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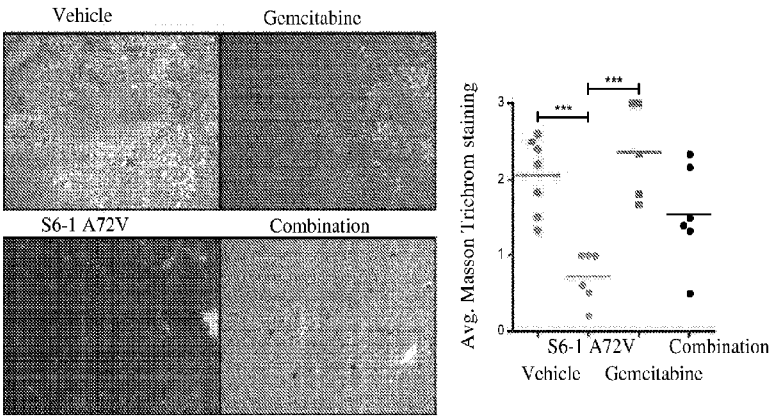

FIGURE 1

(57) **Abstract**: Compositions and methods are provided for treating fibrosis in a mammal by administering a therapeutic dose of a pharmaceutical composition that inhibits AXL, MER or Tyro3 protein activity, for example by inhibition of the binding interaction between AXL, MER or Tyro3 and its ligand GAS6.

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ANTIFIBROTIC ACTIVITY OF GAS6 INHIBITOR

BACKGROUND OF THE INVENTION

[0001] Fibrosis, defined by the excessive accumulation of extracellular matrix components (ECM) in and around inflamed or damaged tissue, is associated with several inflammatory conditions. In these situations, normal tissue repair response turns into an irreversible fibrotic response through dysregulation of response to stress or injury. Fibrosis can lead to permanent scarring, organ malfunction and, ultimately, death, as seen in end-stage liver disease, kidney disease, idiopathic pulmonary fibrosis (IPF), retinal fibrosis, and heart failure from cardiac fibrosis. Fibrosis also influences tumor invasion and metastasis, chronic graft rejection and the pathogenesis of many progressive myopathies.

[0002] Many distinct triggers can contribute to the development of progressive fibrotic disease, but regardless of the initiating events, a common feature is the activation of ECM-producing myofibroblasts, which are the key mediators of fibrotic tissue remodeling. Many elements of the innate and adaptive immune response participate in the differentiation and activation of fibroblasts. During equilibrium, tissue-resident fibroblasts are quiescent. To repair tissues after injury, these tissue-resident fibroblasts are activated and transformed into myofibroblasts. Myofibroblasts secrete large amounts of ECM, aiding in contracture and closure and orchestrating many aspects of the healing response. Myofibroblast activation, proliferation and survival are mediated by a variety of secreted, soluble and physical factors in the milieu, such as cytokines including IL-1, TNF, TGF-β1 and IL-13, growth factors such as CTGF and PDGF, and matrix factors such as hyaluronan fragments, mechanical stress and stiffness. During normal wound healing, myofibroblasts undergo apoptosis after re-epithelialization of the wound, but myofibroblasts in fibrotic loci are resistant to programmed cell death. Pathways that elicit and recruit high numbers of myofibroblasts and those that engender resistance to apoptosis are active areas of fibrosis research.

[0003] Because ECM-producing myofibroblasts are the final common pathogenic cell in fibrotic diseases, any therapy that successfully ablates their activity could have broad antifibrotic activity. Targeting key inflammatory pathways may also be useful in the treatment of fibrosis. Because TNF-α has emerged as a key driver of fibrosis in many experimental studies, clinical trials have been initiated to examine whether inhibitors of the TNF α pathway could be used to treat IPF and other scarring disorders.

[0004] Antifibrotic compositions and methods of use thereof are of great clinical and humanitarian interest. The present invention addresses this need.

SUMMARY OF THE INVENTION

[0005] The present invention provides compositions and methods useful for inhibiting fibrosis via inhibition of AXL and/or GAS6 related pathways. In some embodiments the inhibitor is a high affinity soluble AXL variant polypeptide. In some embodiments the fibrosis is associated with cancer and tumor growth, i.e. tumor related tissue fibrosis, including without limitation pancreatic cancer. In other embodiments the fibrosis is associated with chronic inflammation or injury in other tissues, including without limitation liver, lung, kidney, and the like..

[0006] In some embodiments, the inhibitor is a polypeptide, a polynucleotide, a small molecule, an antibody, an antibody fragment or antibody drug-conjugate capable of binding to GAS6 with increased affinity compared to wild-type AXL, MER or Tyro3. In some embodiments, the inhibitor agent binds to two or more epitopes on a single GAS6. In some embodiments, the inhibitor agent is capable of binding to the major and minor AXL, MER or Tyro3 binding sites on a single GAS6. In some embodiments, the inhibitor agent is capable of binding the major AXL, MER or Tyro3 binding site of GAS6 and one or more additional GAS6 epitopes on a single GAS6. In some embodiments, the inhibitor agent is capable of binding to the minor AXL, MER or Tyro3 binding site on GAS6 and one or more additional epitopes on a single GAS6. In some embodiments, the inhibitor agent is capable of binding two or more epitopes on a single GAS6. In some embodiments, the inhibitor agent is capable of antagonizing the major and/or minor GAS6/receptor binding interaction, and wherein the receptor is selected from AXL, MER and Tyro3. In some embodiments, the inhibitor agent is capable of antagonizing the major GAS6/receptor binding interaction, and wherein the receptor is selected from AXL, MER and Tyro3. In some embodiments, the inhibitor agent is capable of antagonizing the minor GAS6/receptor binding interaction, and wherein the receptor is selected from AXL, MER and Tyro3. In some embodiments the inhibitor is a small molecule that binds to the kinase domain of AXL and inhibit the intracellular signaling of AXL activation.

[0007] In some embodiments, the inhibitor agent is a small molecule, polypeptide, a polypeptide-carrier fusion, a polypeptide-Fc fusion, polypeptide-conjugate, a polypeptide-drug conjugate, an antibody, a bispecific antibody, an antibody drug conjugate, an antibody fragment, an antibody-related structure, or a combination thereof. In some embodiments, the inhibitor agent is a natural or synthetic polypeptide. In some embodiments, the inhibitor agent is a non-antibody polypeptide.

[0008] In some embodiments, the inhibitor agent is a darpin, an avimer, an adnectin, an anticalin, an affibody, a maxibody or a combination thereof. In some embodiments, the inhibitor

agent is a polypeptide-conjugate or an antibody-conjugate. In some embodiments, the inhibitor agent comprises a polypeptide-polymer conjugate, and wherein the polymer is a PEG, a PEG-containing polymer, a degradable polymer, a biocompatible polymer or a hydrogel.

[0009] In some embodiments, the inhibitor agent is a polypeptide, wherein the polypeptide comprises a soluble AXL variant polypeptide wherein the AXL polypeptide lacks the AXL transmembrane domain and has at least one mutation relative to wild-type that increases affinity of the AXL polypeptide binding to GAS6 compared to wild-type AXL.

[0010] In some embodiments, the inhibitor agent is a polypeptide, wherein the polypeptide comprises a soluble MER variant polypeptide wherein said MER polypeptide lacks the MER transmembrane domain and has at least one mutation relative to wild-type that increases affinity of the MER polypeptide binding to GAS6 compared to wild-type MER.

[0011] In some embodiments, the inhibitor agent is a polypeptide, wherein said polypeptide comprises a soluble Tyro3 variant polypeptide wherein said Tyro3 polypeptide lacks the Tyro3 transmembrane domain and has at least one mutation relative to wild-type that increases affinity of the Tyro3 polypeptide binding to GAS6 compared to wild-type Tyro3.

[0012] In some embodiments, the AXL, MER or Tyro3 variant polypeptide inhibits binding between a wild-type AXL, MER and/or Tyro3 polypeptide and a GAS6 protein in vivo or in vitro.

[0013] In some embodiments, the AXL, MER or Tyro3 variant polypeptide lacks a functional fibronectin (FN) domain and/or wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

[0014] In some embodiments, the AXL, MER or Tyro3 variant polypeptide lacks the transmembrane domain, has more than one Ig1 domain and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

[0015] In some embodiments, the polypeptide has two Ig1 domains. In some embodiments, the polypeptide has three Ig1 domains. In some embodiments, the soluble AXL, MER or Tyro3 variant polypeptide lacks the transmembrane domain, has more than one Ig2 domain and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3. In some embodiments, the polypeptide has two Ig2 domains.

[0016] In some embodiments, the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said soluble AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, has more than one Ig1 domain, more than one Ig2 domain,

and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

[0017] In some embodiments, the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said soluble AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, lacks a functional fibronectin (FN) domain, has more than one Ig1 domain, more than one Ig2 domain, and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

[0018] In some embodiments, the soluble AXL, MER or Tyro3 variant polypeptide has two Ig1 domains and two Ig2 domains. In some embodiments, the immunoglobulin domains are connected directly. In some embodiments, the immunoglobulin domains are connected indirectly. In some embodiments, the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, is capable of binding both the major and minor binding site of a single GAS6 and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 polypeptide binding to GAS6.

[0019] In some embodiments, the polypeptide has one Ig1 domain and lacks a functional Ig2 domain. In some embodiments, the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said soluble AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, has one Ig1 domain, lacks a functional Ig2 domain and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

[0020] In some embodiments, the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said soluble AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, lacks a functional fibronectin (FN) domain, has one Ig1 domain, lacks a functional Ig2 domain and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

[0021] In some embodiments, the AXL, MER or Tyro3 variant polypeptide is a fusion protein comprising an Fc domain. In some embodiments, the variant polypeptide lacks the AXL, MER or Tyro3 intracellular domain. In some embodiments, the soluble AXL, MER or Tyro3 variant polypeptide further lacks a functional fibronectin (FN) domain and wherein said variant polypeptide exhibits increased affinity of the polypeptide binding to GAS6. In some

embodiments, the soluble AXL, MER or Tyro3 variant polypeptide comprises at least one amino acid modification relative to the wild-type AXL, MER or Tyro3 sequence.

[0022] In some embodiments, the soluble AXL variant polypeptide comprises at least one amino acid modification within a region selected from the group consisting of 1) between 15-50, 2) between 60-120, and 3) between 125-135 of the wild-type AXL sequence (SEQ ID NO:1).

[0023] In some embodiments, the soluble AXL variant polypeptide comprises at least one amino acid modification at position 19, 23, 26, 27, 32, 33, 38, 44, 61, 65, 72, 74, 78, 79, 86, 87, 88, 90, 92, 97, 98, 105, 109, 112, 113, 116, 118, or 127 of the wild-type AXL sequence (SEQ ID NO: 1) or a combination thereof.

[0024] In some embodiments, the soluble AXL variant polypeptide comprises at least one amino acid modification selected from the group consisting of 1) A19T, 2) T23M, 3) E26G, 4) E27G or E27K 5) G32S, 6) N33S, 7) T38I, 8) T44A, 9) H61Y, 10) D65N, 11) A72V, 12) S74N, 13) Q78E, 14) V79M, 15) Q86R, 16) D87G, 17) D88N, 18) I90M or I90V, 19) V92A, V92G or V92D, 20) I97R, 21) T98A or T98P, 22) T105M, 23) Q109R, 24) V112A, 25) F113L, 26) H116R, 27) T118A, 28) G127R or G127E, and 29) G129E and a combination thereof.

[0025] In some embodiments, the AXL variant polypeptide comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) valine 92; and (d) glycine 127.

[0026] In some embodiments, the AXL variant polypeptide comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following positions: (a) aspartic acid 87 and (b) valine 92.

[0027] In some embodiments, the AXL variant polypeptide comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) valine 92; (d) glycine 127 and (e) alanine 72.

[0028] In some embodiments, the AXL variant polypeptide comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following position: alanine 72.

[0029] In some embodiments, in the AXL variant polypeptide glycine 32 residue is replaced with a serine residue, aspartic acid 87 residue is replaced with a glycine residue, valine 92 residue is replaced with an alanine residue, or glycine 127 residue is replaced with an arginine residue or a combination thereof.

[0030] In some embodiments, in the AXL variant polypeptide aspartic acid 87 residue is replaced with a glycine residue or valine 92 residue is replaced with an alanine residue or a combination thereof.

[0031] In some embodiments, in the AXL variant polypeptide alanine 72 residue is replaced with a valine residue.

[0032] In some embodiments, in the AXL variant polypeptide glycine 32 residue is replaced with a serine residue, aspartic acid 87 residue is replaced with a glycine residue, valine 92 residue is replaced with an alanine residue, glycine 127 residue is replaced with an arginine residue or an alanine 72 residue is replaced with a valine residue or a combination thereof.

[0033] In some embodiments, the AXL variant comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following positions: (a) glutamic acid 26; (b) valine 79; (c) valine 92; and (d) glycine 127.

[0034] In some embodiments, in the AXL variant polypeptide glutamic acid 26 residue is replaced with a glycine residue, valine 79 residue is replaced with a methionine residue, valine 92 residue is replaced with an alanine residue, or glycine 127 residue is replaced with an arginine residue or a combination thereof.

[0035] In some embodiments, in the AXL variant polypeptide comprises at least an amino acid region selected from the group consisting of amino acid region 19-437, 130-437, 19-132, 21-121, 26-132, 26-121 and 1-437 of the wild-type AXL polypeptide (SEQ ID NO: 1), and wherein one or more amino acid modifications occur in said amino acid region.

[0036] In some embodiments, in the AXL variant polypeptide comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; and valine 92.

[0037] In some embodiments, in the AXL variant polypeptide glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, and valine 92 is replaced with an alanine residue, or a combination thereof.

[0038] In some embodiments, the soluble AXL polypeptide is a fusion protein comprising an Fc domain and wherein said AXL variant comprises amino acid changes relative to wild-type AXL sequence (SEQ ID NO:1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; and (d) valine 92.

[0039] In some embodiments, the soluble AXL polypeptide is a fusion protein comprising an Fc domain and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, and valine 92 is replaced with an alanine residue, or a combination thereof.

[0040] In some embodiments, the soluble AXL polypeptide is a fusion protein comprising an Fc domain and wherein said AXL variant comprises amino acid changes relative to wild-type AXL

sequence (SEQ ID NO:1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; (d) valine 92; and (e) glycine 127.

[0041] In some embodiments, the soluble AXL polypeptide is a fusion protein comprising an Fc domain and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, valine 92 is replaced with an alanine residue, and glycine 127 is replaced with an arginine residue or a combination thereof.

[0042] In some embodiments, the soluble AXL polypeptide is a fusion protein comprising an Fc domain, lacks a functional FN domain, and wherein said AXL variant comprises amino acid changes relative to wild-type AXL sequence (SEQ ID NO:1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; and (d) valine 92.

[0043] In some embodiments, the soluble AXL variant is a fusion protein comprising an Fc domain, lacks a functional FN domain, and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, and valine 92 is replaced with an alanine residue, or a combination thereof.

[0044] In some embodiments, the soluble AXL polypeptide is a fusion protein comprising an Fc domain, lacks a functional FN domain, and wherein said AXL variant comprises amino acid changes relative to wild-type AXL sequence (SEQ ID NO:1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; (d) valine 92; and (e) glycine 127.

[0045] In some embodiments, the soluble AXL variant is a fusion protein comprising an Fc domain, lacks a functional FN domain, and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, valine 92 is replaced with an alanine residue, and glycine 127 is replaced with an arginine residue or a combination thereof.

[0046] In some embodiments, the soluble AXL polypeptide is a fusion protein comprising an Fc domain, lacks a functional FN domain, lacks an Ig2 domain, and wherein said AXL variant comprises amino acid changes relative to wild-type AXL sequence (SEQ ID NO:1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72 and (d) valine 92.

[0047] In some embodiments, the soluble AXL variant is a fusion protein comprising an Fc domain, lacks a functional FN domain, lacks an Ig2 domain and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, and valine 92 is replaced with an alanine residue or a combination thereof.

[0048] In some embodiments, the soluble AXL polypeptide is a fusion protein comprising an Fc domain, lacks a functional FN domain, lacks an Ig2 domain, and wherein said AXL variant comprises amino acid changes relative to wild-type AXL sequence (SEQ ID NO:1) at the

following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; (d) valine 92; and (e) glycine 127.

[0049] In some embodiments, the soluble AXL variant is a fusion protein comprising an Fc domain, lacks a functional FN domain, lacks an Ig2 domain and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, valine 92 is replaced with an alanine residue, and glycine 127 is replaced with an arginine residue or a combination thereof.

[0050] In some embodiments, the soluble AXL variant polypeptide has an affinity of at least about 1×10^{-8} M, 1×10^{-9} M, 1×10^{-10} M, 1×10^{-11} M or 1×10^{-12} M for GAS6.

[0051] In some embodiments, the soluble AXL variant polypeptide exhibits an affinity to GAS6 that is at least about 5-fold stronger, at least about 10-fold stronger or at least about 20-fold stronger than the affinity of the wild-type AXL polypeptide.

[0052] In some embodiments, the soluble AXL, MER or Tyro3 variant polypeptide further comprises a linker. In some embodiments, the linker comprises one or more $(GLY)_4SER$ units. In some embodiments, the linker comprises 1, 2, 3 or 5 $(GLY)_4SER$ units.

[0053] In some embodiments, the soluble AXL MER and/or Tyro3 variant polypeptide inhibits binding between wild-type AXL, MER and/or Tyro3 polypeptide and a GAS6 protein *in vivo* or *in vitro*.

[0054] In some embodiments, the soluble AXL variant polypeptide is a fusion polypeptide comprising an Fc domain.

[0055] Thus, the invention relates to an inhibitor of AXL and/or GAS6 related pathways for use for preventing or treating fibrosis, comprising administering to an individual in need thereof a therapeutically effective amount of an inhibitor of the invention.

[0056] Also provided is a pharmaceutical composition comprising an inhibitor of AXL and/or GAS6 related pathways as described above, and additionally at least one other antifibrotic compound; or if appropriate in combination with a chemotherapeutic drug for the treatment of cancer. Also provided is the use of an inhibitor of the invention for the manufacture of a medicament for preventing or treating fibrosis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0057] Figure 1. Analysis of pancreatic cancer fibrosis after treatment with inhibitory axl polypeptide.

DEFINITIONS

[0058] In the description that follows, a number of terms conventionally used in the field of cell culture are utilized extensively. In order to provide a clear and consistent understanding of the specification and claims, and the scope to be given to such terms, the following definitions are provided.

[0059] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of two or more amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymers. The terms “antibody” and “antibodies” are used interchangeably herein and refer to a polypeptide capable of interacting with and/or binding to another molecule, often referred to as an antigen. Antibodies can include, for example “antigen-binding polypeptides” or “target-molecule binding polypeptides.” Antigens of the present invention can include for example any polypeptides described in the present invention.

[0060] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, *e.g.*, hydroxyproline, gamma-carboxyglutamate, and O-phosphoserine. Amino acid analogs refer to compounds that have the same basic chemical structure as a naturally occurring amino acid, *i.e.*, an .alpha. carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, *e.g.*, homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (*e.g.*, norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid. All single letters used in the present invention to represent amino acids are used according to recognized amino acid symbols routinely used in the field, *e.g.*, A means Alanine, C means Cysteine, etc. An amino acid is represented by a single letter before and after the relevant position to reflect the change from original amino acid (before the position) to changed amino acid (after position). For example, A19T means that amino acid alanine at position 19 is changed to threonine.

[0061] The terms “subject,” “individual,” and “patient” are used interchangeably herein to refer to a mammal being assessed for treatment and/or being treated. In an embodiment, the mammal is a human. The terms “subject,” “individual,” and “patient” thus encompass individuals

having cancer, including without limitation, pancreatic cancer, adenocarcinoma of the ovary or prostate, breast cancer, glioblastoma, *etc.*, including those who have undergone or are candidates for resection (surgery) to remove cancerous tissue. Subjects may be human, but also include other mammals, particularly those mammals useful as laboratory models for human disease, *e.g.* mouse, rat, *etc.*

[0062] The definition of an appropriate patient sample encompasses blood and other liquid samples of biological origin, solid tissue samples such as a biopsy specimen or tissue cultures or cells derived there from and the progeny thereof. The definition also includes samples that have been manipulated in any way after their procurement, such as by treatment with reagents; washed; or enrichment for certain cell populations, such as endometrial cells, kidney disease cells, inflammatory disease cells and/or transplant rejection (GVHD) cells. The definition also includes sample that have been enriched for particular types of molecules, *e.g.*, nucleic acids, polypeptides, *etc.* The term "biological sample" encompasses a clinical sample, and also includes tissue obtained by surgical resection, tissue obtained by biopsy, cells in culture, cell supernatants, cell lysates, tissue samples, organs, bone marrow, blood, plasma, serum, and the like. A "biological sample" includes a sample obtained from a patient's sample cell, *e.g.*, a sample comprising polynucleotides and/or polypeptides that is obtained from a patient's sample cell (*e.g.*, a cell lysate or other cell extract comprising polynucleotides and/or polypeptides); and a sample comprising sample cells from a patient. A biological sample comprising a sample cell from a patient can also include normal, non-diseased cells.

[0063] The term "diagnosis" is used herein to refer to the identification of a molecular or pathological state, disease or condition, such as the identification of fibrosis.

[0064] Fibrosis is the excessive accumulation of extracellular matrix components (ECM) in and around inflamed or damaged tissue, often associated with chronic inflammation or cancer. The presence of fibrosis can be detected by means known in the art, for example by examination of tissue for excess scarring. Prior to fibrosis, an individual may be determined to be susceptible based on undesirable increase in inflammatory mediators that can exacerbate tissue injury, such as IL-1β, TNF-α and reactive oxygen and nitrogen species. Profibrotic mediators such as TGF-β1 may be present. Also present are activated myofibroblasts, which may be resistant to induction of apoptosis.

[0065] Exemplary forms of fibrosis include, but are not limited to, tumor fibrosis, cardiac fibrosis, liver fibrosis, kidney fibrosis, lung fibrosis, dermal scarring and keloids, and Alzheimer's disease. In still further embodiments, cardiac fibrosis is associated with hypertension, hypertensive heart

disease (HHD), myocardial infarction (MI), cardiac scarring related to ischemia congestive heart failure, cardiomyopathy, post-myocardial infarction defects in heart function, atherosclerosis, and restenosis. Kidney fibrosis may include, but not be limited to, diabetic nephropathy, vesicoureteral reflux, tubulointerstitial renal fibrosis, glomerulonephritis or glomerular nephritis (GN), focal segmental glomerulosclerosis, membranous glomerulonephritis, or mesangiocapillary GN. Liver fibrosis may include, but not be limited to, cirrhosis, and associated conditions such as chronic viral hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic steatohepatitis (ASH), non-alcoholic steatohepatitis (NASH), primary biliary cirrhosis (PBC), biliary cirrhosis, autoimmune hepatitis). Lung fibrosis may include idiopathic pulmonary fibrosis (IPF) or cryptogenic fibrosing alveolitis, chronic fibrosing interstitial pneumonia, interstitial lung disease (ILD), and diffuse parenchymal lung disease (DPLD)), lung scarring including without limitation damage from bacterial viral or fungal infection, emphysema, chronic obstructive pulmonary disease (COPD); and chronic asthma may also be prevented, treated, or ameliorated with compositions of described herein. Also included is glaucoma; age-related macular degeneration (wet AMD and dry AMD).

[0066] Renal fibrosis is the consequence of an excessive accumulation of extracellular matrix that occurs in virtually every type of chronic kidney disease. The pathogenesis of renal fibrosis is a progressive process that ultimately leads to end-stage renal failure, a devastating disorder that requires dialysis or kidney transplantation. In a simplistic view, renal fibrosis represents a failed wound-healing process of the kidney tissue after chronic, sustained injury. Several cellular pathways, including mesangial and fibroblast activation as well as tubular epithelial-mesenchymal transition, have been identified as the major avenues for the generation of the matrix-producing cells in diseased conditions.

[0067] Pulmonary fibrosis is characterized by lung inflammation and abnormal tissue repair, resulting in the replacement of normal functional tissue with an abnormal accumulation of fibroblasts and deposition of collagen in the lung. This process involves cellular interactions via a complex cytokine-signaling mechanism and heightened collagen gene expression, ultimately resulting in its abnormal collagen deposition in the lung. In addition to inflammatory cells, the fibroblast and signaling events that mediate fibroblast proliferation and myofibroblasts play important roles in the fibrotic process. However, the most potent anti-inflammatory drugs that have been widely used in the treatment of pulmonary fibrosis do not seem to interfere with the fibrotic disease progression.

[0068] Hepatic fibrosis is an accumulation in the liver of connective tissue in response to hepatocellular damage of nearly any cause. It results from excessive production or deficient

degradation of the extracellular matrix. Fibrosis itself causes no symptoms but can lead to portal hypertension or cirrhosis.

[0069] Systemic sclerosis is a chronic disease of unknown cause characterized by diffuse fibrosis, degenerative changes, and vascular abnormalities in the skin, joints, and internal organs (especially the esophagus, lower GI tract, lung, heart, and kidney). Common symptoms include Raynaud's phenomenon, polyarthralgia, dysphagia, heartburn, and swelling and eventually skin tightening and contractures of the fingers. Lung, heart, and kidney involvement accounts for most deaths. Specific treatment is difficult, and emphasis is often on treatment of complications.

[0070] A variety of drugs have been tried in various fibroses, particularly lung fibrosis, with very little success. Anti-inflammatory drugs including prednisolone and azathioprine have little effect on fibrosis suggesting that inflammation is only the initiator, but not the driver of the disease. The use of non-specific anti-proliferatives like colchicine and cyclophosphamide will also prevent repair of the fibrotic tissue by impairing e.g. epithelial growth. Treatment with IFN-γ has shown some utility but is limited by severe side effects.

[0071] By the time a typical patient presents with fibrosis-related symptoms (e.g. difficulty breathing for lung fibrosis, cirrhosis for liver fibrosis, etc.), the fibrosis in the target organ is often quite severe, with much of the target organ architecture having been replaced with extracellular matrix. Stopping this ongoing fibrosis can extend lifespan and improve quality of life. Areas of the target organ where the fibrosis is not extensive may be restored to normal architecture with suitable treatment.

[0072] In some embodiments, tumor fibrosis is associated with pancreatic cancer. Pancreatic cancer is characterized by a prominent desmoplastic/stromal reaction. Pancreatic stellate cells (PSCs) are the principal source of fibrosis in the stroma and interact closely with cancer cells to create a tumor facilitatory environment that stimulates local tumor growth and distant metastasis. Pancreatic fibrosis is initiated when PSCs become activated and undergo morphological and functional changes, so that the rate of extracellular matrix (ECM) deposition exceeds the rate of ECM degradation in the gland. It is now well established that pancreatic cancer cells activate PSCs leading to increased fibrosis. There is significant evidence showing that the intense stromal/ desmoplastic reaction around tumor elements (a feature of the majority of pancreatic cancers) plays an important role in tumor progression.

[0073] A key histopathological feature of pancreatic cancer which is associated with its innate clinical and biological aggressiveness is its desmoplastic (stromal) reaction. Stroma production

is stimulated by cancer-cell derived growth factors including transforming growth factor-β (TGFβ), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), insulin-like growth factor 1 (IGF-1) and epidermal growth factor (EGF). The desmoplastic reaction is composed of extracellular matrix (ECM) proteins, primarily type I and III collagen, fibronectin and proteoglycans; small endothelium lined vessels; and a diverse population of cells including inflammatory cells, fibroblasts and stellate cells. The stroma can form up to 90% of the tumor volume, a property which is unique to pancreatic cancer. The tumor microenvironment in pancreatic cancer plays a role in its chemoresistance.

[0074] While stromal cells do not exhibit the genetic transformations seen in malignant pancreatic cancer cells, they are altered by cytokines and growth factors secreted by inflammatory cells and tumor cells. Reciprocally, the stromal cells promote tumor cell migration, growth, invasion and resistance to drugs and apoptosis. Staining pancreatic cancer tissue sections of patients for alpha smooth muscle actin (α-SMA the cytoskeletal protein marker for PSC activation) and collagen shows a high activated stroma index (α-SMA/collagen) correlated with a poor prognosis. The extensive ECM deposition by PSCs in pancreatic cancer causes distortion and compression of tumor vasculature by fibrous tissue which contributes to tumor hypoxia, a determinant of chemoresistance.

[0075] "Inhibitors," "activators," and "modulators" of AXL, MER or Tyro3 or its ligand GAS6 are used to refer to inhibitory, activating, or modulating molecules, respectively, identified using *in vitro* and *in vivo* assays for receptor or ligand binding or signaling, *e.g.*, ligands, receptors, agonists, antagonists, and their homologs and mimetics.

[0076] By "inhibitor" is meant an agent that is able to reduce or to abolish the interaction between GAS6 and a TAM receptor. Preferably, said inhibitor is able to reduce or to abolish the interaction by at least 10, 20, 30, 40 %, more preferably by at least 50, 60, 70 %, and most preferably by at least 75, 80, 85, 90, 95, 96, 97, 98, 99, or 100%. Included are polypeptides including without limitation antibodies, polynucleotides, small molecules and the like that act to inhibit the GAS6 and/or AXL signaling pathways.

[0077] Non limiting examples of small molecule inhibitors include ONO-9330547, which is a small molecule inhibitor that binds to Axl and Mer kinase with a potency (IC) of 2.2 and 0.4 nM, see ASH abstracts 2014, #999. The Axl-specific inhibitor, TP-0903 (Tolero Pharmaceuticals), see ASH abstracts 2014, #2350 may be used alone or in combination with FLT3 inhibitor PKC412 (Park et al, *Blood* 121, 2064-73, 2013).

[0078] Inhibitors of interest also include LY2801653 (Eli Lilly and Co) Journal of the American Association for Cancer Research. 2013; 19:5699–5710. Investigational new drugs. 2013; 31:833–844; MP-470 or Amuvatinib (Astex Pharm). Oncogene. 2007; 26:3909–3919; SKI-606, PF-5208763, or Bosutinib, (Pfizer), Carcinogenesis. 2014; 35:769–775; MGCD 265 (Mirati). Journal of Clinical Oncology. 2010; 28:e13595. European journal of cancer. 2012; 48:95–96; MGCD 516 (Mirati). Poster:#6130 Proceedings: AACR 104th Annual Meeting 2013; Apr 6–10, 2013; (Washington, DC); ASP2215 (Astellas) J Clin Oncol 32:5s, 2014 (suppl; abstr 7071), J Clin Oncol 32:5s, 2014 (suppl; abstr 7070), Blood. 2013; 121:2064–2073; XL184/Cabozanitinib (Exelixis). Molecular cancer therapeutics. 2011;10:2298–2308; BMS 777607 or ASLAN 002. Journal of medicinal chemistry 52, 1251---1254 (2009); GSK163089/XL880 or Foretinib (GSK). Cancer research. 2009; 69:6871–6878; SGI-7079 (Astex Pharma) Cancer research. 2013; 73:6516–6525., Clinical cancer research: 2013; 19:279–290; S49076 (Servier) Molecular cancer therapeutics. 2013; 12:1749–1762; R428/BGB324, (BergenBio). Oncogene. 1997; 14:2619–2631.Nature biotechnology. 2013; 31:775–776; DP3975 (Deciphera Biotech). Oncogene.2011; 30:1643–1652; NPS-1034 (NeoPharma). Cancer research. 2014; 74:253–262; LDC 126. Nature. 2014; 507:508–512; NA80x1. Cancer research. 2008; 68:1905–1915; PF-2341066/Crizotinib (Pfizer) Nature biotechnology 29, 1046---1051 (2011), ACS medicinal chemistry letters 2, 907---912 (2011); Vandetinib. Nature biotechnology 29, 1046---1051 (2011); Sunitinib. (Pfizer). Nature biotechnology 29, 1046---1051 (2011). Br J Cancer 101, 1717---1723 (2009); Lestaurtinib/CEP-701. Nature biotechnology 29, 1046---1051 (2011); CEP-40783 (Teva) . Abstract #C272, EORTC- AACR Oct. 19-23, 2013, Abstract #C275, EORTC- AACR Oct. 19-23, 2013; Neratinib. Nature biotechnology 29, 1046---1051 (2011); AT9283. Journal of medicinal chemistry 52, 379---388 (2009); R406. Nature biotechnology 29, 1046---1051 (2011); MK-2461. Journal of medicinal chemistry 52, 1251---1254 (2009); SU-14813. Nature biotechnology 29, 1046---1051 (2011); BMS-796302. Nature reviews. Clinical oncology 9, 314---326 (2012); JNJ---28312141. Nature biotechnology 29, 1046---1051 (2011). Molecular cancer therapeutics 8, 3151---3161 (2009); Diaminopyrimidine. ACS medicinal chemistry letters 2, 907---912 (2011); Warfarin. JASN (1999) vol. 10 no. 12 2503-2509; UNC569, UNC1062, UNC1666 , UNC2025 described in ACS medicinal chemistry letters 3, 129- -134 (2012). Molecular cancer therapeutics 12, 2367---2377 (2013). J Clin Invest 123, 2257-2267 (2013). European journal of medicinal chemistry 65, 83---93 (2013). Blood 122, 3849 (2013). American Association of Cancer Researchers Annual Meeting, San Diego, CA, Abstract #1740 (2014). Journal of medicinal chemistry 57, 7031---7041 (2014).

[0079] Monoclonal antibodies that specifically target AXL have been described, including 12A11, Mab173, YW327.6S2 and, more recently, D9 and E8. Others included Chugai monoclonal antibody to AXL, BergenBio monoclonal antibody to AXL, and Amgen's monoclonal against GAS6. Antibody mediated decreases in cell-surface AXL expression induced apoptosis, enhanced sensitivity to chemotherapy and inhibited xenograft growth of NSCLC, pancreatic cancer and Kaposi's sarcoma. Similarly, an antibody that recognizes MERTK inhibited migration in glioblastoma cells and decreased colony-forming potential and chemoresistance of NSCLC cell lines, which phenocopies the effects of MERTK knockdown.

[0080] Antibodies that block TYRO3-dependent signaling have also been reported. An aptamer with high affinity for AXL (with a dissociation constant (Kd) of 12 nM) has been developed and was shown to mediate inhibition of AXL activity in NSCLC models, decreasing tumour cell migration, invasion and xenograft tumour growth. TAM RTK extracellular domains can bind to ligand with high affinity and may thereby function as 'sinks' to eliminate free ligand. Recombinant proteins consisting of all or part of the extracellular domain of AXL, MERTK or TYRO3 fused to an Fc domain derived from human immunoglobulin G (IgG) have been generated, and they inhibit both GAS6-dependent tumour cell survival in culture and metastasis in animal models. In addition, both AXL and MERTK ligand sinks have been effective in preventing platelet aggregation and clot formation in vivo.

[0081] See, for example, Varnum et al. Nature 373, 623–626 (1995); Stitt et al. Cell 80, 661–670 (1995); Nagata et al. J. Biol. Chem. 271, 30022–30027 (1996); Angelillo-Scherrer et al. J. Clin. Invest. 115, 237–246 (2005); Park et al. Blood 121, 2064–2073 (2013); Rankin et al. Proc. Natl Acad. Sci. USA 111 13373–13378 (2014); Liu et al. Blood 116, 297–305 (2010); Rogers et al. Oncogene 31, 4171–4181 (2012); Li et al. Oncogene 28, 3442–3455 (2009); Ye et al. Oncogene 29, 5254–5264 (2010); Leconet et al. Oncogene (2013); Kariolis et al. Nature Chem. Biol. 10, 977–983 (2014); Cummings et al. Oncotarget 26 June 2014; Demarest et al. Biochemistry 52, 3102–3118 (2013); Cerchia, L. et al. Mol. Ther. 20, 2291–2303 (2012); Avilla, E. et al. Cancer Res. 71, 1792–1804 (2011); Sather, S. et al. Blood 109, 1026–1033 (2007); ANTICANCER RESEARCH 34: 1821-1828 (2014); Abstract 5158_ AACR April 13 _2013: Generation of a fully human Gas6 neutralizing antibody with anti-tumor activity in vivo

[0082] As used herein, the terms "treatment," "treating," and the like, refer to administering an agent, or carrying out a procedure for the purposes of obtaining an effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of effecting a partial or complete cure for a disease and/or

symptoms of the disease. “Treatment,” as used herein, covers any treatment of fibrosis in a mammal, particularly in a human, and includes: (a) preventing the development of fibrosis; (b) inhibiting ongoing fibrosis, *i.e.*, arresting its development; and (c) relieving fibrosis, *i.e.*, causing regression.

[0083] Treating may refer to any indicia of success in the treatment or amelioration or prevention of fibrosis, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the disease condition more tolerable to the patient; slowing in the rate of degeneration or decline; or making the final point of degeneration less debilitating. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of an examination by a physician. Accordingly, the term "treating" includes the administration of the compounds or agents of the present invention to prevent or delay, to alleviate, or to arrest or inhibit development of the symptoms or conditions associated with fibrosis. The term "therapeutic effect" refers to the reduction, elimination, or prevention of the disease, symptoms of the disease, or side effects of the disease in the subject.

[0084] "In combination with", "combination therapy" and "combination products" refer, in certain embodiments, to the concurrent administration to a patient of a first therapeutic (*i.e.*, first therapeutic agent) and the compounds as used herein. When administered in combination, each component can be administered at the same time or sequentially in any order at different points in time. Thus, each component can be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. First therapeutic agents contemplated for use with the methods of the present invention include any other agent for use in the treatment of fibrosis. Examples of such therapeutic agents include but are not limited anti-fibrotic agents.

[0085] "Concomitant administration" of a known therapeutic agent with a pharmaceutical composition of the present invention means administration of the therapeutic agent and inhibitor agent at such time that both the known therapeutic agent and the composition of the present invention will have a therapeutic effect. Such concomitant administration may involve concurrent (*i.e.* at the same time), prior, or subsequent administration of the drug with respect to the administration of a compound of the present invention. A person of ordinary skill in the art would have no difficulty determining the appropriate timing, sequence and dosages of administration for particular drugs and compositions of the present invention. Therapeutic agents contemplated for concomitant administration according to the methods of the present invention include any other agent for use in the treatment of fibrosis.

[0086] As used herein, the term “correlates,” or “correlates with,” and like terms, refers to a statistical association between instances of two events, where events include numbers, data sets, and the like. For example, when the events involve numbers, a positive correlation (also referred to herein as a “direct correlation”) means that as one increases, the other increases as well. A negative correlation (also referred to herein as an “inverse correlation”) means that as one increases, the other decreases.

[0087] "Dosage unit" refers to physically discrete units suited as unitary dosages for the particular individual to be treated. Each unit can contain a predetermined quantity of active compound(s) calculated to produce the desired therapeutic effect(s) in association with the required pharmaceutical carrier. The specification for the dosage unit forms can be dictated by (a) the unique characteristics of the active compound(s) and the particular therapeutic effect(s) to be achieved, and (b) the limitations inherent in the art of compounding such active compound(s).

[0088] "Pharmaceutically acceptable excipient "means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for veterinary use as well as for human pharmaceutical use. Such excipients can be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous.

[0089] The terms "pharmaceutically acceptable", "physiologically tolerable" and grammatical variations thereof, as they refer to compositions, carriers, diluents and reagents, are used interchangeably and represent that the materials are capable of administration to or upon a human without the production of undesirable physiological effects to a degree that would prohibit administration of the composition.

[0090] A "therapeutically effective amount" means the amount that, when administered to a subject for treating a disease, is sufficient to effect treatment for that disease.

[0091] The phrase “determining the treatment efficacy” and variants thereof can include any methods for determining that a treatment is providing a benefit to a subject. The term “treatment efficacy” and variants thereof are generally indicated by alleviation of one or more signs or symptoms associated with the disease and can be readily determined by one skilled in the art. “Treatment efficacy” may also refer to the prevention or amelioration of signs and symptoms of toxicities typically associated with standard or non-standard treatments of a disease. Determination of treatment efficacy is usually indication and disease specific and can include any methods known or available in the art for determining that a treatment is providing a beneficial effect to a patient. For example, evidence of treatment efficacy can include but is not

limited to remission of the disease or indication. Further, treatment efficacy can also include general improvements in the overall health of the subject, such as but not limited to enhancement of patient life quality, increase in predicted subject survival rate, decrease in depression or decrease in rate of recurrence of the indication (increase in remission time). (See, *e.g.*, *Physicians' Desk Reference (2010).)*

DETAILED DESCRIPTION OF THE EMBODIMENTS

[0092] AXL, MER, Tyro3 and GAS6, as well as related pathways, have been described in WO2011/091305, as well as United States Application Serial Nos. 13/554,954 and 13/595,936; all of which are incorporated herein by reference in their entireties for all purposes.

[0093] In some embodiments, the methods of the present invention can be used for treatment, prevention or reduction of fibrosis, with an effective dose of an inhibitor of a GAS6 or AXL associated signaling pathways.

[0094] In some embodiments, the inhibitor agent binds to two or more epitopes on a single GAS6 molecule. The two or more epitopes can include at least one of the major and/or minor AXL, MER and/or Tyro3 binding site on GAS6. In some embodiments, the epitopes are separate or distinct epitopes. In some embodiments the epitopes overlap. In some embodiments, the epitopes do not overlap. In some embodiments, the epitopes are adjacent. In some embodiments, the epitopes are not adjacent. In some embodiments, the epitopes include the major and/or minor AXL, MER and/or Tyro3 binding site on GAS6. These GAS6 epitopes of the present invention, and to which the inhibitor agents of the present invention bind, can be located on one or more GAS6 molecules. In some embodiments, the epitopes are located on a single GAS6 molecule.

[0095] In some embodiments, the inhibitor agent is capable of binding to the major and/or minor AXL, MER and/or Tyro3 binding sites on a single GAS6. In some embodiments, the inhibitor agent is capable of binding the major AXL, MER and/or Tyro3 binding site of GAS6 and one or more additional GAS6 epitopes. In other embodiments, the inhibitor agent is capable of binding to the AXL, MER and/or Tyro3 minor binding site on GAS6 and one or more additional epitopes. In some other embodiments, the inhibitor agent is capable of binding two or more distinct epitopes on GAS6. The additional GAS6 epitopes can include any epitopes on GAS6 which lead to increased affinity and/or increased avidity of the inhibitor agent binding to GAS6 as compared to wild-type AXL, MER and/or Tyro3. In some embodiments, the AXL, MER and/or Tyro3 variant polypeptides of the present invention bind two epitopes on a single GAS6

molecule. In some embodiments, the two epitopes are the major and minor AXL, MER and/or Tyro3 binding sites.

[0096] According to the invention, GAS6 receptors include AXL, MER and Tyro3. The inhibitor agents of the present invention can also in some embodiments antagonize the major and/or minor GAS6/receptor interaction. In some embodiments, the inhibitor agent is capable of antagonizing the major and/or minor GAS6/receptor binding interaction. In other embodiments, the inhibitor agent is capable of antagonizing the major GAS6/receptor binding interaction (*e.g.*, interfering with and/or inhibiting the major GAS6/receptor binding interaction). In some embodiments, the inhibitor agent is capable of antagonizing the minor GAS6/receptor binding interaction (*e.g.*, interfering with and/or inhibiting the minor GAS6/receptor binding interaction).

[0097] Inhibitor agents can also include for example protein scaffolds (*i.e.*, smaller proteins that are capable of achieving comparable affinity and specificity using molecular structures that can be for example one-tenth the size of full antibodies). The inhibitor agents can also include non-antibody polypeptides. In some embodiments, the inhibitor agent is a non-antibody polypeptide. In some embodiments, the non-antibody polypeptide can include but is not limited to peptibodies, darpins, avimers, adnectins, anticalins, affibodies, maxibodies, or other protein structural scaffold, or a combination thereof.

[0098] In some embodiments the inhibitor agent provided by the present invention is an AXL, MER and/or Tyro3 variant polypeptide, *e.g.*, an AXL, MER and/or Tyro3 variant polypeptide that has a binding activity to GAS6 that is substantially equal to or better than the binding activity of a wild-type AXL, MER and/or Tyro3 polypeptide. In some embodiments of the present invention, the AXL, MER and/or Tyro3 variant polypeptides are utilized as therapeutic agents.

[0099] The AXL protein, with reference to the native sequence of SEQ ID NO: 1, comprises an immunoglobulin (Ig)-like domain from residues 27-128, a second Ig-like domain from residues 139-222, fibronectin type 3 domains from residues 225-332 and 333-427, intracellular domain from residues 473-894 including tyrosine kinase domain. The tyrosine residues at 779, 821 and 866 become autophosphorylated upon receptor dimerization and serve as docking sites for intracellular signaling molecules. The native cleavage site to release the soluble form of the polypeptide lies at residues 437-451.

[00100] For the purposes of the invention, a soluble form of AXL (soluble AXL, sAXL or sAXL polypeptide) includes both wild-type AXL and AXL variant polypeptides and is the portion of the polypeptide that is sufficient to bind GAS6 at a recognizable affinity, *e.g.*, high affinity, which normally lies between the signal sequence and the transmembrane domain, *i.e.* generally from about SEQ ID NO: 1 residue 19-437, but which may comprise or consist essentially of a

truncated version of from about residue 19, 25, 30, 35, 40, 45, 50 to about residue 132, 450, 440, 430, 420, 410, 400, 375, 350, to 321, *e.g.*, residue 19-132. According to the methods of the present invention, SEQ ID NO:1 can be used interchangeably with amino acids 8-894 of SEQ ID NO: 1, both of which refer to the wild-type AXL sequence. In some embodiments, a soluble form of AXL lacks the transmembrane domain, and optionally the intracellular domain.

[00101] In some embodiments, the inhibitor agent is an AXL variant polypeptide that lacks the AXL transmembrane domain and has at least one mutation relative to wild-type that increases affinity of the AXL polypeptide binding to GAS6 as compared to wild-type GAS6.

[00102] The MER protein, with reference to the native SEQ ID NO:2, comprises an immunoglobulin (Ig)-like domain from residues 81-186, a second Ig-like domain from residues 197-273, fibronectin type 3 domains from residues 284-379 and 383-482, intracellular domain from residues 527-999 including tyrosine kinase domain. The tyrosine residues at 749, 753, 754 and 872 become autophosphorylated upon receptor dimerization and serve as docking sites for intracellular signaling molecules.

[00103] For the purposes of the invention, a soluble form of MER (sMER) is the portion of the polypeptide that is sufficient to bind GAS6 at a recognizable affinity, *e.g.*, high affinity, which normally lies between the signal sequence and the transmembrane domain, *i.e.* generally from about SEQ ID NO: 2 residue 21-526, but which may comprise or consist essentially of a truncated version In some embodiments, a soluble form of MER lacks the transmembrane domain (*i.e.*, generally from about SEQ ID NO: 2 residue 506-526), and optionally the intracellular domain (*i.e.*, generally from about SEQ ID NO: 2 residue 527-999).

[00104] In some embodiments, the inhibitor agent is a soluble MER variant polypeptide wherein said MER polypeptide lacks the MER transmembrane domain and has at least one mutation relative to wild-type that increases affinity of the MER polypeptide binding to GAS6 as compared to wild-type MER.

[00105] The Tyro3 protein, with reference to the native SEQ ID NO:3, comprises an immunoglobulin (Ig)-like domain from residues 41-128, a second Ig-like domain from residues 139-220, fibronectin type 3 domains from residues 225-317 and 322-413, intracellular domain from residues 451-890 including tyrosine kinase domain. The tyrosine residues at 681, 685, 686 and 804 become autophosphorylated upon receptor dimerization and serve as docking sites for intracellular signaling molecules.

[00106] For the purposes of the invention, a soluble form of Tyro3 (sTyro3) is the portion of the Tyro3 polypeptide that is sufficient to bind GAS6 at a recognizable affinity, *e.g.*, high affinity, which normally lies between the signal sequence and the transmembrane domain, *i.e.* generally

from about SEQ ID NO: 3 residue 41-450, but which may comprise or consist essentially of a truncated version In some embodiments, a soluble form of AXL lacks the transmembrane domain (*i.e.*, generally from about SEQ ID NO: 3 residue 430-450), and optionally the intracellular domain (*i.e.*, generally from about SEQ ID NO: 3 residue 451-890).

[00107] In some embodiments, the inhibitor agent is a soluble Tyro3 variant polypeptide wherein said Tyro3 polypeptide lacks the Tyro3 transmembrane domain and has at least one mutation relative to wild-type Tyro3 that increases affinity of the Tyro3 polypeptide binding to GAS6 as compared to wild-type Tyro3.

[00108] In some embodiments, the AXL, MET or Tyro3 variant polypeptide lacks the AXL, MET or Tyro3 transmembrane domain and is a soluble variant polypeptide, *e.g.*, polypeptides (sAXL, sMER or sTyro3 variant polypeptide). In some embodiments, the AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 intracellular domain. In some embodiments, the inhibitor agent of the present invention inhibits binding between a wild-type AXL, MER and/or Tyro3 polypeptide and a GAS6 protein *in vivo* or *in vitro*. In some embodiments, the AXL, MER or Tyro3 variant polypeptide inhibits binding between a wild-type AXL, MER and/or Tyro3 polypeptide and a GAS6 protein *in vivo* or *in vitro*.

[00109] The inhibitor agents of the present invention can also exhibit an enhanced or better pharmacokinetic profile. In some embodiments, the enhanced or better pharmacokinetic profile includes for example but is not limited to a better absorption profile, better distribution profile, better metabolism profile, better excretion profile, better liberation profile, increased half-life, decrease half-life, faster rate of action, longer duration of effect as compared to AXL, MER and/or Tyro3 wild-type polypeptides which do not lack a transmembrane domain. One of skill in the art would understand preferred pharmacokinetic profile parameters for particular needs including for example treatment regimens, and how to appropriately implement such parameters in treatment regimens.

[00110] The wild-type AXL, MER and Tyro3 all contain two fibronectin domains. In some embodiments, the AXL, MER and Tyro3 polypeptides of the invention lack a functional fibronectin (FN) domain. Lacks or lacking a functional fibronectin domain can include but is not limited to deletion of one or both fibronectin domains and/or introducing mutations that inhibit, reduce or remove the functionality of one or both fibronectin domains, where such mutations can include for example but are not limited to substitution, deletion and insertion mutations. In some embodiments, the polypeptides of the invention have fibronectin 1 (FN1) deleted, fibronectin 2 (FN2) deleted, or FN1 and FN2 both deleted. In some embodiments, the

polypeptides of the invention have portions of FN1 mutated and/or deleted, FN2 mutated and/or deleted, or FN1and FN2 mutated and/or deleted.

[00111] In some embodiments, the AXL, MER or Tyro3 variant polypeptide lacks a functional AXL, MER or Tyro3 fibronectin (FN) domain. In some embodiments, the AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the polypeptide binding to GAS6 as compared to wild-type AXL, MER and/or Tyro3. In some embodiments, the AXL, MER or Tyro3 variant polypeptide lacks a functional fibronectin (FN) domain also exhibits increased affinity of the polypeptide binding to GAS6 as compared to wild-type AXL, MER and/or Tyro3.

[00112] In some embodiments, the lack of a functional fibronectin domain results in increased affinity of the AXL, MER or Tyro3 polypeptide binding to GAS6. In some embodiments, the lack of a functional fibronectin domain results in an enhanced or better pharmacokinetic profile, including for example but not limited to a better absorption profile, better distribution profile, better metabolism profile, better excretion profile, better liberation profile, increased half-life, decreased half-life, faster rate of action, longer duration of effect as compared to other wild-type polypeptides or other polypeptides which do not lack a functional fibronectin domain. One of skill in the art would understand preferred pharmacokinetic profile parameters for particular needs including for example treatment regimens, and how to appropriately implement such parameters in treatment regimens.

[00113] In some embodiments, the AXL, MER or Tyro3 variant polypeptide lacks the transmembrane domain and has more than one Ig1 domain and exhibits increased affinity of the AXL, MER or Tyro3 polypeptide binding to GAS6 as compared to wild-type AXL, MER and/or Tyro3. In some embodiments, the AXL, MER or Tyro3 polypeptide has two Ig1 domains. In some embodiments, the AXL, MER or Tyro3 polypeptide has three Ig1 domains. In some embodiments, the AXL, MER or Tyro3 polypeptide has more than one Ig1domain and/or more than one Ig2 domain. In some embodiments, the AXL, MER or Tyro3 polypeptide has two Ig2 domains. In some embodiments, the AXL, MER or Tyro3 polypeptide has two Ig1 domains and 2 Ig2 domains. In some embodiments, the AXL, MER or Tyro3 polypeptide includes for example but is not limited to one of the following Ig domain configurations, as well as any combinations or variations thereof: Ig1; Ig1 – Ig2; Ig1 – Ig1; Ig1 – Ig1 – Ig1; Ig1 – Ig2 – Ig1; Ig1 – Ig2 – Ig1 – Ig2.

[00114] In some embodiments, the AXL, MER or Tyro3 polypeptide also lacks the AXL, MER or Tyro3 transmembrane domain and/or exhibits increased affinity of the AXL, MER or Tyro3 polypeptide binding to GAS6. In some embodiments, the AXL, MER or Tyro3 variant polypeptide lacks the transmembrane domain, has more than one Ig1 domain, has more than

one Ig2 domain and exhibits increased affinity of the AXL, MER or Tyro3 polypeptide binding to GAS6 as compared to wild-type AXL, MER and/or Tyro3.

[00115] In some embodiments, the AXL, MER or Tyro3 has the immunoglobulin domains connected directly to one another. In some embodiments, the AXL, MER or Tyro3 has the immunoglobulin domains connected indirectly, *e.g.*, through a linker molecule including for example any amino acid linker known in the art.

[00116] In some embodiments, the one or more AXL, MER or Tyro3 Ig1 and/or 1 or more AXL, MER or Tyro3 Ig2 domains result in an enhanced or better pharmacokinetic profile, including for example but not limited to a better absorption profile, better distribution profile, better metabolism profile, better excretion profile, better liberation profile, increased half-life, decreased half-life, faster rate of action, longer duration of effect as compared to other wild-type polypeptides or other polypeptides which do not lack a functional fibronectin domain. One of skill in the art would understand preferred pharmacokinetic profile parameters for particular needs including for example treatment regimens, and how to appropriately implement such parameters in treatment regimens.

[00117] In some embodiments, the AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain and is capable of binding two or more epitopes on a single GAS6. In some embodiments, the AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain and is capable of binding both the major and minor AXL, MER and/or Tyro3 binding sites on a single GAS6. In some embodiments, the binding of both the major and minor AXL, MER and/or Tyro3 binding is simultaneous. In some embodiments, the binding of both the major and minor AXL, MER and/or Tyro3 binding sites is simultaneous on a single GAS6.

[00118] The present invention also provides AXL, MER or Tyro3 variant polypeptides that do not bind two epitopes on a single GAS6 molecule. The present invention also provides AXL, MER or Tyro3 variant polypeptides that do not bind two epitopes on a single GAS6 molecule simultaneously. In some embodiments, the AXL, MER and/or Tyro3 variant polypeptide is not capable of binding two epitopes on a single GAS6, this includes for example monomeric AXL, MER and/or Tyro3 variant polypeptides. In some embodiments, the monomeric AXL, MER or Tyro3 variant polypeptide comprises one Ig1 domain. In some embodiments, the monomeric AXL, MER and/or Tyro3 variant polypeptide is an Fc fusion polypeptide that does not bind to more than one site on a single Gas6 molecule simultaneously. In some embodiments, the monomeric AXL, MER and/or Tyro3 variant polypeptide that is not capable of binding two epitopes on a single GAS6 comprises two AXL, MER and/or Tyro3 variant polypeptides each of

which are not capable of binding two epitopes on a single GAS6 simultaneously. In some embodiments, the monomeric AXL, MER and/or Tyro3 variant polypeptide that is not capable of simultaneously binding two epitopes on a single GAS6 has one Ig1 domain. In some embodiments, the monomeric AXL, MER and/or Tyro3 variant polypeptide that is not capable of simultaneously binding two epitopes on a single GAS6 has an altered half-life when compared to AXL, MER and/or Tyro3 variant polypeptides that are capable of binding two epitopes on a single GAS6. In some embodiments, the polypeptide has one Ig1 domain and lacks a functional Ig2 domain. In some embodiments, the Ig1 domain comprises amino acids 1-131 of AXL (SEQ ID NO:1). In some embodiments, the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said soluble AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, has one Ig1 domain, lacks a functional Ig2 domain and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3. In some embodiments, the polypeptide of any of the preceding claims, wherein the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said soluble AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, lacks a functional fibronectin (FN) domain, has one Ig1 domain, lacks a functional Ig2 domain and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

[00119] The wild-type AXL, MER and Tyro3 all contain an Ig2 domain. In some embodiments, the AXL, MER and Tyro3 polypeptides of the invention lack a functional Ig2 domain. Lacks or lacking a functional Ig2 domain can include but is not limited to deletion of the Ig2 domain and/or introduction of mutations that inhibit, reduce or remove the functionality of the Ig2 domain, where such mutations can include for example but are not limited to substitution, deletion and insertion mutations. In some embodiments, the polypeptides of the invention lack a functional Ig2 domain. In some embodiments, the polypeptides of the invention lack a functional Ig2 domain and have a wild-type AXL, MER and/or Tyro3 Ig1 domain. In some embodiments, the polypeptides of the invention lack a functional Ig2 domain and have one or more mutations in the Ig1 domain relative to the wild-type AXL, MER and/or Tyro3 Ig1 domain.

[00120] In some embodiments, the AXL, MER and/or Tyro3 variant polypeptide includes a linker. A wide variety of linkers are known in the art and any known linker can be employed with the methods of the present invention. In some embodiments, the AXL, MER or Tyro3 variant polypeptide includes one or more linkers or linker units. In some embodiments, the linker is an amino acid linker, including an amino acid sequence of 2, 3, 4 or 5 amino acids which are

different that the wild-type AXL, MER and/or Tyro3 sequences. In some embodiments, the linker has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more units. In some embodiments, the linker is $(GLY)_4SER$ (SEQ ID NO:10). In some embodiments, the linker has 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more $(GLY)_4SER$ units. In some embodiments, the linker has 1, 2, 3 or 5 $(GLY)_4SER$ units. In some embodiments, the linkers are between the AXL, MER or Tyro3 variant polypeptide and the Fc portion of a fusion polypeptide. In some embodiments, the linkers are between the AXL, MER or Tyro3 variant polypeptide and the Fc portion of a fusion polypeptide and the AXL, MER or Tyro3 variant polypeptide lacks a functional fibronectin domain.

[00121] In some embodiments, AXL, MER and/or Tyro3 variant polypeptides of the present invention also include one or more amino acid modifications within the soluble form of wild-type AXL, MER and/or Tyro3, *e.g.*, one or more amino acid modifications that increase its affinity for GAS6. According to the present invention, amino acid modifications include any naturally occurring or man-made amino acid modifications known or later discovered in the field. In some embodiments, amino acid modifications include any naturally occurring mutation, *e.g.*, substitution, deletion, addition, insertion, *etc.* In some other embodiments, amino acid modifications include replacing existing amino acid with another amino acid, *e.g.*, a conservative equivalent thereof. In yet some other embodiments, amino acid modifications include replacing one or more existing amino acids with non-natural amino acids or inserting one or more non-natural amino acids. In still some other embodiments, amino acid modifications include at least 1, 2, 3, 4, 5, or 6 or 10 amino acid mutations or changes.

[00122] In some exemplary embodiments, one or more amino acid modifications can be used to alter properties of the soluble form of AXL, MER and/or Tyro3 *e.g.*, affecting the stability, binding activity and/or specificity, *etc.* Techniques for *in vitro* mutagenesis of cloned genes are known.

[00123] In some embodiments, AXL variant polypeptides, including for example sAXL variants, of the present invention include one or more amino acid modifications within one or more regions of residue 18 to 130, residue 10 to 135, residue 15 to 45, residue 60 to 65, residue 70 to 80, residue 85 to 90, residue 91 to 99, residue 104 to 110, residue 111 to 120, residue 125 to 130, residue 19 to 437, residue 130 to 437, residue 19 to 132, residue 21 to 132, residue 21 to 121, residue 26 to 132, or residue 26 to 121 of wild-type AXL. In some other embodiments, AXL variant polypeptides of the present invention include one or more amino acid modifications within one or more regions of residue 20 to 130, residue 37 to 124 or residue 141 to 212 of wild-type AXL. In yet some other embodiments, variants of the present invention include one or more amino acid modifications at one or more positions of position 19, 23, 26, 27, 32, 33, 38,

44, 61, 65, 72, 74, 78, 79, 86, 87, 88, 90, 92, 97, 98, 105, 109, 112, 113, 116, 118, 127, or 129 of wild-type AXL.

[00124] In yet some other embodiments, AXL polypeptide variants of the present invention include one or more amino acid modifications including without any limitation 1) A19T, 2) T23M, 3) E26G, 4) E27G or E27K, 5) G32S, 6) N33S, 7) T38I, 8) T44A, 9) H61Y, 10) D65N, 11) A72V, 12) S74N, 13) Q78E, 14) V79M, 15) Q86R, 16) D87G, 17) D88N, 18) I90M or I90V, 19) V92A, V92G or V92D, 20) I97R, 21) T98A or T98P, 22) T105M, 23) Q109R, 24) V112A, 25) F113L, 26) H116R, 27) T118A, 28) G127R or G127E, and 29) E129K and a combination thereof.

[00125] In yet some other embodiments, AXL variant polypeptides of the present invention include one or more amino acid modifications at position 32, 87, 92, or 127 of wild-type AXL (SEQ ID NO: 1) or a combination thereof, *e.g.*, G32S; D87G; V92A and/or G127R. In yet some other embodiments, AXL polypeptide variants of the present invention include one or more amino acid modifications at position 26, 79, 92, 127 of wild-type AXL (SEQ ID NO: 1) or a combination thereof, *e.g.*, E26G, V79M; V92A and/or G127E. In yet some other embodiments, AXL variant polypeptides of the present invention include one or more amino acid modifications at position 32, 87, 92, 127 and/or 72 of wild-type AXL or a combination thereof, *e.g.*, G32S; D87G; V92A; G127R and/or A72V. In yet some other embodiments, AXL variant polypeptides of the present invention include one or more amino acid modifications at position 87, 92 and/or 127 of wild-type AXL (SEQ ID NO: 1) or a combination thereof, *e.g.*, D87G; V92A; and/or G127R. In yet some other embodiments, AXL variant polypeptides of the present invention include one or more amino acid modifications at position 32, 92, and/or 127 of wild-type AXL (SEQ ID NO: 1) or a combination thereof, *e.g.*, G32S; V92A; and/or G127R. In yet some other embodiments, AXL variant polypeptides of the present invention include one or more amino acid modifications at position 32, 87 and/or 127 of wild-type AXL (SEQ ID NO: 1) or a combination thereof, *e.g.*, G32S; D87G; and/or G127R. In yet some other embodiments, AXL polypeptide variants of the present invention include one or more amino acid modifications at position 32, 87 and/or 92 of wild-type AXL (SEQ ID NO: 1) or a combination thereof, *e.g.*, G32S; D87G; and/or V92A. In yet some other embodiments, AXL variant polypeptides of the present invention include one or more amino acid modifications at position 26, 79, 92, 127 of wild-type AXL (SEQ ID NO: 1) or a combination thereof, *e.g.*, E26G, V79M; V92A and/or G127E. In yet some other embodiments, AXL variant polypeptides of the present invention include one or more amino acid modifications at position 87 and 92 of wild-type AXL (SEQ ID NO: 1) or a combination thereof, *e.g.*, D87G and V92A. In yet some other embodiments, AXL variant polypeptides of the present

invention include at least one amino acid modification at position 72 of wild-type AXL (SEQ ID NO: 1), *e.g.*, A72V.

[00126] According to the present invention, the inhibitor agent can include but is not limited to a polypeptide, a polypeptide-carrier fusion, a polypeptide-Fc fusion, polypeptide-conjugate, a polypeptide-drug conjugate, an antibody, a bispecific antibody, an antibody-drug conjugate, an antibody fragment, an antibody-related structure, or a combination thereof.

[00127] The inhibitor agents of the present invention can include peptides or polypeptides. The peptides and polypeptides of the present invention can include natural and/or synthetic polypeptides. Synthetic polypeptides and methods of making synthetic polypeptides are well known in the art and any known methods for making synthetic polypeptides can be employed with the methods of the present invention. In some embodiments, the inhibitor agent is a natural or synthetic polypeptide. In some embodiments, the inhibitor agent is a natural or synthetic polypeptide–fusion. In some embodiments, the inhibitor agent is a natural or synthetic polypeptide-Fc fusion. In some embodiments the natural or synthetic polypeptide–fusion is a fusion with another protein structural class or scaffold or a natural or synthetic polypeptide-fusion with a polymer or hydrogel or related structure.

[00128] According to the present invention, the AXL, MER or Tyro3 variant polypeptides of the present invention can be further modified, *e.g.*, joined to a wide variety of other oligopeptides or proteins for a variety of purposes. For instance, various post-translation or post-expression modifications can be carried out with respect to AXL, MER or Tyro3 variant polypeptides of the present invention. For example, by employing the appropriate coding sequences, one may provide farnesylation or prenylation. In some embodiments, the AXL, MER or Tyro3 variant polypeptides of the present invention can be PEGylated, where the polyethyleneoxy group provides for enhanced lifetime in the blood stream. The AXL, MER or Tyro3 variant polypeptides of the present invention can also be combined with other proteins, such as the Fc of an IgG isotype, which can be complement binding. The inhibitor agents of the present invention can include polypeptide conjugates and antibody-conjugates. In some embodiments, the inhibitor agent is a polypeptide-conjugate or antibody-conjugate. In some embodiments, the polypeptide conjugate is a drug conjugate. In some embodiments, the peptide or polypeptide conjugate is an antibody-drug conjugates. In some embodiments, the polypeptide conjugate is a polymer conjugate. Polymers of the present invention include but are not limited to PEG, PEG-containing polymers, degradable polymers, biocompatible polymers, hydrogels, as well as other polymer structures that could be conjugated to a polypeptide, and can include combinations thereof.

[00129] In some embodiments, the AXL, MER or Tyro3 variant polypeptide of the present invention is a fusion protein, *e.g.*, fused in frame with a second polypeptide. In some embodiments, the second polypeptide is capable of increasing the size of the fusion protein, *e.g.*, so that the fusion protein will not be cleared from the circulation rapidly. In some other embodiments, the second polypeptide is part or whole of Fc region. In some other embodiments, the second polypeptide is any suitable polypeptide that is substantially similar to Fc, *e.g.*, providing increased size and/or additional binding or interaction with Ig molecules. In some embodiments, the sAXL-Fc fusion molecule is a soluble molecule. In some embodiments, the sAXL-Fc fusion has enhanced affinity toward GAS6. In some embodiments, the sAXL-Fc fusion is a soluble molecule that has enhanced affinity toward GAS6. In some other embodiments, the second polypeptide is any suitable polypeptide that is substantially similar to Fc, *e.g.*, providing increased size and/or additional binding or interaction with Ig molecules. In yet some other embodiments, the second polypeptide is part or whole of an albumin protein, *e.g.*, a human serum albumin protein. In some embodiments, the second polypeptide is a protein or peptide that binds to albumin.

[00130] In some other embodiments, the second polypeptide is useful for handling the AXL, MER or Tyro3 variant polypeptides, *e.g.*, purification of AXL, MER or Tyro3 variant polypeptides or for increasing its stability *in vitro* or *in vivo*. For example, AXL, MER or Tyro3 variant polypeptides of the present invention can be combined with parts of the constant domain of immunoglobulins (IgG), resulting in chimeric or fusion polypeptides. These fusion proteins facilitate purification and show an increased half-life *in vivo*. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. EP A 394,827; *Traunecker et al.*, Nature, 331: 84-86, 1988. Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. *Fountoulakis et al.*, J. Biochem. 270: 3958-3964,1995.

[00131] In yet some other embodiments, the second polypeptide is a marker sequence, such as a peptide which facilitates purification of the fused polypeptide. For example, the marker amino acid sequence can be a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, Calif., 91311), among others, many of which are commercially available. As described in *Gentz et al.*, Proc. Natl. Acad. Sci. USA 86: 821-824, 1989, for instance, hexa-histidine provides for convenient purification of the fusion protein.

Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. *Wilson et al.*, Cell 37: 767, 1984.

[00132] In still some other embodiments, the second polypeptide is an entity useful for improving the characteristics of AXL, MER or Tyro3 polypeptide variants of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the AXL, MER or Tyro3 polypeptide variants of the present invention to facilitate purification and subsequently removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

[00133] In still yet some embodiments, AXL, MER or Tyro3 variant polypeptides of the present invention have a binding activity to GAS6 that is at least equal or better than the wild-type AXL, MER or Tyro3.. In some other embodiments, AXL, MER or Tyro3 variant polypeptides of the present invention has a binding activity or affinity to GAS6 that is at least 1-fold, 2-fold, 3-fold, 4-fold, 5-fold, or 6-fold greater than that of the wild-type AXL, MER or Tyro3.. In some other embodiments, AXL, MER or Tyro3 polypeptide variant of the present invention has a binding activity or affinity to GAS6 of at least about $1x10^{-6}$, $1x10^{-7}$, $1x10^{-8}$ or $1x10^{-9}$ M, 1×10^{-10}M, $1x10^{-11}$M or $1x10^{-12}$M. In yet some other embodiments, sAXL polypeptides of the present invention is capable of inhibiting, inhibit or compete with wild-type AXL binding to GAS6 either *in vivo, in vitro* or both. In yet some other embodiments, sAXL polypeptides of the present invention inhibit or compete with the binding of AXL S6-1, AXL S6-2, and/or AXL S6-5 (as described in WO2011/091305). In yet some other embodiments, sAXL polypeptides of the present invention inhibit or compete with the binding of any sAXL variant as described in WO2011/091305.

[00134] The inhibitor agents of the present invention bind to GAS6 with increased affinity. In some embodiments, the AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 polypeptide binding to GAS6 as compared to wild-type AXL, MER or Tyro3. In some embodiments, AXL, MER or Tyro3 variant polypeptide exhibits an affinity to GAS6 that is at least about 5-fold stronger, at least about 10-fold stronger or at least about 20-fold stronger, 50-fold stronger, 100-fold stronger or at least 200-fold stronger, *etc.* than the affinity of the wild-type AXL, MER or Tyro3 polypeptide. In some embodiments, the soluble AXL has a about a 115-fold stronger affinity to GAS6 than the affinity of the wild-type AXL polypeptide.

[00135] The ability of a molecule to bind to GAS6 can be determined, for example, by the ability of the putative ligand to bind to GAS6 coated on an assay plate. In one embodiment, the binding activity of AXL, MER or Tyro3 variant polypeptides of the present invention to a GAS6

can be assayed by either immobilizing the ligand, *e.g.*, GAS6 or the AXL, MER or Tyro3 variant polypeptides. For example, the assay can include immobilizing GAS6 fused to a His tag onto Ni-activated NTA resin beads. Agents can be added in an appropriate buffer and the beads incubated for a period of time at a given temperature. After washes to remove unbound material, the bound protein can be released with, for example, SDS, buffers with a high pH, and the like and analyzed.

[00136] In still yet other embodiments, AXL, MER or Tyro3 variant polypeptides of the present invention has a better thermal stability than the thermal stability of a wild-type AXL. In some embodiments, the melting temperature of AXL, MER or Tyro3 variant polypeptides of the present invention is at least 5°C, 10°C, 15°C, or 20°C higher than the melting temperature of a wild-type AXL.

[00137] According to the present invention, AXL, MER or Tyro3 variant polypeptides of the present invention can also include one or more modifications that do not alter primary sequences of the AXL, MER or Tyro3 variant polypeptides of the present invention. For example, such modifications can include chemical derivatization of polypeptides, *e.g.*, acetylation, amidation, carboxylation, *etc.* Such modifications can also include modifications of glycosylation, *e.g.* those made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing or in further processing steps; *e.g.* by exposing the polypeptide to enzymes which affect glycosylation, such as mammalian glycosylating or deglycosylating enzymes. In some embodiments, AXL, MER or Tyro3 polypeptide variants of the present invention include AXL, MER or Tyro3 variant polypeptides having phosphorylated amino acid residues, *e.g.* phosphotyrosine, phosphoserine, or phosphothreonine.

[00138] In some other embodiments, AXL, MER or Tyro3 variant polypeptides of the present invention include AXL, MER or Tyro3 variant polypeptides further modified to improve their resistance to proteolytic degradation or to optimize solubility properties or to render them more suitable as a therapeutic agent. For example, AXL, MER or Tyro3 polypeptide variants of the present invention further include analogs of AXL, MER or Tyro3 variant polypeptides containing residues other than naturally occurring L-amino acids, *e.g.* D-amino acids or non-naturally occurring synthetic amino acids. D-amino acids may be substituted for some or all of the amino acid residues.

[00139] In yet some other embodiments, AXL, MER or Tyro3 variant polypeptides of the present invention include at least two same or different AXL, MER or Tyro3 variant polypeptides linked covalently or non-covalently. For example, in some embodiments, AXL, MER or Tyro3 polypeptide variants of the present invention include two, three, four, five, or six same or

different AXL, MER or Tyro3 variant polypeptides linked covalently, *e.g.*, so that they will have the appropriate size, but avoiding unwanted aggregation.

[00140] According to the present invention, AXL, MER or Tyro3 variant polypeptides of the present invention can be produced by any suitable means known or later discovered in the field, *e.g.*, produced from eukaryotic or prokaryotic cells, synthesized *in vitro, etc.* Where the protein is produced by prokaryotic cells, it may be further processed by unfolding, *e.g.* heat denaturation, DTT reduction, *etc.* and may be further refolded, using methods known in the art.

[00141] The AXL, MER or Tyro3 variant polypeptides may be prepared by *in vitro* synthesis, using conventional methods as known in the art. Various commercial synthetic apparatuses are available, for example, automated synthesizers by Applied Biosystems, Inc., Foster City, CA, Beckman, *etc.* By using synthesizers, naturally occurring amino acids may be substituted with unnatural amino acids. The particular sequence and the manner of preparation will be determined by convenience, economics, purity required, and the like.

[00142] The AXL, MER or Tyro3 variant polypeptides may also be isolated and purified in accordance with conventional methods of recombinant synthesis. A lysate may be prepared of the expression host and the lysate purified using HPLC, exclusion chromatography, gel electrophoresis, affinity chromatography, or other purification technique. For the most part, the compositions which are used will comprise at least 20% by weight of the desired product, more usually at least about 75% by weight, preferably at least about 95% by weight, and for therapeutic purposes, usually at least about 99.5% by weight, in relation to contaminants related to the method of preparation of the product and its purification. Usually, the percentages will be based upon total protein.

[00143] Methods which are well known to those skilled in the art can be used to construct expression vectors containing coding sequences and appropriate transcriptional/translational control signals. These methods include, for example, *in vitro* recombinant DNA techniques, synthetic techniques and *in vivo* recombination/genetic recombination. Alternatively, RNA capable of encoding the polypeptides of interest may be chemically synthesized. One of skill in the art can readily utilize well-known codon usage tables and synthetic methods to provide a suitable coding sequence for any of the polypeptides of the invention. Direct chemical synthesis methods include, for example, the phosphotriester method of *Narang et al.* (1979) Meth. Enzymol. 68: 90-99; the phosphodiester method of *Brown et al.* (1979) Meth. Enzymol. 68: 109-151; the diethylphosphoramidite method of *Beaucage et al.* (1981) Tetra. Lett., 22: 1859-1862; and the solid support method of U.S. Patent No. 4,458,066. Chemical synthesis produces a single stranded oligonucleotide. This can be converted into double stranded DNA by

hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the single strand as a template. While chemical synthesis of DNA is often limited to sequences of about 100 bases, longer sequences can be obtained by the ligation of shorter sequences. Alternatively, subsequences may be cloned and the appropriate subsequences cleaved using appropriate restriction enzymes.

[00144] The nucleic acids may be isolated and obtained in substantial purity. Usually, the nucleic acids, either as DNA or RNA, will be obtained substantially free of other naturally-occurring nucleic acid sequences, generally being at least about 50%, usually at least about 90% pure and are typically "recombinant," *e.g.*, flanked by one or more nucleotides with which it is not normally associated on a naturally occurring chromosome. The nucleic acids of the invention can be provided as a linear molecule or within a circular molecule, and can be provided within autonomously replicating molecules (vectors) or within molecules without replication sequences. Expression of the nucleic acids can be regulated by their own or by other regulatory sequences known in the art. The nucleic acids of the invention can be introduced into suitable host cells using a variety of techniques available in the art, such as transferrin polycation-mediated DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated DNA transfer, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, gene gun, calcium phosphate-mediated transfection, and the like.

[00145] In some embodiments, the present invention provides expression vectors for *in vitro* or *in vivo* expression of one or more AXL, MER and/or Tyro3 polypeptide variants of the present invention, either constitutively or under one or more regulatory elements. In some embodiments, the present invention provides a cell population comprising one or more expression vectors for expressing AXL, MER and/or Tyro3 polypeptide variants of the present invention, either constitutively or under one or more regulatory elements.

[00146] According to the present invention, the AXL, MER or Tyro3 variant polypeptides can be provided in pharmaceutical compositions suitable for therapeutic use, *e.g.*, for human treatment. In some embodiments, pharmaceutical compositions of the present invention include one or more therapeutic entities of the present invention, *e.g.*, AXL polypeptide variants or pharmaceutically acceptable salts, esters or solvates thereof or any prodrug thereof. In some other embodiments, pharmaceutical compositions of the present invention include one or more therapeutic entities of the present invention in combination with another therapeutic agent, *e.g.*, another agent for treatment of fibrosis.

[00147] Pirfenidone, marketed under the names Esbriet and Pirespa, is the first targeted antifibrotic drug to be approved for the treatment of IPF in Europe and Japan. Although its exact mechanism of action remains unclear, pirfenidone is believed to attenuate fibroblast proliferation and the production by activated myofibroblasts of fibrosis-associated mediators and ECM components. Pirfenidone has also shown efficacy in preclinical models of liver fibrosis, renal fibrosis, hypertrophic cardiomyopathy and radiation-induced fibrosis, suggesting that it may have broad antifibrotic activity. Therapeutic antibodies to TGF-β1, a key cytokine involved in the activation of myofibroblasts; CTGF, a matrix-associated, heparin-binding protein that mirrors the profibrotic activity of TGF-β on fibroblasts; and integrin $\alpha_v\beta_6$, which is responsible for the activation of constitutively expressed latent TGF-β, are also being investigated for their antifibrotic activity. A humanized monoclonal antibody to $\alpha_v\beta_6$ developed by Stromedix and Biogen Idec is being investigated as a treatment for interstitial fibrosis and tubular atrophy in kidney-transplant recipients and as a therapy for IPF. Genzyme is also exploring a humanized pan–TGF-β inhibitor (fresolimumab) as a treatment for patients with early-stage diffuse systemic sclerosis, focal segmental glomerulosclerosis, IPF and myelofibrosis, and antibodies and antisense drugs targeting CTGF are being investigated in IPF and scar-revision surgery. Antagonists of the lysophosphatidic acid-1 receptor, a growth factor that induces CTGF and TGF-β1 expression, are being considered as treatments for kidney fibrosis, IPF and systemic sclerosis. Bone morphogenetic protein-7 has also been identified as a potential therapeutic agent for chronic renal injury because it can counteract TGF-β1–induced EMT. An antagonist of the endothelin receptor, which promotes myofibroblast contraction and migration, is being explored in cardiovascular disease and IPF. A humanized monoclonal antibody targeting lysyl oxidase–like-2, an enzyme that catalyzes the cross-linking of collagen, is being explored by Gilead Sciences as a treatment for cardiac fibrosis, IPF and liver fibrosis. Other matrix assembly proteins, such as prolyl hydroxylases, are being investigated preclinically for antifibrotic activity. Bortezomib, a proteasomal inhibitor, inhibits TGF-β1 signaling *in vitro* and has been shown to protect mice from bleomycin-induced skin and lung fibrosis. It also induces apoptosis of hepatic stellate cells. Consequently, bortezomib may prove efficacious for diseases in which TGF-β1, ER stress and activated myofibroblasts have been identified as key pathogenic mediators. Studies are also under way to examine whether a serine/threonine protein kinase inhibitor reduces the number of circulating fibrocytes in individuals with IPF.

[00148] The T_H2-associated cytokine IL-13 has emerged as a key driver of infection and allergen-driven fibrosis. IL-13 and its receptors have also been detected at high levels in the lungs and blood of patients with IPF. Because a growing number of chronic fibrotic diseases are

characterized by the excess production of IL-13 and/or increased expression of IL-13–inducible genes, many individuals with fibrosis might benefit from the neutralization of IL-13.

[00149] In yet some other embodiments, pharmaceutical compositions of the present invention include one or more therapeutic entities of the present invention in combination with a pharmaceutically acceptable excipient.

[00150] In still some other embodiments, therapeutic entities of the present invention are often administered as pharmaceutical compositions comprising an active therapeutic agent, *i.e.*, and a variety of other pharmaceutically acceptable components. (See Remington's Pharmaceutical Science, 15th ed., Mack Publishing Company, Easton, Pa., 1980). The preferred form depends on the intended mode of administration and therapeutic application. The compositions can also include, depending on the formulation desired, pharmaceutically-acceptable, non-toxic carriers or diluents, which are defined as vehicles commonly used to formulate pharmaceutical compositions for animal or human administration. The diluent is selected so as not to affect the biological activity of the combination. Examples of such diluents are distilled water, physiological phosphate-buffered saline, Ringer's solutions, dextrose solution, and Hank's solution. In addition, the pharmaceutical composition or formulation may also include other carriers, adjuvants, or nontoxic, nontherapeutic, nonimmunogenic stabilizers and the like.

[00151] In still some other embodiments, pharmaceutical compositions of the present invention can also include large, slowly metabolized macromolecules such as proteins, polysaccharides such as chitosan, polylactic acids, polyglycolic acids and copolymers (such as latex functionalized Sepharose^{TM}, agarose, cellulose, and the like), polymeric amino acids, amino acid copolymers, and lipid aggregates (such as oil droplets or liposomes). Additionally, these carriers can function as immunostimulating agents (*i.e.*, adjuvants).

[00152] In yet other embodiments, methods of the present invention include administering to a subject in need of treatment a therapeutically effective amount or an effective dose of a therapeutic entity (*e.g.*, inhibitor agent) of the present invention, *e.g.*, an inhibitor of AXL, MER and/or Tyro3 activity or GAS6 activity or an inhibitor of interaction between AXL, MER and/or Tyro3 and GAS6. In some embodiments, effective doses of the therapeutic entity of the present invention described herein vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Usually, the patient is a human but nonhuman mammals including transgenic mammals can also be treated. Treatment dosages need to be titrated to optimize safety and efficacy.

[00153] In some embodiments, the dosage may range from about 0.0001 to 100 mg/kg, and more usually 0.01 to 5 mg/kg, of the host body weight. For example dosages can be 1 mg/kg body weight or 10 mg/kg body weight or within the range of 1-10 mg/kg. An exemplary treatment regime entails administration once per every two weeks or once a month or once every 3 to 6 months. Therapeutic entities of the present invention are usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of the therapeutic entity in the patient. Alternatively, therapeutic entities of the present invention can be administered as a sustained release formulation, in which case less frequent administration is required. Dosage and frequency vary depending on the half-life of the polypeptide in the patient.

[00154] In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patent can be administered a prophylactic regime.

[00155] In still yet some other embodiments, for prophylactic applications, pharmaceutical compositions or medicaments are administered to a patient susceptible to, or otherwise at risk of a disease or condition in an amount sufficient to eliminate or reduce the risk, lessen the severity, or delay the outset of the disease, including biochemical, histologic and/or behavioral symptoms of the disease, its complications and intermediate pathological phenotypes presenting during development of the disease.

[00156] In still yet some other embodiments, for therapeutic applications, therapeutic entities of the present invention are administered to a patient suspected of, or already suffering from such a disease in an amount sufficient to cure, or at least partially arrest, the symptoms of the disease (biochemical, histologic and/or behavioral), including its complications and intermediate pathological phenotypes in development of the disease. An amount adequate to accomplish therapeutic or prophylactic treatment is defined as a therapeutically- or prophylactically-effective dose. In both prophylactic and therapeutic regimes, agents are usually administered in several dosages until a sufficient response has been achieved.

[00157] According to the present invention, compositions can be administered by parenteral, topical, intravenous, oral, subcutaneous, intraarterial, intracranial, intraperitoneal, intranasal or intramuscular means. The most typical route of administration is intravenous although other routes can be equally effective.

[00158] For parenteral administration, compositions of the invention can be administered as injectable dosages of a solution or suspension of the substance in a physiologically acceptable diluent with a pharmaceutical carrier that can be a sterile liquid such as water, oils, saline, glycerol, or ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents, surfactants, pH buffering substances and the like can be present in compositions. Other components of pharmaceutical compositions are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, and mineral oil. In general, glycols such as propylene glycol or polyethylene glycol are preferred liquid carriers, particularly for injectable solutions. Antibodies and/or polypeptides can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained release of the active ingredient. An exemplary composition comprises polypeptide at 1 mg/mL, formulated in aqueous buffer consisting of 10 mM Tris, 210 mM sucrose, 51 mM L-arginine, 0.01% polysorbate 20, adjusted to pH 7.4 with HCl or NaOH.

[00159] Typically, compositions are prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection can also be prepared. The preparation also can be emulsified or encapsulated in liposomes or micro particles such as polylactide, polyglycolide, or copolymer for enhanced adjuvant effect, as discussed above. Langer, Science 249: 1527, 1990 and Hanes, Advanced Drug Delivery Reviews 28: 97-119, 1997. The agents of this invention can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained or pulsatile release of the active ingredient.

[00160] Additional formulations suitable for other modes of administration include oral, intranasal, and pulmonary formulations, suppositories, and transdermal applications.

[00161] For suppositories, binders and carriers include, for example, polyalkylene glycols or triglycerides; such suppositories can be formed from mixtures containing the active ingredient in the range of 0.5% to 10%, preferably 1%-2%. Oral formulations include excipients, such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, and magnesium carbonate. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain 10%-95% of active ingredient, preferably 25%-70%.

[00162] Topical application can result in transdermal or intradermal delivery. Topical administration can be facilitated by co-administration of the agent with cholera toxin or detoxified derivatives or subunits thereof or other similar bacterial toxins. *Glenn et al.*, Nature 391: 851,

1998. Co-administration can be achieved by using the components as a mixture or as linked molecules obtained by chemical crosslinking or expression as a fusion protein.

[00163] Alternatively, transdermal delivery can be achieved using a skin patch or using transferosomes. *Paul et al., Eur. J. Immunol.* 25: 3521-24, 1995; *Cevc et al.*, Biochem. Biophys. Acta 1368: 201-15, 1998.

[00164] The pharmaceutical compositions are generally formulated as sterile, substantially isotonic and in full compliance with all Good Manufacturing Practice (GMP) regulations of the U.S. Food and Drug Administration. Preferably, a therapeutically effective dose will provide therapeutic benefit without causing substantial toxicity.

[00165] Toxicity of the proteins described herein can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, by determining the LD_{50} (the dose lethal to 50% of the population) or the LD_{100} (the dose lethal to 100% of the population). The dose ratio between toxic and therapeutic effect is the therapeutic index. The data obtained from these cell culture assays and animal studies can be used in formulating a dosage range that is not toxic for use in human. The dosage of the proteins described herein lies preferably within a range of circulating concentrations that include the effective dose with little or no toxicity. The dosage can vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition. (See, *e.g.*, *Fingl et al.*, 1975, In: The Pharmacological Basis of Therapeutics, Ch. 1).

[00166] Also within the scope of the invention are kits comprising the compositions (*e.g.*, AXL, MER orTyro3 variant polypeptides and formulations thereof) of the invention and instructions for use. The kit can further contain a least one additional reagent. Kits typically include a label indicating the intended use of the contents of the kit. The term label includes any writing, or recorded material supplied on or with the kit, or which otherwise accompanies the kit.

[00167] All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

[00168] As will be apparent to those of skill in the art upon reading this disclosure, each of the individual embodiments described and illustrated herein has discrete components and features which may be readily separated from or combined with the features of any of the other several embodiments without departing from the scope or spirit of the present invention. Any recited method can be carried out in the order of events recited or in any other order which is logically possible. It is also understood that the terminology used herein is for the purposes of describing particular embodiments

[00169] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or only and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

[00170] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the appended claims.

EXPERIMENTAL

Experimental Methods and Procedures

[00171] Cell Culture. LM-P tumor cells (Clin Cancer Res 2010 July 15; 16(14): 3684 – 3695) were maintained in vitro as a monolayer culture in DMEM medium supplemented with 10% heat inactivated fetal calf serum, 100 U/ml penicillin and 100 µg/ml streptomycin, and L-glutamine (2 mM) at 37°C in an atmosphere of 5% CO_2 in air. The tumor cells were routinely subcultured twice weekly by trypsin-EDTA treatment. Cells growing in an exponential growth phase were harvested and counted using a Beckman Coulter particle counter prior to tumor inoculation.

[00172] Tumor Inoculation. Each mouse was inoculated subcutaneously on the right flank with PDA1-1 tumor cells (1×10^6) in 0.1 ml of sterile saline for tumor development. Subcutaneous tumors were grown for two – three weeks. To establish orthotopic tumors, mice harboring the subcutaneous tumors were sacrificed and the tumors were isolated and cut into small 3 – 4 mm fragments. Laparotomies were performed and a tumor fragment was secured to the tail of the pancreas using resorbable sutures. After implantation, the pancreas was returned to the peritoneal cavity and the incision was closed. Mice received daily injections of carprofen on the day of implantation and on each of the three days post-op for pain management.

[00173] At day four post-surgery, mice were randomly divided into four groups consisting of 10 or 14 animals. The testing articles were administrated to the mice according to the predetermined regimen shown below.

Compounds	Preparation	Concentration	Storage
High affinity AXL variant polypeptide	0.2μm filter sterilized in optimized formulation	1 mg/ml	4°C
Gemcitabine	0.2μm filter sterilized in saline	2 mg/ml	Room temp

[00174] Masson Trichrome staining. Primary tumor tissue was obtained from each mouse upon sacrifice, and was fixed in in 10% formalin. Fixed tissue was mounted and the amount of collagen present was visualized by Masson Trichrome staining. Staining was performed according the manufacturer's protocol (American MasterTech, Lodi, California).

[00175] For each tissue section, at least two fields of view were scored from 0 – 4, with: 0 having no fibrosis; 1 <20 % collagen staining; 2 20 – 40% collagen staining; 3 40 – 60 % collagen staining; 4 >60% collagen staining. Average scores for each tissue section were calculated and reported.

[00176] All the procedures related to animal handling, care, and treatment in this study were performed according to guidelines approved by the Institutional Animal Care and Use Committee (IACUC) of Stanford University following the guidance of the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC). At the time of routine monitoring, the animals were checked for any effects of tumor growth on normal behavior such as mobility, food and water consumption (by looking only), body weight gain/loss, eye/hair matting and any other abnormal effect. Death and observed clinical signs were recorded on the basis of the numbers of animals within each subset.

Results

[00177] Tumor fibrosis. Amount of fibrosis in primary tumor sections, as assessed by Masson Trichrome staining is shown in Figure 1. Fibrotic tissue is labeled by the blue stain in the representative images on the left. The averaged, quantified labeling is reported in the graph on the right.

[00178] Treatment with high affinity AXL variant polypeptide decreased fibrosis within primary tumor tissue, as assessed by collagen content through Masson Trichrome staining.

WHAT IS CLAIMED IS:

1. A method of treating, reducing, reversing, slowing down, or preventing fibrosis in a mammalian patient, the method comprising:

administering one or more inhibitor agents selected from the group consisting of (a) an inhibitor of AXL, MER and/or Tyro3 activity (b) an inhibitor of GAS6 activity; and (c) an inhibitor of AXL, MER or Tyro3-GAS6 interaction.

2. The method of any of the preceding claims wherein the inhibitor is a polypeptide capable of binding to GAS6 with increased affinity compared to wild-type AXL, MER or Tyro3.

3. The method of any of the preceding claims wherein the inhibitor agent is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said polypeptide lacks the AXL, MER or Tyro3 transmembrane domain and comprises at least one amino acid modification relative to the wild-type AXL, MER or Tyro3 sequence, and wherein said change increases the affinity of the AXL, MER or Tyro3 polypeptide binding to GAS6.

4. The method of any of the preceding claims wherein the inhibitor agent is a polypeptide-conjugate.

5. The method of any of the preceding claims wherein the inhibitor agent comprises a polypeptide-polymer conjugate, and wherein the polymer is a PEG, a PEG-containing polymer, a degradable polymer, a biocompatible polymer or a hydrogel.

6. The method of any of the preceding claims wherein the inhibitor agent is a polypeptide, wherein the polypeptide comprises a soluble AXL variant polypeptide wherein the AXL polypeptide lacks the AXL transmembrane domain and has at least one mutation relative to wild-type that increases affinity of the AXL polypeptide binding to GAS6 compared to wild-type AXL.

7. The method of any of the preceding claims wherein the inhibitor agent is a polypeptide, wherein the polypeptide comprises a soluble MER variant polypeptide wherein said MER polypeptide lacks the MER transmembrane domain and has at least one mutation relative to wild-type that increases affinity of the MER polypeptide binding to GAS6 compared to wild-type MER.

8. The method of any of the preceding claims wherein the inhibitor agent is a polypeptide, wherein said polypeptide comprises a soluble Tyro3 variant polypeptide wherein said Tyro3 polypeptide lacks the Tyro3 transmembrane domain and has at least one mutation relative to wild-type that increases affinity of the Tyro3 polypeptide binding to GAS6 compared to wild-type Tyro3.

9. The method of any of the preceding claims wherein the AXL, MER or Tyro3 variant polypeptide lacks a functional fibronectin (FN) domain and/or wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

10. The method of any of the preceding claims wherein the AXL, MER or Tyro3 variant polypeptide lacks the transmembrane domain, has more than one Ig1 domain and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

11. The method of any of the preceding claims wherein the polypeptide has two Ig1 domains.

12. The method of any of the preceding claims wherein the polypeptide has three Ig1 domains.

13. The method of any of the preceding claims wherein the soluble AXL, MER or Tyro3 variant polypeptide lacks the transmembrane domain, has more than one Ig2 domain and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

14. The method of any of the preceding claims wherein the polypeptide has two Ig2 domains.

15. The method of any of the preceding claims wherein the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said soluble AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, has more than one Ig1 domain, more than one Ig2 domain, and wherein said AXL, MER or Tyro3 variant polypeptide exhibits

increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

16. The method of any of the preceding claims wherein the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said soluble AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, lacks a functional fibronectin (FN) domain, has more than one Ig1 domain, more than one Ig2 domain, and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

17. The method of any of the preceding claims wherein the soluble AXL, MER or Tyro3 variant polypeptide has two Ig1 domains and two Ig2 domains.

18. The method of any of the preceding claims wherein the immunoglobulin domains are connected directly.

19. The method of any of the preceding claims wherein the immunoglobulin domains are connected indirectly.

20. The method of any of the preceding claims wherein the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, is capable of binding both the major and minor binding site of a single GAS6 and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 polypeptide binding to GAS6.

21. The method of any of the preceding claims wherein the polypeptide has one Ig1 domain and lacks a functional Ig2 domain.

22. The method of any of the preceding claims wherein the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said soluble AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, has one Ig1 domain, lacks a functional Ig2 domain and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

23. The method of any of the preceding claims wherein the polypeptide is a soluble AXL, MER or Tyro3 variant polypeptide, wherein said soluble AXL, MER or Tyro3 variant polypeptide lacks the AXL, MER or Tyro3 transmembrane domain, lacks a functional fibronectin (FN) domain, has one Ig1 domain, lacks a functional Ig2 domain and wherein said AXL, MER or Tyro3 variant polypeptide exhibits increased affinity of the AXL, MER or Tyro3 variant polypeptide binding to GAS6 compared to wild-type AXL, MER or Tyro3.

24. The method of any of the preceding claims wherein the AXL, MER or Tyro3 variant polypeptide is a fusion protein comprising an Fc domain.

25. The method of any of the preceding claims wherein the variant polypeptide lacks the AXL, MER or Tyro3 intracellular domain.

26. The method of any of the preceding claims wherein the soluble AXL, MER or Tyro3 variant polypeptide further lacks a functional fibronectin (FN) domain and wherein said variant polypeptide exhibits increased affinity of the polypeptide binding to GAS6.

27. The method of any of the preceding claims wherein the soluble AXL, MER or Tyro3 variant polypeptide comprises at least one amino acid modification relative to the wild-type AXL, MER or Tyro3 sequence.

28. The method of any of the preceding claims wherein the soluble AXL variant polypeptide comprises at least one amino acid modification within a region selected from the group consisting of 1) between 15-50, 2) between 60-120, and 3) between 125-135 of the wild-type AXL sequence (SEQ ID NO:1).

29. The method of any of the preceding claims wherein the soluble AXL variant polypeptide comprises at least one amino acid modification at position 19, 23, 26, 27, 32, 33, 38, 44, 61, 65, 72, 74, 78, 79, 86, 87, 88, 90, 92, 97, 98, 105, 109, 112, 113, 116, 118, or 127 of the wild-type AXL sequence (SEQ ID NO: 1) or a combination thereof.

30. The method of any of the preceding claims wherein the soluble AXL variant polypeptide comprises at least one amino acid modification selected from the group consisting of 1) A19T,

2) T23M, 3) E26G, 4) E27G or E27K 5) G32S, 6) N33S, 7) T38I, 8) T44A, 9) H61Y, 10) D65N, 11) A72V, 12) S74N, 13) Q78E, 14) V79M, 15) Q86R, 16) D87G, 17) D88N, 18) I90M or I90V, 19) V92A, V92G or V92D, 20) I97R, 21) T98A or T98P, 22) T105M, 23) Q109R, 24) V112A, 25) F113L, 26) H116R, 27) T118A, 28) G127R or G127E, and 29) G129E and a combination thereof.

31. The method of any of the preceding claims wherein the AXL variant polypeptide comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) valine 92; and (d) glycine 127.

32. The method of any of the preceding claims wherein the AXL variant polypeptide comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following positions: (a) aspartic acid 87 and (b) valine 92.

33. The method of any of the preceding claims wherein the AXL variant polypeptide comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) valine 92; (d) glycine 127 and (e) alanine 72.

34. The method of any of the preceding claims wherein the AXL variant polypeptide comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following position: alanine 72.

35. The method of any of the preceding claims wherein in the AXL variant polypeptide glycine 32 residue is replaced with a serine residue, aspartic acid 87 residue is replaced with a glycine residue, valine 92 residue is replaced with an alanine residue, or glycine 127 residue is replaced with an arginine residue or a combination thereof.

36. The method of any of the preceding claims wherein in the AXL variant polypeptide aspartic acid 87 residue is replaced with a glycine residue or valine 92 residue is replaced with an alanine residue or a combination thereof.

37. The method of any of the preceding claims wherein in the AXL variant polypeptide alanine 72 residue is replaced with a valine residue.

38. The method of any of the preceding claims wherein in the AXL variant polypeptide glycine 32 residue is replaced with a serine residue, aspartic acid 87 residue is replaced with a glycine residue, valine 92 residue is replaced with an alanine residue, glycine 127 residue is replaced with an arginine residue or an alanine 72 residue is replaced with a valine residue or a combination thereof.

39. The method of any of the preceding claims wherein said AXL variant comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following positions: (a) glutamic acid 26; (b) valine 79; (c) valine 92; and (d) glycine 127.

40. The method of any of the preceding claims wherein in the AXL variant polypeptide glutamic acid 26 residue is replaced with a glycine residue, valine 79 residue is replaced with a methionine residue, valine 92 residue is replaced with an alanine residue, or glycine 127 residue is replaced with an arginine residue or a combination thereof.

41. The method of any of the preceding claims, wherein the AXL variant polypeptide comprises at least an amino acid region selected from the group consisting of amino acid region 19-437, 130-437, 19-132, 21-121, 26-132, 26-121 and 1-437 of the wild-type AXL polypeptide (SEQ ID NO: 1), and wherein one or more amino acid modifications occur in said amino acid region.

42. The method of any of the preceding claims, wherein the AXL variant polypeptide comprises amino acid changes relative to the wild-type AXL sequence (SEQ ID NO: 1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; and valine 92.

43. The method of any of the preceding claims wherein in the AXL variant polypeptide glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, and valine 92 is replaced with an alanine residue, or a combination thereof.

44. The method of any of the preceding claims wherein in the soluble AXL polypeptide is a fusion protein comprising an Fc domain and wherein said AXL variant comprises amino acid

changes relative to wild-type AXL sequence (SEQ ID NO:1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; and (d) valine 92.

45. The method of any of the preceding claims wherein the soluble AXL polypeptide is a fusion protein comprising an Fc domain and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, and valine 92 is replaced with an alanine residue, or a combination thereof.

46. The method of any of the preceding claims, wherein the soluble AXL polypeptide is a fusion protein comprising an Fc domain and wherein said AXL variant comprises amino acid changes relative to wild-type AXL sequence (SEQ ID NO:1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; (d) valine 92; and (e) glycine 127.

47. The method of any of the preceding claims, wherein the soluble AXL polypeptide is a fusion protein comprising an Fc domain and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, valine 92 is replaced with an alanine residue, and glycine 127 is replaced with an arginine residue or a combination thereof.

48. The method of any of the preceding claims, wherein the soluble AXL polypeptide is a fusion protein comprising an Fc domain, lacks a functional FN domain, and wherein said AXL variant comprises amino acid changes relative to wild-type AXL sequence (SEQ ID NO:1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; and (d) valine 92.

49. The method of any of the preceding claims, wherein said soluble AXL variant is a fusion protein comprising an Fc domain, lacks a functional FN domain, and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, and valine 92 is replaced with an alanine residue, or a combination thereof.

50. The method of any of the preceding claims, wherein the soluble AXL polypeptide is a fusion protein comprising an Fc domain, lacks a functional FN domain, and wherein said AXL variant comprises amino acid changes relative to wild-type AXL sequence (SEQ ID NO:1) at the

following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; (d) valine 92; and (e) glycine 127.

51. The method of any of the preceding claims, wherein said soluble AXL variant is a fusion protein comprising an Fc domain, lacks a functional FN domain, and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, valine 92 is replaced with an alanine residue, and glycine 127 is replaced with an arginine residue or a combination thereof.

52. The method of any of the preceding claims, wherein the soluble AXL polypeptide is a fusion protein comprising an Fc domain, lacks a functional FN domain, lacks an Ig2 domain, and wherein said AXL variant comprises amino acid changes relative to wild-type AXL sequence (SEQ ID NO:1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72 and (d) valine 92.

53. The method of any of the preceding claims, wherein said soluble AXL variant is a fusion protein comprising an Fc domain, lacks a functional FN domain, lacks an Ig2 domain and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, and valine 92 is replaced with an alanine residue or a combination thereof.

54. The method of any of the preceding claims, wherein the soluble AXL polypeptide is a fusion protein comprising an Fc domain, lacks a functional FN domain, lacks an Ig2 domain, and wherein said AXL variant comprises amino acid changes relative to wild-type AXL sequence (SEQ ID NO:1) at the following positions: (a) glycine 32; (b) aspartic acid 87; (c) alanine 72; (d) valine 92; and (e) glycine 127.

55. The method of any of the preceding claims, wherein said soluble AXL variant is a fusion protein comprising an Fc domain, lacks a functional FN domain, lacks an Ig2 domain and wherein glycine 32 is replaced with a serine residue, aspartic acid 87 is replaced with a glycine residue, alanine 72 is replaced with a valine residue, valine 92 is replaced with an alanine residue, and glycine 127 is replaced with an arginine residue or a combination thereof.

56. The method of any of the preceding claims, wherein said soluble AXL variant polypeptide has an affinity of at least about 1 x 10^{-8} M,1 x 10^{-9} M, 1 x 10^{-10} M, 1 x 10^{-11} M or 1 x 10^{-12} M for GAS6.

57. The method of any of the preceding claims, wherein said soluble AXL variant polypeptide exhibits an affinity to GAS6 that is at least about 5-fold stronger, at least about 10-fold stronger or at least about 20-fold stronger than the affinity of the wild-type AXL polypeptide.

58. The method of any of the preceding claims wherein the soluble AXL, MER or Tyro3 variant polypeptide further comprises a linker.

59. The method of any of the preceding claims, wherein said linker comprises one or more $(GLY)_4SER$ units.

60. The method of the any of the preceding claims, wherein said linker comprises 1, 2, 3 or 5 $(GLY)_4SER$ units.

61. The method of any of the preceding claims, wherein said soluble AXL variant polypeptide inhibits binding between wild-type AXL, MER and/or Tyro3 polypeptide and a GAS6 protein *in vivo* or *in vitro*.

62. The method of any of the preceding claims, wherein said soluble AXL variant polypeptide is a fusion polypeptide comprising an Fc domain.

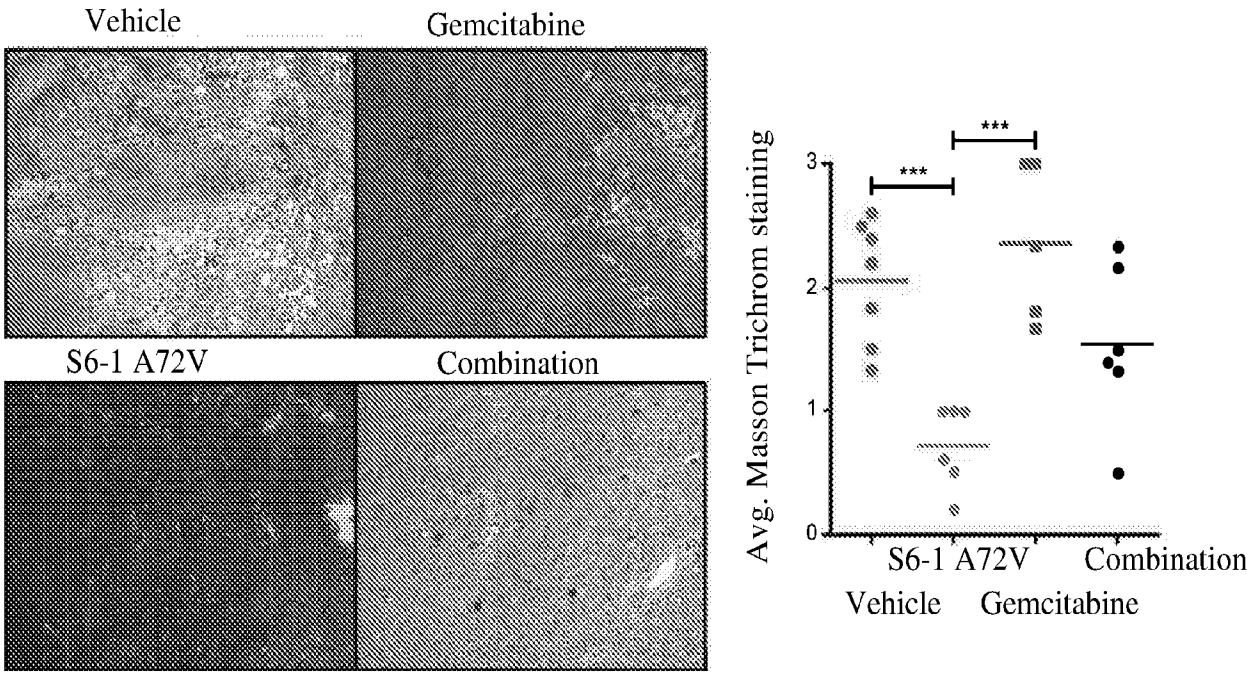
63. The method of any one of the preceding claims, wherein the fibrosis is associated with cancer.

64. The method of Claim 63, wherein the cancer is pancreatic cancer.

65. The method of any one of Claims 1-63, wherein the fibrosis is selected from tumor fibrosis, cardiac fibrosis, liver fibrosis, kidney fibrosis, lung fibrosis, retinal fibrosis, dermal scarring and keloids, Alzheimer's disease; age-related macular degeneration.

66. The method according to any one of the preceding claims wherein the inhibitor is selected from ONO-9330547; TP-0903; LY2801653; MP-470; Amuvatinib; SKI-606, PF-5208763, Bosutinib; MGCD 265; MGCD 516; ASP2215; XL184/Cabozanitinib; BMS 777607 or ASLAN 002; GSK163089/XL880 or Foretinib; SGI-7079; S49076; R428/BGB324; DP3975; NPS-1034; LDC 126; NA80x1; PF-2341066/Crizotinib; Vandetinib; Sunitinib; Lestaurtinib/CEP-701; CEP-40783; Neratinib; AT9283; MK-2461; SU-14813; BMS-796302; JNJ---28312141; Diaminopyrimidine; Warfarin; UNC569, UNC1062, UNC1666, UNC2025.

67. The method according to any of Claims 1-65, wherein the inhibitor is selected from monoclonal antibody 12A11, Mab173, YW327.6S2, D9, E8; antibodies against GAS6, antibodies against AXL; antibodies against MERTK; antibodies that block TYRO3; aptamers that bind to AXL; TAM RTK extracellular domains; recombinant proteins consisting of all or part of the extracellular domain of AXL, MERTK or TYRO3 fused to an Fc domain.


Vehicle
Gemcitabine
S6-1 A72V
Combination
Avg. Masson Trichrom staining
***
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3
2
1
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S6-1 A72V
Combination
Vehicle
Gemcitabine

FIGURE 1