Thr	Val	Phe	Asn	Pro
	1295					1300					1305			
Tyr	Asn	Asn	Arg	Lys	Ser	Glu	Gly	Arg	Ile	Val	Tyr	Gly	Leu	Arg
	1310					1315					1320			
Pro	Gly	Arg	Ser	Tyr	Gln	Phe	Asn	Val	Lys	Thr	Val	Ser	Gly	Asp
	1325					1330					1335			
Ser	Trp	Lys	Thr	Tyr	Ser	Lys	Pro	Ile	Phe	Gly	Ser	Val	Arg	Thr
	1340					1345					1350			
Lys	Pro	Asp	Lys	Ile	Gln	Asn	Leu	His	Cys	Arg	Pro	Gln	Asn	Ser
	1355					1360					1365			
Thr	Ala	Ile	Ala	Cys	Ser	Trp	Ile	Pro	Pro	Asp	Ser	Asp	Phe	Asp
	1370					1375					1380			
Gly	Tyr	Ser	Ile	Glu	Cys	Arg	Lys	Met	Asp	Thr	Gln	Glu	Val	Glu
	1385					1390					1395			
Phe	Ser	Arg	Lys	Leu	Glu	Lys	Glu	Lys	Ser	Leu	Leu	Asn	Ile	Met
	1400					1405					1410			
Met	Leu	Val	Pro	His	Lys	Arg	Tyr	Leu	Val	Ser	Ile	Lys	Val	Gln
	1415					1420					1425			
Ser	Ala	Gly	Met	Thr	Ser	Glu	Val	Val	Glu	Asp	Ser	Thr	Ile	Thr
	1430					1435					1440			
Met	Ile	Asp	Arg	Pro	Pro	Pro	Pro	Pro	Pro	His	Ile	Arg	Val	Asn
	1445					1450					1455			
Glu	Lys	Asp	Val	Leu	Ile	Ser	Lys	Ser	Ser	Ile	Asn	Phe	Thr	Val
	1460					1465					1470			
Asn	Cys	Ser	Trp	Phe	Ser	Asp	Thr	Asn	Gly	Ala	Val	Lys	Tyr	Phe
	1475					1480					1485			

233106-331560_Seq_Listing_ST25. txt

Thr Val Val Val Arg Glu Ala Asp Gly Asn Asp Glu Leu Lys Pro
1490 1495 1500

Glu Gln Gln His Pro Leu Pro Ser Tyr Leu Glu Tyr Arg His Asn
1505 1510 1515

Ala Ser Ile Arg Val Tyr Gln Thr Asn Tyr Phe Ala Ser Lys Cys
1520 1525 1530

Ala Glu Asn Pro Asn Ser Asn Ser Lys Ser Phe Asn Ile Lys Leu
1535 1540 1545

Gly Ala Glu Met Glu Ser Leu Gly Gly Lys Cys Asp Pro Thr Gln
1550 1555 1560

Gln Lys Phe Cys Asp Gly Pro Leu Lys Pro His Thr Ala Tyr Arg
1565 1570 1575

Ile Ser Ile Arg Ala Phe Thr Gln Leu Phe Asp Glu Asp Leu Lys
1580 1585 1590

Glu Phe Thr Lys Pro Leu Tyr Ser Asp Thr Phe Phe Ser Leu Pro
1595 1600 1605

Ile Thr Thr Glu Ser Glu Pro Leu Phe Gly Ala Ile Glu
1610 1615 1620

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233106-331560_Seq_Li st i ng_ST25. txt

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233106-331560_Seq_Li sti ng_ST25. txt

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233106-331560_Seq_Li sti ng_ST25. txt

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aaaaaaaa	aaaaaaaa											6199

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 <212> PRT
 <213> Mus muscul us

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			20					25					30		
Glu	Ser	Arg	Val	Ser	Ser	Leu	Ser	Ala	Ser	Ile	Gln	Trp	Arg	Thr	Phe
		35					40					45			

233106-331560_Seq_Listing_ST25.txt

Ala Ser Pro Cys Asn Phe Ser Leu Ile Tyr Ser Ser Asp Thr Ser Gly
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Pro Met Trp Cys His Pro Ile Arg Ile Asp Asn Phe Thr Tyr Gly Cys
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Asn Pro Lys Asp Leu Gln Ala Gly Thr Val Tyr Asn Phe Arg Ile Val
85 90 95

Ser Leu Asp Gly Glu Glu Ser Thr Leu Val Leu Gln Thr Asp Pro Leu
100 105 110

Pro Pro Ala Arg Phe Glu Val Asn Arg Glu Lys Thr Ala Ser Thr Thr
115 120 125

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

Val Gln Leu Phe Asp His Asn Asn Gln Lys Ile Gln Glu Val Gln Val
145 150 155 160

Gln Glu Ser Thr Thr Trp Ser Gln Tyr Thr Phe Leu Asn Leu Thr Glu
165 170 175

Gly Asn Ser Tyr Lys Val Ala Ile Thr Ala Val Ser Gly Glu Lys Arg
180 185 190

Ser Phe Pro Val Tyr Ile Asn Gly Ser Thr Val Pro Ser Pro Val Lys
195 200 205

Asp Leu Gly Ile Ser Pro Asn Pro Asn Ser Leu Leu Ile Ser Trp Ser
210 215 220

Arg Gly Ser Gly Asn Val Glu Gln Tyr Arg Leu Val Leu Met Asp Lys
225 230 235 240

Gly Ala Ile Val Gln Asp Thr Asn Val Asp Arg Arg Asp Thr Ser Tyr
245 250 255

Ala Phe His Glu Leu Thr Pro Gly His Leu Tyr Asn Leu Thr Ile Val
260 265 270

Thr Met Ala Ser Gly Leu Gln Asn Ser Arg Trp Lys Leu Val Arg Thr
275 280 285

Ala Pro Met Glu Val Ser Asn Leu Lys Val Thr Asn Asp Gly Arg Leu
290 295 300

Thr Ser Leu Asn Val Lys Trp Gln Lys Pro Pro Gly Asp Val Asp Ser
305 310 315 320

233106-331560_Seq_Listing_ST25.txt

Tyr Ser Ile Thr Leu Ser His Gln Gly Thr Ile Lys Glu Ser Lys Thr
 325 330 335
 Leu Ala Pro Pro Val Thr Glu Thr Gln Phe Lys Asp Leu Val Pro Gly
 340 345 350
 Arg Leu Tyr Gln Val Thr Ile Ser Cys Ile Ser Gly Glu Leu Ser Ala
 355 360 365
 Glu Lys Ser Ala Ala Gly Arg Thr Val Pro Glu Lys Val Arg Asn Leu
 370 375 380
 Val Ser Tyr Asn Glu Ile Trp Met Lys Ser Phe Thr Val Asn Trp Thr
 385 390 395 400
 Pro Pro Ala Gly Asp Trp Glu His Tyr Arg Ile Val Leu Phe Asn Glu
 405 410 415
 Ser Leu Val Leu Leu Asn Thr Thr Val Gly Lys Glu Glu Thr His Tyr
 420 425 430
 Ala Leu Asp Gly Leu Glu Leu Ile Pro Gly Arg Gln Tyr Glu Ile Glu
 435 440 445
 Val Ile Val Glu Ser Gly Asn Leu Arg Asn Ser Glu Arg Cys Gln Gly
 450 455 460
 Arg Thr Val Pro Leu Ala Val Leu Gln Leu Arg Val Lys His Ala Asn
 465 470 475 480
 Glu Thr Ser Leu Gly Ile Thr Trp Arg Ala Pro Leu Gly Glu Trp Glu
 485 490 495
 Lys Tyr Ile Ile Ser Leu Met Asp Arg Glu Leu Leu Val Ile His Lys
 500 505 510
 Ser Leu Ser Lys Asp Ala Lys Glu Phe Thr Phe Thr Asp Leu Met Pro
 515 520 525
 Gly Arg Asn Tyr Lys Ala Thr Val Thr Ser Met Ser Gly Asp Leu Lys
 530 535 540
 Gln Ser Ser Ser Ile Lys Gly Arg Thr Val Pro Ala Gln Val Thr Asp
 545 550 555 560
 Leu His Val Asn Asn Gln Gly Met Thr Ser Ser Leu Phe Thr Asn Trp
 565 570 575
 Thr Lys Ala Leu Gly Asp Val Glu Phe Tyr Gln Val Leu Leu Ile His
 580 585 590

233106-331560_Seq_Listing_ST25.txt

Glu Asn Val Val Val Lys Asn Glu Ser Val Ser Ser Asp Thr Ser Arg
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 Tyr Ser Phe Arg Ala Leu Lys Pro Gly Ser Leu Tyr Ser Val Val Val
 610 615 620
 Thr Thr Val Ser Gly Gly Ile Ser Ser Arg Gln Val Val Ala Glu Gly
 625 630 635
 Arg Thr Val Pro Ser Ser Val Ser Gly Val Thr Val Asn Asn Ser Gly
 645 650 655
 Arg Asn Asp Tyr Leu Ser Val Ser Trp Leu Pro Ala Pro Gly Glu Val
 660 665 670
 Asp His Tyr Val Val Ser Leu Ser His Glu Gly Lys Val Asp Gln Phe
 675 680 685
 Leu Ile Ile Ala Lys Ser Val Ser Glu Cys Ser Phe Ser Ser Leu Thr
 690 695 700
 Pro Gly Arg Leu Tyr Asn Val Thr Val Thr Thr Lys Ser Gly Asn Tyr
 705 710 715 720
 Ala Ser His Ser Phe Thr Glu Glu Arg Thr Val Pro Asp Lys Val Gln
 725 730 735
 Gly Ile Ser Val Ser Asn Ser Ala Arg Ser Asp Tyr Leu Lys Val Ser
 740 745 750
 Trp Val His Ala Thr Gly Asp Phe Asp His Tyr Glu Val Thr Ile Lys
 755 760 765
 Asn Arg Glu Ser Phe Ile Gln Thr Lys Thr Ile Pro Lys Ser Glu Asn
 770 775 780
 Glu Cys Glu Phe Ile Glu Leu Val Pro Gly Arg Leu Tyr Ser Val Thr
 785 790 795 800
 Val Ser Thr Lys Ser Gly Gln Tyr Glu Ala Ser Glu Gln Gly Thr Gly
 805 810 815
 Arg Thr Ile Pro Glu Pro Val Lys Asp Leu Thr Leu Leu Asn Arg Ser
 820 825 830
 Thr Glu Asp Leu His Val Thr Trp Ser Arg Ala Asn Gly Asp Val Asp
 835 840 845
 Gln Tyr Glu Val Gln Leu Leu Phe Asn Asp Met Lys Val Phe Pro His
 850 855 860

233106-331560_Seq_Listing_ST25.txt

Ile His Leu Val Asn Thr Ala Thr Glu Tyr Lys Phe Thr Ala Leu Thr
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Pro Gly Arg His Tyr Lys Ile Leu Val Leu Thr Ile Ser Gly Asp Val
885 890 895

Gln Gln Ser Ala Phe Ile Glu Gly Leu Pro Val Pro Ser Thr Val Lys
900 905 910

Asn Ile His Ile Ser Ala Asn Gly Ala Thr Asp Arg Leu Met Val Thr
915 920 925

Trp Ser Pro Gly Gly Gly Asp Val Asp Ser Tyr Val Val Ser Ala Phe
930 935 940

Arg Gln Asp Glu Lys Val Asp Ser Gln Thr Ile Pro Lys His Ala Ser
945 950 955 960

Glu His Thr Phe His Arg Leu Glu Ala Gly Ala Lys Tyr Arg Ile Ala
965 970 975

Ile Val Ser Val Ser Gly Ser Leu Arg Asn Gln Ile Asp Ala Leu Gly
980 985 990

Gln Thr Val Pro Ala Ser Val Gln Gly Val Val Ala Ala Asn Ala Tyr
995 1000 1005

Ser Ser Asn Ser Leu Thr Val Ser Trp Gln Lys Ala Leu Gly Val
1010 1015 1020

Ala Glu Arg Tyr Asp Ile Leu Leu Leu Asn Glu Asn Gly Leu Leu
1025 1030 1035

Leu Ser Asn Val Ser Glu Pro Ala Thr Ala Arg Gln His Lys Phe
1040 1045 1050

Glu Asp Leu Thr Pro Gly Lys Lys Tyr Lys Met Gln Ile Leu Thr
1055 1060 1065

Val Ser Gly Gly Leu Phe Ser Lys Glu Ser Gln Ala Glu Gly Arg
1070 1075 1080

Thr Val Pro Ala Ala Val Thr Asn Leu Arg Ile Thr Glu Asn Ser
1085 1090 1095

Ser Arg Tyr Leu Ser Phe Gly Trp Thr Ala Ser Glu Gly Glu Leu
1100 1105 1110

Ser Trp Tyr Asn Ile Phe Leu Tyr Asn Pro Asp Arg Thr Leu Gln
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233106-331560_Seq_Listing_ST25.txt

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1145						1150					1155			
Ser	Gly	Glu	Leu	Ser	Asn	Glu	Ser	Phe	Ile	Phe	Gly	Arg	Thr	Val
1160						1165					1170			
Pro	Ala	Ala	Val	Asn	His	Leu	Lys	Gly	Ser	His	Arg	Asn	Thr	Thr
1175						1180					1185			
Asp	Ser	Leu	Trp	Phe	Ser	Trp	Ser	Pro	Ala	Ser	Gly	Asp	Phe	Asp
1190						1195					1200			
Phe	Tyr	Glu	Leu	Ile	Leu	Tyr	Asn	Pro	Asn	Gly	Thr	Lys	Lys	Glu
1205						1210					1215			
Asn	Trp	Lys	Glu	Lys	Asp	Val	Thr	Glu	Trp	Arg	Phe	Gln	Gly	Leu
1220						1225					1230			
Val	Pro	Gly	Arg	Lys	Tyr	Thr	Leu	Tyr	Val	Val	Thr	His	Ser	Gly
1235						1240					1245			
Asp	Leu	Ser	Asn	Lys	Val	Thr	Gly	Glu	Gly	Arg	Thr	Ala	Pro	Ser
1250						1255					1260			
Pro	Pro	Ser	Leu	Leu	Ser	Phe	Ala	Asp	Val	Ala	Asn	Thr	Ser	Leu
1265						1270					1275			
Ala	Ile	Thr	Trp	Lys	Gly	Pro	Pro	Asp	Trp	Thr	Asp	Tyr	Asn	Asp
1280						1285					1290			
Phe	Glu	Leu	Gln	Trp	Phe	Pro	Gly	Asp	Ala	Leu	Thr	Ile	Phe	Asn
1295						1300					1305			
Pro	Tyr	Ser	Ser	Arg	Lys	Ser	Glu	Gly	Arg	Ile	Val	Tyr	Gly	Leu
1310						1315					1320			
His	Pro	Gly	Arg	Ser	Tyr	Gln	Phe	Ser	Val	Lys	Thr	Val	Ser	Gly
1325						1330					1335			
Asp	Ser	Trp	Lys	Thr	Tyr	Ser	Lys	Pro	Ile	Ser	Gly	Ser	Val	Arg
1340						1345					1350			
Thr	Lys	Pro	Asp	Lys	Ile	Gln	Asn	Leu	His	Cys	Arg	Pro	Gln	Asn
1355						1360					1365			
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233106-331560_Seq_Listing_ST25.txt

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1400						1405					1410			
Met	Met	Leu	Val	Pro	His	Lys	Arg	Tyr	Leu	Val	Ser	Ile	Lys	Val
1415						1420					1425			
Gln	Ser	Ala	Gly	Met	Thr	Ser	Glu	Val	Val	Glu	Asp	Ser	Thr	Ile
1430						1435					1440			
Thr	Met	Ile	Asp	Arg	Pro	Pro	Gln	Pro	Pro	Pro	His	Ile	Arg	Val
1445						1450					1455			
Asn	Glu	Lys	Asp	Val	Leu	Ile	Ser	Lys	Ser	Ser	Ile	Asn	Phe	Thr
1460						1465					1470			
Val	Asn	Cys	Ser	Trp	Phe	Ser	Asp	Thr	Asn	Gly	Ala	Val	Lys	Tyr
1475						1480					1485			
Phe	Ala	Val	Val	Val	Arg	Glu	Ala	Asp	Ser	Met	Asp	Glu	Leu	Lys
1490						1495					1500			
Pro	Glu	Gln	Gln	His	Pro	Leu	Pro	Ser	Tyr	Leu	Glu	Tyr	Arg	His
1505						1510					1515			
Asn	Ala	Ser	Ile	Arg	Val	Tyr	Gln	Thr	Asn	Tyr	Phe	Ala	Ser	Lys
1520						1525					1530			
Cys	Ala	Glu	Ser	Pro	Asp	Ser	Ser	Ser	Lys	Ser	Phe	Asn	Ile	Lys
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Leu	Gly	Ala	Glu	Met	Asp	Ser	Leu	Gly	Gly	Lys	Cys	Asp	Pro	Ser
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Gln	Gln	Lys	Phe	Cys	Asp	Gly	Pro	Leu	Lys	Pro	His	Thr	Ala	Tyr
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Arg	Ile	Ser	Ile	Arg	Ala	Phe	Thr	Gln	Leu	Phe	Asp	Glu	Asp	Leu
1580						1585					1590			
Lys	Glu	Phe	Thr	Lys	Pro	Leu	Tyr	Ser	Asp	Thr	Phe	Phe	Ser	Met
1595						1600					1605			
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1610						1615					1620			
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1625						1630					1635			

233106-331560_Seq_Listing_ST25.txt

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His	Leu	Asn	Leu	Gly	Gln	Lys	Gly	Asn	Arg	Lys	Thr	Ser	Cys	Pro
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Ile	Lys	Ile	Asn	Gln	Phe	Glu	Gly	His	Phe	Met	Lys	Leu	Gln	Ala
	1685					1690					1695			
Asp	Ser	Asn	Tyr	Leu	Leu	Ser	Lys	Glu	Tyr	Glu	Asp	Leu	Lys	Asp
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Val	Gly	Arg	Ser	Gln	Ser	Cys	Asp	Ile	Ala	Leu	Leu	Pro	Glu	Asn
	1715					1720					1725			
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	1835					1840					1845			
Ile	Cys	Ser	Glu	Glu	Gln	Leu	Asp	Ala	His	Arg	Leu	Ile	Arg	His
	1850					1855					1860			
Phe	His	Tyr	Thr	Val	Trp	Pro	Asp	His	Gly	Val	Pro	Glu	Thr	Thr
	1865					1870					1875			
Gln	Ser	Leu	Ile	Gln	Phe	Val	Arg	Thr	Val	Arg	Asp	Tyr	Ile	Asn
	1880					1885					1890			

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Arg Ser Pro Gly Ala Gly Pro Thr Val Val His Cys Ser Ala Gly
1895 1900 1905

Val Gly Arg Thr Gly Thr Phe Val Ala Leu Asp Arg Ile Leu Gln
1910 1915 1920

Gln Leu Asp Ser Lys Asp Ser Val Asp Ile Tyr Gly Ala Val His
1925 1930 1935

Asp Leu Arg Leu His Arg Val His Met Val Gln Thr Glu Cys Gln
1940 1945 1950

Tyr Val Tyr Leu His Gln Cys Val Arg Asp Val Leu Arg Ala Lys
1955 1960 1965

Lys Leu Arg Asn Glu Gln Glu Asn Pro Leu Phe Pro Ile Tyr Glu
1970 1975 1980

Asn Val Asn Pro Glu Tyr His Arg Asp Ala Ile Tyr Ser Arg His
1985 1990 1995

<210> 7
<211> 1619
<212> PRT
<213> Mus musculus
<400> 7

Met Leu Arg His Gly Ala Leu Thr Ala Leu Trp Ile Thr Leu Ser Val
1 5 10 15

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

Glu Ser Arg Val Ser Ser Leu Ser Ala Ser Ile Gln Trp Arg Thr Phe
35 40 45

Ala Ser Pro Cys Asn Phe Ser Leu Ile Tyr Ser Ser Asp Thr Ser Gly
50 55 60

Pro Met Trp Cys His Pro Ile Arg Ile Asp Asn Phe Thr Tyr Gly Cys
65 70 75 80

Asn Pro Lys Asp Leu Gln Ala Gly Thr Val Tyr Asn Phe Arg Ile Val
85 90 95

Ser Leu Asp Gly Glu Glu Ser Thr Leu Val Leu Gln Thr Asp Pro Leu
100 105 110

Pro Pro Ala Arg Phe Glu Val Asn Arg Glu Lys Thr Ala Ser Thr Thr
115 120 125

Leu Gln Val Arg Trp Thr Pro Ser Ser Gly Lys Val Ser Trp Tyr Glu
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140

Val Gln Leu Phe Asp His Asn Asn Gln Lys Ile Gln Glu Val Gln Val
145 150 155 160

Gln Glu Ser Thr Thr Trp Ser Gln Tyr Thr Phe Leu Asn Leu Thr Glu
165 170 175

Gly Asn Ser Tyr Lys Val Ala Ile Thr Ala Val Ser Gly Glu Lys Arg
180 185 190

Ser Phe Pro Val Tyr Ile Asn Gly Ser Thr Val Pro Ser Pro Val Lys
195 200 205

Asp Leu Gly Ile Ser Pro Asn Pro Asn Ser Leu Leu Ile Ser Trp Ser
210 215 220

Arg Gly Ser Gly Asn Val Glu Gln Tyr Arg Leu Val Leu Met Asp Lys
225 230 235 240

Gly Ala Ile Val Gln Asp Thr Asn Val Asp Arg Arg Asp Thr Ser Tyr
245 250 255

Ala Phe His Glu Leu Thr Pro Gly His Leu Tyr Asn Leu Thr Ile Val
260 265 270

Thr Met Ala Ser Gly Leu Gln Asn Ser Arg Trp Lys Leu Val Arg Thr
275 280 285

Ala Pro Met Glu Val Ser Asn Leu Lys Val Thr Asn Asp Gly Arg Leu
290 295 300

Thr Ser Leu Asn Val Lys Trp Gln Lys Pro Pro Gly Asp Val Asp Ser
305 310 315 320

Tyr Ser Ile Thr Leu Ser His Gln Gly Thr Ile Lys Glu Ser Lys Thr
325 330 335

Leu Ala Pro Pro Val Thr Glu Thr Gln Phe Lys Asp Leu Val Pro Gly
340 345 350

Arg Leu Tyr Gln Val Thr Ile Ser Cys Ile Ser Gly Glu Leu Ser Ala
355 360 365

Glu Lys Ser Ala Ala Gly Arg Thr Val Pro Glu Lys Val Arg Asn Leu
370 375 380

Val Ser Tyr Asn Glu Ile Trp Met Lys Ser Phe Thr Val Asn Trp Thr
385 390 395 400

Pro Pro Ala Gly Asp Trp Glu His Tyr Arg Ile Val Leu Phe Asn Glu
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405

410

415

Ser Leu Val Leu Leu Asn Thr Thr Val Gly Lys Glu Glu Thr His Tyr
 420 425 430

Ala Leu Asp Gly Leu Glu Leu Ile Pro Gly Arg Gln Tyr Glu Ile Glu
 435 440 445

Val Ile Val Glu Ser Gly Asn Leu Arg Asn Ser Glu Arg Cys Gln Gly
 450 455 460

Arg Thr Val Pro Leu Ala Val Leu Gln Leu Arg Val Lys His Ala Asn
 465 470 475 480

Glu Thr Ser Leu Gly Ile Thr Trp Arg Ala Pro Leu Gly Glu Trp Glu
 485 490 495

Lys Tyr Ile Ile Ser Leu Met Asp Arg Glu Leu Leu Val Ile His Lys
 500 505 510

Ser Leu Ser Lys Asp Ala Lys Glu Phe Thr Phe Thr Asp Leu Met Pro
 515 520 525

Gly Arg Asn Tyr Lys Ala Thr Val Thr Ser Met Ser Gly Asp Leu Lys
 530 535 540

Gln Ser Ser Ser Ile Lys Gly Arg Thr Val Pro Ala Gln Val Thr Asp
 545 550 555 560

Leu His Val Asn Asn Gln Gly Met Thr Ser Ser Leu Phe Thr Asn Trp
 565 570 575

Thr Lys Ala Leu Gly Asp Val Glu Phe Tyr Gln Val Leu Leu Ile His
 580 585 590

Glu Asn Val Val Val Lys Asn Glu Ser Val Ser Ser Asp Thr Ser Arg
 595 600 605

Tyr Ser Phe Arg Ala Leu Lys Pro Gly Ser Leu Tyr Ser Val Val Val
 610 615 620

Thr Thr Val Ser Gly Gly Ile Ser Ser Arg Gln Val Val Ala Glu Gly
 625 630 635 640

Arg Thr Val Pro Ser Ser Val Ser Gly Val Thr Val Asn Asn Ser Gly
 645 650 655

Arg Asn Asp Tyr Leu Ser Val Ser Trp Leu Pro Ala Pro Gly Glu Val
 660 665 670

Asp His Tyr Val Val Ser Leu Ser His Glu Gly Lys Val Asp Gln Phe

675

680

685

Leu Ile Ile Ala Lys Ser Val Ser Glu Cys Ser Phe Ser Ser Leu Thr
 690 695 700

Pro Gly Arg Leu Tyr Asn Val Thr Val Thr Thr Lys Ser Gly Asn Tyr
 705 710 715

Ala Ser His Ser Phe Thr Glu Glu Arg Thr Val Pro Asp Lys Val Gln
 725 730 735

Gly Ile Ser Val Ser Asn Ser Ala Arg Ser Asp Tyr Leu Lys Val Ser
 740 745 750

Trp Val His Ala Thr Gly Asp Phe Asp His Tyr Glu Val Thr Ile Lys
 755 760 765

Asn Arg Glu Ser Phe Ile Gln Thr Lys Thr Ile Pro Lys Ser Glu Asn
 770 775 780

Glu Cys Glu Phe Ile Glu Leu Val Pro Gly Arg Leu Tyr Ser Val Thr
 785 790 795 800

Val Ser Thr Lys Ser Gly Gln Tyr Glu Ala Ser Glu Gln Gly Thr Gly
 805 810 815

Arg Thr Ile Pro Glu Pro Val Lys Asp Leu Thr Leu Leu Asn Arg Ser
 820 825 830

Thr Glu Asp Leu His Val Thr Trp Ser Arg Ala Asn Gly Asp Val Asp
 835 840 845

Gln Tyr Glu Val Gln Leu Leu Phe Asn Asp Met Lys Val Phe Pro His
 850 855 860

Ile His Leu Val Asn Thr Ala Thr Glu Tyr Lys Phe Thr Ala Leu Thr
 865 870 875 880

Pro Gly Arg His Tyr Lys Ile Leu Val Leu Thr Ile Ser Gly Asp Val
 885 890 895

Gln Gln Ser Ala Phe Ile Glu Gly Leu Pro Val Pro Ser Thr Val Lys
 900 905 910

Asn Ile His Ile Ser Ala Asn Gly Ala Thr Asp Arg Leu Met Val Thr
 915 920 925

Trp Ser Pro Gly Gly Gly Asp Val Asp Ser Tyr Val Val Ser Ala Phe
 930 935 940

Arg Gln Asp Glu Lys Val Asp Ser Gln Thr Ile Pro Lys His Ala Ser

945

950

955

960

Glu His Thr Phe His Arg Leu Glu Ala Gly Ala Lys Tyr Arg Ile Ala
 965 970 975

Ile Val Ser Val Ser Gly Ser Leu Arg Asn Gln Ile Asp Ala Leu Gly
 980 985 990

Gln Thr Val Pro Ala Ser Val Gln Gly Val Val Ala Ala Asn Ala Tyr
 995 1000 1005

Ser Ser Asn Ser Leu Thr Val Ser Trp Gln Lys Ala Leu Gly Val
 1010 1015 1020

Ala Glu Arg Tyr Asp Ile Leu Leu Leu Asn Glu Asn Gly Leu Leu
 1025 1030 1035

Leu Ser Asn Val Ser Glu Pro Ala Thr Ala Arg Gln His Lys Phe
 1040 1045 1050

Glu Asp Leu Thr Pro Gly Lys Lys Tyr Lys Met Gln Ile Leu Thr
 1055 1060 1065

Val Ser Gly Gly Leu Phe Ser Lys Glu Ser Gln Ala Glu Gly Arg
 1070 1075 1080

Thr Val Pro Ala Ala Val Thr Asn Leu Arg Ile Thr Glu Asn Ser
 1085 1090 1095

Ser Arg Tyr Leu Ser Phe Gly Trp Thr Ala Ser Glu Gly Glu Leu
 1100 1105 1110

Ser Trp Tyr Asn Ile Phe Leu Tyr Asn Pro Asp Arg Thr Leu Gln
 1115 1120 1125

Glu Arg Ala Gln Val Asp Pro Leu Val Gln Ser Phe Ser Phe Gln
 1130 1135 1140

Asn Leu Leu Gln Gly Arg Met Tyr Lys Met Val Ile Val Thr His
 1145 1150 1155

Ser Gly Glu Leu Ser Asn Glu Ser Phe Ile Phe Gly Arg Thr Val
 1160 1165 1170

Pro Ala Ala Val Asn His Leu Lys Gly Ser His Arg Asn Thr Thr
 1175 1180 1185

Asp Ser Leu Trp Phe Ser Trp Ser Pro Ala Ser Gly Asp Phe Asp
 1190 1195 1200

Phe Tyr Glu Leu Ile Leu Tyr Asn Pro Asn Gly Thr Lys Lys Glu

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1205

1210

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Asn Trp Lys Glu Lys Asp Val Thr Glu Trp Arg Phe Gln Gly Leu
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Val Pro Gly Arg Lys Tyr Thr Leu Tyr Val Val Thr His Ser Gly
1235 1240 1245

Asp Leu Ser Asn Lys Val Thr Gly Glu Gly Arg Thr Ala Pro Ser
1250 1255 1260

Pro Pro Ser Leu Leu Ser Phe Ala Asp Val Ala Asn Thr Ser Leu
1265 1270 1275

Ala Ile Thr Trp Lys Gly Pro Pro Asp Trp Thr Asp Tyr Asn Asp
1280 1285 1290

Phe Glu Leu Gln Trp Phe Pro Gly Asp Ala Leu Thr Ile Phe Asn
1295 1300 1305

Pro Tyr Ser Ser Arg Lys Ser Glu Gly Arg Ile Val Tyr Gly Leu
1310 1315 1320

His Pro Gly Arg Ser Tyr Gln Phe Ser Val Lys Thr Val Ser Gly
1325 1330 1335

Asp Ser Trp Lys Thr Tyr Ser Lys Pro Ile Ser Gly Ser Val Arg
1340 1345 1350

Thr Lys Pro Asp Lys Ile Gln Asn Leu His Cys Arg Pro Gln Asn
1355 1360 1365

Ser Thr Ala Ile Ala Cys Ser Trp Ile Pro Pro Asp Ser Asp Phe
1370 1375 1380

Asp Gly Tyr Ser Ile Glu Cys Arg Lys Met Asp Thr Gln Glu Ile
1385 1390 1395

Glu Phe Ser Arg Lys Leu Glu Lys Glu Lys Ser Leu Leu Asn Ile
1400 1405 1410

Met Met Leu Val Pro His Lys Arg Tyr Leu Val Ser Ile Lys Val
1415 1420 1425

Gln Ser Ala Gly Met Thr Ser Glu Val Val Glu Asp Ser Thr Ile
1430 1435 1440

Thr Met Ile Asp Arg Pro Pro Gln Pro Pro Pro His Ile Arg Val
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Asn Glu Lys Asp Val Leu Ile Ser Lys Ser Ser Ile Asn Phe Thr

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1460

1465

1470

Val Asn Cys Ser Trp Phe Ser Asp Thr Asn Gly Ala Val Lys Tyr
 1475 1480 1485

Phe Ala Val Val Val Arg Glu Ala Asp Ser Met Asp Glu Leu Lys
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Pro Glu Gln Gln His Pro Leu Pro Ser Tyr Leu Glu Tyr Arg His
 1505 1510 1515

Asn Ala Ser Ile Arg Val Tyr Gln Thr Asn Tyr Phe Ala Ser Lys
 1520 1525 1530

Cys Ala Glu Ser Pro Asp Ser Ser Ser Lys Ser Phe Asn Ile Lys
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Leu Gly Ala Glu Met Asp Ser Leu Gly Gly Lys Cys Asp Pro Ser
 1550 1555 1560

Gln Gln Lys Phe Cys Asp Gly Pro Leu Lys Pro His Thr Ala Tyr
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Arg Ile Ser Ile Arg Ala Phe Thr Gln Leu Phe Asp Glu Asp Leu
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Lys Glu Phe Thr Lys Pro Leu Tyr Ser Asp Thr Phe Phe Ser Met
 1595 1600 1605

Pro Ile Thr Thr Glu Ser Glu Pro Leu Phe Gly
 1610 1615