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(54) Title: THERAPEUTIC CHIMERIC LIGAND BINDING PROTEINS AND METHODS FOR THEIR USE

(57) Abstract: Therapeutic chimeric ligand binding proteins are disclosed that are made from portions of at least two receptors that are fused into a single polypeptide sequence. The fused receptor portions can be derived from ErbB, an Axl receptor, FGFR, PDG-FR, an Eph receptor, a Tie receptor, c-Kit receptor, a Trk receptor, a FLT3 receptor, the c-Met oncogene, or their family members and their isoforms. The resulting fusion protein has detectable binding activity for ligands that bind to each of its receptor substituents. DNA sequences that encode the chimeric ligand binding proteins are also contemplated along with sequences that facilitate expression and host cells for the maintenance and expression of such DNA sequences. Pharmaceutical compositions that contain the chimeric ligand binding proteins and a pharmaceutically acceptable excipient are also contemplated. Methods for treating patients having diseases that are associated with ligand binding are also contemplated that involve administering a pharmaceutical composition that contain therapeutically effective amounts of one or more of the chimeric ligand binding protein in a pharmaceutically acceptable excipient or using the chimeric ligand binding proteins to filter bodily fluids.

TITLE

THERAPEUTIC CHIMERIC LIGAND BINDING PROTEINS AND METHODS FOR THEIR USE

BACKGROUND

[0001] Receptor tyrosine kinases (RTKs) are involved in stimulating the growth of many cancers. In general, receptor tyrosine kinases are glycoproteins which consist of (1) an extracellular domain that is able to bind with a specific ligand, (2) a transmembrane region, (3) a juxtamembrane domain which may regulate the receptor activity by, for instance, protein phosphorylation, (4) a tyrosine kinase domain that is the enzymatic component of the receptor, and (5) a carboxyterminal tail. The receptor tyrosine kinases are divided into approximately 17 different types or classes based on architecture and domain organization. As an example, members of the ErbB family of RTKs make up the type I family and constitute one important class of receptors because of their importance in mediating cell growth, differentiation and survival in many solid tumors. Members of this receptor family include ErbBl (also known as HERl), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4). More than a dozen ligands bind to and activate the ErbB-family of receptors. For example, EGF, Transforming Growth Factor alpha (TGFα), and amphiregulin all bind to ErbB1. Isoforms of neuregulin, also known as Heregulin and Neu Differentiation Factor (NDF) have specific affinity for ErbB3 and ErbB4. Ligands such as betacellulin, heparin-binding EGF and epiregulin bind to both ErbB1 and ErbB4.

[0002] It is becoming clear that over expression of ErbB activating ligands can cause uncontrolled cellular proliferation similar to that of a deregulated receptor. This is true not only for the ErbB family, but for other classes of RTK also. In such cases, interference with the binding of the activating ligand to its receptor may provide an effective therapeutic strategy or that could accentuate current receptor targeted therapies. One example of a ligand interference strategy is designing a recombinant molecule that has ligand binding affinity and can therefore "trap" ligands and effectively reduce their concentration so that they cannot activate receptors. Thus, binding molecules that can trap and sequester ligands that activate RTKs may be of use in the treatment of cancer. Binding molecules may be of even more use in the treatment of cancer than some current therapeutics, such as monoclonal antibodies, if they can be designed to have affinity for more than 1 activating ligand. The importance of this is demonstrated by the fact that there are approximately 12 known activating ligands to the ErbB receptor family, many of which have been implicated in cancer. Therefore, a binding molecule that could bind to and trap multiple ErbB ligands, or the full spectrum of ErbB ligands, may have even greater use in the treatment of cancer.

[0003] Several therapeutics exist that have attempted this trapping or "decoy" strategy. For example, Enbrel® (etanercept - Amgen) is a soluble, modified version of the TNFR receptor that binds and traps the pro-inflammatory ligand TNFα. In addition, a soluble fusion protein of the VEGFRI and VEGFR2 receptors, called a VEGF Trap, is currently in clinical trials for the treatment of both macular degeneration and several forms of cancer (Regeneron Pharmaceuticals). An ErbB3 trap has also shown potency *in vitro* at enhancing the effects of a dual EGFR/ErbB2 inhibitor and reversed GW2974 (a small molecule inhibitor of ErbB1 and ErbB2) resistance in cells treated with NDF.

[0004] This strategy of trapping ligands with binding molecules could be expanded to include any class of RTK that has a known activating ligand or ligands. The more ligands there are for any particular receptor tyrosine kinase, the more efficacious the trapping strategy is, since a single binding molecule could be constructed that binds to multiple ligands. Ligand binding molecules can be constructed from parts of the extracellular binding domains of RTKs. The entire extracellular binding domain of a RTK is not always necessary for ligand binding. Joining together pieces of extracellular domains from different types or classes of RTKs could result in a binding molecule that can trap ligands from multiple classes of RTKs.

SUMMARY OF INVENTION

[0005] Chimeric ligand binding proteins that could trap ligands to both type I and type III receptors, or type 3 and type 5 receptors, are disclosed. Chimeric ligand binding proteins are disclosed that are made from portions of at least two receptors that are fused into a single polypeptide sequence. The fused receptor portions can be derived from ErbB, an Axl receptor, FGFR, PDGFR, an Eph receptor, a Tie receptor, c-Kit receptor, a Trk receptor, a FLT3 receptor, the c-Met oncogene, or their family members and their isoforms. The resulting fusion protein has detectable binding activity for ligands that bind to each of its receptor substituents.

[0006] DNA sequences that encode the chimeric ligand binding proteins are also contemplated along with sequences, such as Kozak sequences, that facilitate expression and host cells for the maintenance and expression of such DNA sequences.

[0007] Pharmaceutical compositions that contain the chimeric ligand binding proteins and a pharmaceutically acceptable excipient are also contemplated.

[0008] Methods for treating patients having diseases that are associated with ligand binding are also contemplated that involve administering a pharmaceutical composition that contain therapeutically effective amounts of one or more of the chimeric ligand binding protein in a pharmaceutically acceptable excipient or using the chimeric ligand binding proteins to filter bodily fluids.

FIGURES

[0009] Figure 1 illustrates a protein fusion made from ErbB4 and Axl receptor portions in either order with an Fc portion of IgG shown at the carboxy terminus.

[0010] Figure 2 illustrates a protein fusion made from ErbB4 and the Ig2(D2) and Ig3(D3) domains of FGFR1 (Fibroblast Growth Factor Receptor 1) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0011] Figure 3 illustrates a protein fusion made from ErbB4 and the Ig1, Ig2 and Ig3 domains of PDGFRα (Platelet-Derived Growth Factor Receptor α) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0012] Figure 4 illustrates a protein fusion made from ErbB4 and the Ig1 domain of EphB2 (Ephrin Type-B Receptor 2) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0013] Figure 5 illustrates a protein fusion made from ErbB4 and the Ig1 and Ig2 domains of Tie2 (Tyrosine kinase with immunoglobulin-like and EGF-like domains 1) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0014] Figure 6 illustrates a protein fusion made from ErbB4 and the Ig1, Ig2 and Ig3 domains of c-Kit (Cytokine Receptor) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0015] Figure 7 illustrates a protein fusion made from ErbB4 and the d5(Ig) domain of TrkA (Tropomysin receptor kinase A) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0016] Figure 8 illustrates a protein fusion made from ErbB4 and the Ig1, Ig2 and Ig3 domains of FLT3 (FMS-like Tyrosine Kinase Receptor-3) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0017] Figure 9 illustrates a protein fusion construct made from ErbB4 and amino acids 25- 519 of c-Met (met proto-oncogene that encodes a protein known as hepatocyte growth factor receptor) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0018] Figure 10 illustrates a protein fusion made from ErbB1 and Axl receptor portions in either order with an Fc portion of IgG shown at the carboxy terminus.

[0019] Figure 11 illustrates a protein fusion made from ErbB1 and the Ig2(D2) and Ig3(D3) domains of FGFR1 (Fibroblast Growth Factor Receptor 1) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0020] Figure 12 illustrates a protein fusion made from ErbB1 and the Ig1, Ig2 and Ig3 domains of PDGFRα (Platelet-Derived Growth Factor Receptor α) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0021] Figure 13 illustrates a protein fusion made from ErbB1 and the Ig1 domain of EphB2 (Ephrin Type-B Receptor 2) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0022] Figure 14 illustrates a protein fusion made from ErbB1 and the Ig1 and Ig2 domains of Tie2 (Tyrosine kinase with immunoglobulin-like and EGF-like domains 1) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0023] Figure 15 illustrates a protein fusion made from ErbB1 and the Ig1, Ig2 and Ig3 domains of c-Kit (Cytokine Receptor) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0024] Figure 16 illustrates a protein fusion made from ErbB1 and the d5(Ig) domain of TrkA (Tropomysin receptor kinase A) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0025] Figure 17 illustrates a protein fusion made from ErbB1 and the Ig1, Ig2 and Ig3 domains of FLT3 (FMS-like Tyrosine Kinase Receptor-3) in either order with an Fc portion of IgG shown at the carboxy terminus.

[0026] Figure 18 illustrates a protein fusion construct made from ErbB1 and amino acids 25-519 of c-Met (met proto-oncogene that encodes a protein known as hepatocyte growth factor receptor) in either order with an Fc portion of IgG shown at the carboxy terminus.

DETAILED DESCRIPTION OF INVENTION

[0027] The present specification discloses chimeric ligand binding proteins that are useful in the treatment of diseases that are associated with the presence of ligands for those receptors. The chimeric ligand binding proteins include fusions of at least two distinct receptor proteins such that the resulting fused protein (chimeric ligand binding protein) binds ligands from each of its component receptor proteins. The fused proteins are generally extracellular domains of the receptors and are generally soluble in aqueous solutions in the absence of additional chemical modifications.

[0028] For purposes of this specification a fusion is the result of the joining of a region of an amino acid sequence from each of the receptor proteins through a covalent bond. Generally, the covalent bond can include amide bonds of the types normally associated with amino acids in peptide sequences. The fusion proteins provide binding sites that bind a spectrum of ligands that include at least a subset of ligands that bind to each of its component receptor protein. The resulting chimeric ligand binding protein is generally capable of sequestering a broader range of ligands than the extracellular domain of either component receptor protein alone. The chimeric ligand binding proteins are also known as traps since they serve to "trap" ligands and lower their effective concentration. Consequently, they can serve as therapeutics in the treatment of cancer and/or diseases caused or aggravated by the presence of the targeted ligands.

[0029] Generally, any receptor protein known to be involved in disease, particularly diseases associated with ligand stimulated cell proliferation, can be fused with at least a portion of another distinct receptor protein to provide useful chimeric ligand binding proteins. Particularly useful fusions are derived from pairs of receptors that are both known to be involved in the same disease. Specifically, receptors can be ErbB receptors, Axl receptors,

FGFRs, PDGFRs, Eph receptors, Tie receptors, c-Kit receptors, Trk receptors, FLT3 receptors, c-Met oncogenes in addition to their family members and their isoforms.

[0030] For purposes of this specification the phrase "family member" refers to groups of related genes of similar sequence and function that are thought to result from duplication followed by subsequent mutational variation.

[0031] For purposes of this specification the term isoform when used with reference to receptor proteins includes any of several different forms of the same protein. Different forms of a protein may be produced from related genes, or may arise from the same gene by alternative splicing. A large number of isoforms are caused by single-nucleotide polymorphisms or SNPs, small genetic differences between alleles of the same gene. These generally occur at specific individual nucleotide positions within a gene.

[0032] The switch in the amino acid sequence from one receptor to the other can be at any suitable location that provides for broad spectrum and high affinity binding of ligands to both receptor moieties. In some embodiments the switch will occur in regions where amino acid sequences in the regions to be joined are homologous or identical between the receptors being combined.

[0033] When the ErbB receptor is included in the chimeric ligand binding protein it can be derived from ErbB1, ErbB3, or an ErbB4 receptor in addition to their family members and their isoforms. When the receptor is an ErbB4 receptor, a sufficient portion of the receptor can include enough of the LI and SI subdomains so that the ErbB4 binding site retains binding activity for ErbB4 ligands. When the receptor is an ErbB3 receptor, a sufficient portion of the receptor can include enough of the LI and SI subdomains so that the ErbB3 binding site retains binding activity for ErbB3 ligands. When the receptor is an ErbB1 receptor a sufficient portion can include enough of the SI, LII and SII domains so that the ErbB1 binding site retains binding activity for at least some or all of its ligands.

[0034] When a portion of Axl () is included in the chimeric ligand binding protein it can be derived from Axl, Tyro3, Sky and Mer, in addition to their family members and their isoforms. When a portion of Axl is included in the chimeric ligand binding protein it can include a sufficient amount of subdomains Ig1 and Ig2 to retain binding to at least some or all of its ligands.

[0035] When a portion of FGFR (Fibroblast Growth Factor Receptor) is included in the chimeric ligand binding protein it can be derived from FGFR1, FGFR2, FGFR3, or FGFR4 in addition to their family members and their isoforms. When a portion of FGFR1 is included in the chimeric ligand binding protein it can include a sufficient amount of subdomains Ig2 and Ig3 to retain binding to at least some or all of its ligands.

[0036] When a portion of PDGFR (Platelet Derived Growth Factor Receptor) is included in the chimeric ligand binding protein it can be derived from PDGFRα or PDGFRβ in addition to their family members and their isoforms. When a portion of PDGFRα is included in the chimeric ligand binding protein it can include a sufficient amount of the domains Ig1, Ig2 and Ig3 such that PDGFRα retains binding to at least some or all of its ligands.

[0037] When a portion of the Eph receptor (Ephrin receptor) is included in the chimeric ligand binding protein it can be derived from EphA and EphB receptor in addition to their family members and their isoforms. When the family member EphB2 is included in the chimeric ligand binding protein it can include a sufficient amount of the Ig1 domain so that the receptor retains binding to at least some or all of its ligands.

[0038] When a portion of the Tie receptor (Tyrosine Kinase with Immunoglobulin-Like and Egf-like domains) is included in the chimeric ligand binding protein it can be derived from Tie1 or Tie2 in addition to their family members and their isoforms. When the family member Tie2 is included in the chimeric ligand binding protein it can include a sufficient amount of the Ig1 and Ig2 domains so that the receptor retains binding to at least some or all of its ligands.

[0039] When a portion of the c-Kit receptor (Cytokine Receptor) is included in the chimeric ligand binding protein it can be derived from any CSF receptor, its family members, such as CSF1R or their isoforms. When the c-Kit receptor is included in the chimeric ligand binding protein, it can include a sufficient amount of the Ig1, Ig2, and Ig3 domains so that the receptor retains binding to at least some or all of its ligands.

[0040] When a portion of the Trk receptor (Tropomysin Receptor Kinase A) is included in the chimeric ligand binding protein it can be derived from any of TrkA, TrkB, and TrkC their family members or isoforms. When TrkA is included in the chimeric ligand

binding protein, it can include a sufficient amount of the d5(Ig) domain so that the receptor retains binding to at least some or all of its ligands.

[0041] When a portion of the FLT3 receptor (FMS-Like Tyrosine Kinase Receptor-3) is included in the chimeric ligand binding protein it can be derived from any of its family members or isoforms. When FLT3 is included in the chimeric ligand binding protein, it can include a sufficient amount of the Ig1, Ig2, and Ig3 domains so that the receptor retains binding to at least some or all of its ligands.

[0042] When a portion of the c-Met (Met proto-oncogene that encodes a protein known as hepatocyte growth factor receptor) is included in the chimeric ligand binding protein it can be derived from Ron or Sea or any other of its family members or isoforms. When c-Met is included in the chimeric ligand binding protein, it can include amino acids 25-519 or 25-932 such that the receptor retains binding to at least some or all of its ligands.

[0043] In certain embodiments the chimera can be fused with components that cause aggregative conjugate formation or extend protein half-life. For example, the chimeric ligand binding protein can include the Fc portion of IgG2, although other sequences are also known in the art and can be used. The Fc portion can be fused toward the carboxy terminal end of the chimeric ligand binding protein. In certain embodiments such Fc portions can contain mutations in the hinge region that prevent dimerization through the Fc moieties so that dimerization of the resulting proteins is reduced.

[0044] For purposes of this application desirable binding affinities are affinities that are high enough to bind the receptor ligands in a physiological matrix. Preferably, dissociation constants will be no higher than about 10-fold to about 100-fold above the dissociation constants of the native receptors. More preferably, the dissociation constants for the chimera will be within 10-fold of their native receptor counterparts and more preferably within the same order of magnitude. Most preferably the binding affinities of the chimeric molecules will not be distinguishable from the native counterparts. Nevertheless, any affinity that is sufficient to bind and sequester ligands to thereby prevent or interfere with ligand binding and activating of their corresponding receptors is suitable for use and can find use in the disclosed methods. Binding affinity, which is a proxy for inhibitor potency, of the binding molecules can be measured using biosensor technology or by classic binding assays such as ELISA which are well known in the art.

[0045] DNA that encodes the chimeric ligand binding proteins is also contemplated. One of skill can appreciate that the genetic code can be used to prepare suitable DNA sequences and codon preferences for specific expression hosts can also be incorporated into such sequences. Also contemplated for use with these sequences are additional DNA sequences that can be used for the expression of these DNA sequences. A variety of these are known. As is well known in the art such sequences can also be introduced into host cells for the maintenance of the DNA and for its expression and such hosts that include these DNA sequences are also contemplated.

[0046] Pharmaceutical compositions comprising the disclosed chimeric ligand binding proteins are also contemplated. Such compositions comprise a therapeutically effective amount of a chimeric ligand binding protein, and a pharmaceutically acceptable carrier. The term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle in which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like in which the chimeric ErbB ligand binding molecule is soluble and is chemically stable. The composition can also contain wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. Pharmaceutically acceptable carriers include other ingredients for use in formulations such as DPPC, DOPE, DSPC and DOPC. Natural or synthetic surfactants may be used. PEG may be used (even apart from its use in derivatizing the protein or analog). Dextrans, such as cyclodextran, may be used. Cellulose and cellulose derivatives may be used. Amino acids may be used, such as use in a buffered formulation. Pharmaceutically acceptable diluents include buffers having various contents (e.g., Tris-HCl, acetate, phosphate), pH and ionic strength; additives such as detergents and solubilizing agents (e.g., Polysorbate 80), anti-oxidants (e.g., ascorbic acid, sodium metabisulfite), preservatives (e.g., benzyl alcohol) and bulking substances (e.g., lactose, mannitol); incorporation of the material into particulate

preparations of polymeric compounds such as polylactic acid, polyglycolic acid, etc. or into liposomes. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g., Remington's Pharmaceutical Sciences, 18th Ed. (1990, Mack Publishing Co., Easton, PA 18042) pages 1435-1712 which are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilized form. Implantable sustained release formulations are also contemplated, as are transdermal formulations. Liposome, microcapsule or microsphere, inclusion complexes, or other types of carriers are also contemplated.

[0047] The amount of the active chimeric binding protein that will be effective for its intended therapeutic use can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. Generally, the daily regimen should be in the range of 0.1-1000 micrograms of the active agent (API) kilogram of body weight, preferably 0.1-150 micrograms per kilogram. Effective doses may be extrapolated from dose-response curves derived from in vitro or suitable animal model test systems. Dosage amount and interval may be adjusted individually to provide plasma levels of the compounds that are sufficient to maintain therapeutic effect. In cases of local administration or selective uptake, the effective local concentration of the compounds may not be related to plasma concentration. The dosage regimen involved in a method for treatment can be determined by the attending physician, considering various factors which modify the action of drugs, e.g. the age, condition, body weight, sex and diet of the patient, the severity of disease, time of administration and other clinical factors.

[0048] The amount of compound administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration, and the judgment of the prescribing physician. The therapy may be repeated intermittently while symptoms are detectable or even when they are not detectable. The therapy may be provided alone or in combination with other drugs.

[0049] A method for treating a patient in need of treatment is disclosed that includes obtaining a chimeric ligand binding protein that binds suitable ligands and interferes with the interaction and effect of those ligands on target receptor systems of cells involved in disease, and then administering a therapeutically effective amount of the chimeric ligand binding

protein to a patient. Administration can be by parenteral routes, such as i.v. administration, direct injection into a solid tumor, such as through a syringe, catheter or by i.p. injection.

[0050] In one method of treatment the chimeric ligand binding proteins can be immobilized to a solid support such as an apheresis or biocore support by standard methods. When the binding molecule is immobilized to a solid support; the serum, blood, or other biologically relevant fluid of a patient can be placed in contact with the solid support in the apheresis column to remove ligands from the fluid. The serum, blood or fluid can then be reintroduced into the patient.

[0051] The following examples are given by way of illustration only and in no way should be construed as limiting the subject matter of the present application. Although the following examples disclose the sequence for IgG2Fc fused to the chimera, it should be appreciated that use of IgG2Fc is optional. In addition, the conservative replacement of an amino acid with another similar amino acid that does not substantially (about 10-fold) interfere with ligand binding activity is specifically contemplated. Conventional binding studies of the purified products can be used to determine whether substantial differences in binding affinities exist.

EXAMPLE 1

[0052] Example 1 specifically discloses a chimeric ligand binding protein made of the LI and SI domains of ErbB4 (also known as HER4) joined to the Igl and Ig2 domains of Axl. A portion or all of the ErbB4 SI domain can be used and amino acid substitutions can be included in the joining region to increase the conservation with the native receptor regions and thereby conserve their three dimensional structures. Either ErbB4 or Axl could be toward the amino terminal side of the other in the sequence as shown in Figure 1. In addition the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 1. Other Axl receptor family members such as Tyro3, Sky and Mer and their isoforms could also be used in similar constructs. ErbB3 could be used in place of ErbB4 in this example.

EXAMPLE 2

[0053] Example 2 specifically discloses a chimeric ligand binding protein made of the LI and SI domains of ErbB4 joined to at least a portion of FGFR1, shown in Figure 2 as the Ig2(D2) and Ig3(D3) domains of FGFR1 (Fibroblast Growth Factor Receptor 1). A portion

or all of the ErbB4 SI domain can be used and amino acid substitutions can be included in the joining region to increase amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of FGFR1 can be included in the constructs, including for example Ig1(D1) and/or the acid box of FGFR. Either ErbB4 or FGFR1 portions could be positioned on the amino terminal side of the other sequence as shown in Figure 2. In addition the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 2. Other FGF receptor family members such as FGFR2, FGFR3, FGFR4 and their isoforms could also be used in similar constructs. ErbB3 could be used in place of ErbB4 in this example.

EXAMPLE 3

[0054] Example 3 specifically discloses a chimeric ligand binding protein made of the LI and SI domains of ErbB4 joined to at least a portion of PDGFRα, shown in Figure 3 as the Ig1, Ig2 and Ig3 domains of PDGFRα (Platelet-derived growth factor receptor α). A portion or all of the ErbB4 SI domain could be used and amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of PDGFRα can be included in the constructs, including for example Ig4 and Ig5 domains of PDGFRα could also be included. Either ErbB4 or PDGFRα portions could be positioned on the amino terminal side of the other sequence as shown in Figure 3. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 3. Other PDGFRα family members such as PDGFRβ and their isoforms could also be used in similar constructs. ErbB3 could be used in place of ErbB4 in this example.

EXAMPLE 4

[0055] Example 4 specifically discloses a chimeric ligand binding protein made of the LI and SI domains of ErbB4 joined to at least a portion of EphB2 (Ephrin Type-B Receptor 2), shown in Figure 4 as the Ig1 domain of EphB2. A portion or all of the ErbB4 SI domain could be used and amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of EphB2 can be included in the constructs. Either ErbB4 or EphB2 portions could be positioned on the amino terminal side of the other sequence as shown in Figure 4. In addition, the Fc portion of IgG can be included on the

carboxyl terminus of the constructs as shown in Figure 4. Other family members, including any EphB and any EphA receptor, and their isoforms could also be used in similar constructs. ErbB3 could be used in place of ErbB4 in this example.

EXAMPLE 5

[0056] Example 5 specifically discloses a chimeric ligand binding protein made of the LI and SI domains of ErbB4 joined to at least a portion of Tie2 (Tyrosine Kinase with Immunoglobulin-Like and Egf-Like domains), shown in Figure 5 as the Ig1 and Ig2 domains of Tie2. A portion or all of the ErbB4 SI domain could be used and amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of Tie2 can be included in the constructs, for example the 3 EGF domains, Ig3, and 3 fibronectin domains, or combinations thereof, could also be included. Either ErbB4 or Tie2 portions could be positioned on the amino terminal side of the other sequence as shown in Figure 5. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 5. Other Tie2 family members such as Tie1 and their isoforms could also be used in similar constructs. ErbB3 could be used in place of ErbB4 in this example.

EXAMPLE 6

[0057] Example 6 specifically discloses a chimeric ligand binding protein made of the LI and SI domains of ErbB4 joined to at least a portion of c-Kit (Cytokine Receptor), shown in Figure 6 as the Ig1, Ig2 and Ig3 domains of c-Kit. A portion or all of the ErbB4 SI domain could be used and amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of c-Kit can be included in the constructs, for example, the Ig4 and lg5 domains of c-Kit could also be included. Either ErbB4 or c-Kit portions can be positioned on the amino terminal side of the other sequence as shown in Figure 6. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 6. Other c-Kit family members such as CSF1 receptors and their isoforms could also be used in similar constructs. ErbB3 could be used in place of ErbB4 in this example.

EXAMPLE 7

[0058] Example 7 specifically discloses a chimeric ligand binding protein made of the LI and SI domains of ErbB4 joined to at least a portion of d5(Ig) domain of TrkA (Tropomysin Receptor Kinase A) as shown in Figure 7. A portion or all of the ErbB4 SI domain could be used and amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of TrkA can be included in the constructs, for example, the 2 cysteine rich, leucine rich and d4(Ig) domains, or combinations thereof could also be included. Either ErbB4 or TrkA portions can be positioned on the amino terminal side of the other sequence as shown in Figure 7. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 7. Other TrkA family members, such as TrkB and TrkC and their isoforms, could also be used in similar constructs. ErbB3 could be used in place of ErbB4 in this example.

EXAMPLE 8

[0059] Example 8 specifically discloses a chimeric ligand binding protein made of the LI and SI domains of ErbB4 joined to at least a portion of Ig1, Ig2, and Ig3 domains of FLT3 (FMS-Like Tyrosine Kinase Receptor-3) as shown in Figure 8. A portion or all of the ErbB4 SI domain could be used and amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of FLT3 can be included in the constructs, for example, the Ig4, Ig5 domains, or combinations thereof could also be included. Either ErbB4 or FLT3 portions can be positioned on the amino terminal side of the other sequence as shown in Figure 8. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 8. Other FLT3 family members and their isoforms could also be used in similar constructs. ErbB3 could be used in place of ErbB4 in this example.

EXAMPLE 9

[0060] Example 9 specifically discloses a chimeric ligand binding protein made of the LI and SI domains of ErbB4 joined to amino acids 25-519 of c-Met (Met proto-oncogene that encodes a protein known as hepatocyte growth factor receptor) as shown in Figure 9. A portion or all of the ErbB4 SI domain could be used and amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor

regions and thereby conserve their three dimensional structures. Additional portions of c-Met can be included in the constructs, for example, amino acid residues 25-932 could also be included. Either ErbB4 or TrkA portions can be positioned on the amino terminal side of the other sequence as shown in Figure 9. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 9. Other c-Met family members, such as Ron and Sea and their isoforms, could also be used in similar constructs. ErbB3 could be used in place of ErbB4 in this example.

EXAMPLE 10

[0061] Example 10 specifically discloses a chimeric ligand binding protein made of a portion of the SI domain, the LII domain, and a portion of the SII domain of ErbB1 (also known as HER1) joined to the Igl and Ig2 domains of Axl. Any portion or all of the ErbB1 SI and SII domains can be used so long as the resulting protein retains ligand binding activity for the ErbB1 ligands as assayed using known procedures. In addition, amino acid substitutions can be included in the joining region with Axl to increase the conservation with the native receptor regions and thereby conserve their three dimensional structures. Either ErbB1 or Axl could be toward the amino terminal side of the other in the sequence as shown in Figure 10. In addition the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 10. Other Axl receptor family members such as Tyro3 and Mer and their isoforms could also be used in similar constructs.

EXAMPLE 11

[0062] Example 11 specifically discloses a chimeric ligand binding protein made of a portion of the SI domain, the LII domain, and a portion of the SII domain of ErbB1 joined to at least a portion of FGFR1, shown in Figure 11 as the Ig2(D2) and Ig3(D3) domains of FGFR1 (Fibroblast Growth Factor Receptor 1). Any portion or all of the ErbB1 SI and SII domains can be used so long as the resulting protein retains ligand binding activity for the ErbB1 ligands as assayed using known procedures. In addition, amino acid substitutions can be included in the joining region with FGFR1 to increase the conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of FGFR1 can be included in the constructs, including, for example, Ig1(D1) and/or the acid box of FGFR. Either ErbB1 or FGFR1 portions could be positioned on the amino terminal side of the other sequence as shown in Figure 11. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 11. Other FGF

receptor family members such as FGFR2, FGFR3, FGFR4 and their isoforms could also be used in similar constructs.

EXAMPLE 12

[0063] Example 12 specifically discloses a chimeric ligand binding protein made of a portion of the SI domain, the LII domain, and a portion of the SII domain of ErbB1 joined to at least a portion of PDGFRα, shown in Figure 12 as the Ig1, Ig2 and Ig3 domains of PDGFRα (Platelet-derived growth factor receptor α). Any portion or all of the ErbB1 SI and SII domains can be used so long as the resulting protein retains ligand binding activity for the ErbB1 ligands as assayed using known procedures. In addition, amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of PDGFRα can be included in the constructs, including, for example, Ig4 and Ig5 domains of PDGFRα could also be included. Either ErbB4 or PDGFRα portions could be positioned on the amino terminal side of the other sequence as shown in Figure 12. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 12. Other PDGFRα family members such as PDGFRβ and their isoforms could also be used in similar constructs.

EXAMPLE 13

[0064] Example 13 specifically discloses a chimeric ligand binding protein made of a portion of the SI domain, the LII domain, and a portion of the SII domain of ErbB1 joined to at least a portion of EphB2 (Ephrin Type-B Receptor 2), shown in Figure 13 as the Ig1 domain of EphB2. Any portion or all of the ErbB1 SI and SII domains can be used so long as the resulting protein retains ligand binding activity for the ErbB1 ligands as assayed using known procedures. In addition, amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of EphB2 can be included in the constructs. Either ErbB4 or EphB2 portions could be positioned on the amino terminal side of the other sequence as shown in Figure 13. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 13. Other PDGFRα family members such as PDGFRβ and their isoforms could also be used in similar constructs.

EXAMPLE 14

[0065] Example 14 specifically discloses a chimeric ligand binding protein made of a portion of the SI domain, the LII domain, and a portion of the SII domain of ErbB1 joined to at least a portion of Tie2 (Tyrosine Kinase with Immunoglobulin-Like and Egf-like domains), shown in Figure 14 as the Ig1 and Ig2 domains of Tie2. Any portion or all of the ErbB1 SI and SII domains can be used so long as the resulting protein retains ligand binding activity for the ErbB1 ligands as assayed using known procedures. In addition, amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of Tie2 can be included in the constructs, for example the 3 EGF domains, Ig3, and 3 fibronectin domains, or combinations thereof, could also be included. Either ErbB4 or Tie2 portions could be positioned on the amino terminal side of the other sequence as shown in Figure 14. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 14. Other Tie2 family members such as Tie1 and their isoforms could also be used in similar constructs.

EXAMPLE 15

[0066] Example 15 specifically discloses a chimeric ligand binding protein made of a portion of the SI domain, the LII domain, and a portion of the SII domain of ErbB1 joined to at least a portion of c-Kit (Cytokine Receptor), shown in Figure 15 as the Ig1, Ig2 and Ig3 domains of c-Kit. Any portion or all of the ErbB1 SI and SII domains can be used so long as the resulting protein retains ligand binding activity for the ErbB1 ligands as assayed using known procedures. In addition, amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of c-Kit can be included in the constructs, for example, the Ig4 and lg5 domains of c-Kit could also be included. Either ErbB4 or c-Kit portions can be positioned on the amino terminal side of the other sequence as shown in Figure 15. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 15. Other c-Kit family members such as CSF1 and their isoforms could also be used in similar constructs.

EXAMPLE 16

[0067] Example 16 specifically discloses a chimeric ligand binding protein made of a portion of the SI domain, the LII domain, and a portion of the SII domain of ErbB1 joined to

at least a portion of d5(Ig) domain of TrkA (Tropomysin Receptor Kinase A) as shown in Figure 16. Any portion or all of the ErbB1 SI and SII domains can be used so long as the resulting protein retains ligand binding activity for the ErbB1 ligands as assayed using known procedures. In addition, amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of TrkA can be included in the constructs, for example, the 2 cysteine rich, leucine rich and d4(Ig) domains, or combinations thereof could also be included. Either ErbB4 or TrkA portions can be positioned on the amino terminal side of the other sequence as shown in Figure 16. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 16. Other TrkA family members, such as TrkB and TrkC and their isoforms, could also be used in similar constructs.

EXAMPLE 17

[0068] Example 17 specifically discloses a chimeric ligand binding protein made of a portion of the SI domain, the LII domain, and a portion of the SII domain of ErbB1 joined to at least a portion of Ig1, Ig2, and Ig3 domains of FLT3 (FMS-like Tyrosine Kinase Receptor-3) as shown in Figure 17. Any portion or all of the ErbB1 SI and SII domains can be used so long as the resulting protein retains ligand binding activity for the ErbB1 ligands as assayed using known procedures. In addition, amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of FLT3 can be included in the constructs, for example, the Ig4, Ig5 domains, or combinations thereof could also be included. Either ErbB4 or FLT3 portions can be positioned on the amino terminal side of the other sequence as shown in Figure 17. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 17. Other FLT3 family members and their isoforms could also be used in similar constructs.

EXAMPLE 18

[0069] Example 18 specifically discloses a chimeric ligand binding protein made of a portion of the SI domain, the LII domain, and a portion of the SII domain of ErbB1 joined to amino acids 25-519 of c-Met (Met proto-oncogene that encodes a protein known as hepatocyte growth factor receptor) as shown in Figure 18. Any portion or all of the ErbB1 SI and SII domains can be used so long as the resulting protein retains ligand binding activity

for the ErbB1 ligands as assayed using known procedures. In addition, amino acid substitutions can be included in the joining region to increase the amino acid conservation with the native receptor regions and thereby conserve their three dimensional structures. Additional portions of c-Met can be included in the constructs, for example, amino acid residues 25-932 could also be included. Either ErbB4 or TrkA portions can be positioned on the amino terminal side of the other sequence as shown in Figure 18. In addition, the Fc portion of IgG can be included on the carboxyl terminus of the constructs as shown in Figure 18. Other c-Met family members, such as Ron and Sea and their isoforms, could also be used in similar constructs.

CLAIMS

1. A chimeric ligand binding protein comprising portions of at least two receptors fused to each other in a single polypeptide sequence, wherein the receptors are selected from the group of receptors consisting of ErbB, an Axl receptor, FGFR, PDGFR, an Eph receptor, a Tie receptor, c-Kit receptor, a Trk receptor, a FLT3 receptor, the c-Met oncogene, or their family members and their isoforms, and wherein the resulting fusion protein has detectable binding activity for ligands from each of its receptor substituents.

2. The chimeric ligand binding protein of Claim 1, wherein ErbB receptor is selected from the group of ErbB receptors consisting of ErbB1, ErbB3, and ErbB4.

3. The chimeric ligand binding protein of Claim 1, wherein the portion of the ErbB comprises at least a portion of subdomains LI and SI of the ErbB4 receptor.

4. The chimeric ligand binding protein of Claim 1, wherein the portion of the ErbB comprises at least a portion of subdomains LI and SI of the ErbB3 receptor.

5. The chimeric ligand binding protein of Claim 1, wherein the portion of the ErbB receptor comprises at least a portion of subdomains SI, LII and SII of the ErbB1 receptor.

6. The chimeric ligand binding protein of Claim 1, wherein the Axl is selected from the group of Axl, Tyro3, Sky, and Mer.

7. The chimeric ligand binding protein of Claim 1, wherein the FGFR is selected from the group of FGFRs consisting of FGFR1, FGFR2, FGFR3, and FGFR4.

8. The chimeric ligand binding protein of Claim 1, wherein the PDGFR is selected from the group of PDGFRs consisting of PDGFRα and PDGFRβ.

9. The chimeric ligand binding protein of Claim 1, wherein the Eph receptor is selected from the group of Eph receptors consisting of EphA and EphB.

10. The chimeric ligand binding protein of Claim 1, wherein the Tie receptor is selected from the group of Tie receptors consisting of Tie1 and Tie2.

11. The chimeric ligand binding protein of Claim 1, wherein the c-Kit receptor is selected from the group of c-Kit receptors consisting of CSF.

12. The chimeric ligand binding protein of Claim 1, wherein the Trk receptor is selected from the group of Trk receptors consisting of TrkA, TrkB, and TrkC.

13. The chimeric ligand binding protein of Claim 1, wherein the c-Met receptor is selected from the group of c-Met receptors consisting of Ron and Sea.

14. The chimeric ligand binding protein of Claim 1, wherein an Fc portion of IgG is located toward the carboxy terminal end of the chimeric ligand binding protein.

15. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of an Axl receptor.

16. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion an Axl receptor and at least a portion of the ErbB receptor is positioned toward the amino terminal side of a portion of Ax1 portion.

17. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a FGFR.

18. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a FGFR and at least a portion of the ErbB receptor is positioned toward the amino terminal side of a portion of FGFR.

19. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a FGFR, wherein the portion of FGFR comprises at least a portion of subdomains Ig2 and Ig3 of FGFR1.

20. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a PDGFR.

21. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a PDGFR and at least a portion of the ErbB receptor is positioned toward the amino terminal side of a portion of PDGFR.

22. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of the Ig1, Ig2 and Ig3 domains of PDGFRα.

23. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of an Eph receptor.

24. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of an Eph receptor and at least a portion of the ErbB receptor is positioned toward the amino terminal side of a portion of the Eph receptor.

25. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of the Ig1 domain of EphB2.

26. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a Tie receptor.

27. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a Tie receptor and at least a portion of the ErbB receptor is positioned toward the amino terminal side of a portion of the Tie receptor.

28. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of the Ig1 and a portion of the Ig2 domains of the Tie2 receptor.

29. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a c-Kit receptor.

30. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a c-Kit receptor and at least a portion of the ErbB receptor is positioned toward the amino terminal side of a portion of the c-Kit receptor.

31. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of the Ig1, a portion of the Ig2, and a portion of the Ig3 domains of the c-Kit receptor.

32. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a Trk receptor.

33. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a Trk receptor and at least a portion of the Erb receptor is positioned toward the amino terminal side of a portion of the Trk receptor.

34. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of the d5(Ig) portion of the TrkA receptor.

35. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a FLT3 receptor.

36. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a FLT3 receptor and at least a portion of the ErbB receptor is positioned toward the amino terminal side of a portion of the FLT3 receptor.

37. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of the Ig1, a portion of the Ig2, and a portion of the Ig3 domains of the FLT3 receptor.

38. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a c-Met oncogene.

39. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to at least a portion of a c-Met receptor and at least a portion of the ErbB receptor is positioned toward the amino terminal side of a portion of the c-Met receptor.

40. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to a portion of the c-Met oncogene comprising amino acids 25-519.

41. The chimeric ligand binding protein of Claim 1 having at least a portion of an ErbB receptor fused to a portion of the c-Met oncogene comprising amino acids 25-932.

42. A method for treating a patient in need of treatment comprising identifying a patient having a disease susceptible to treatment by sequestering a ligand for a receptor selected from the group of receptors consisting of ErbB, an Axl receptor, FGFR, PDGFR, an Eph receptor, a Tie receptor, c-Kit receptor, a Trk receptor, a FLT3 receptor, the c-Met oncogene, or their family members and their isoforms and exposing a bodily fluid to a chimeric ligand binding protein comprising portions of at least two receptors fused to each other in a single polypeptide sequence, wherein the receptors are selected from the group of receptors consisting of ErbB, an Axl receptor, FGFR, PDGFR, an Eph receptor, a Tie receptor, c-Kit receptor, a Trk receptor, a FLT3 receptor, the c-Met oncogene, or

their family members and their isoforms, and wherein the resulting fusion protein has detectable binding activity for ligands from each of its receptor substituents.

43. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a chimeric ligand binding protein comprising portions of at least two receptors fused to each other in a single polypeptide sequence, wherein the receptors are selected from the group of receptors consisting of ErbB, an Axl receptor, FGFR, PDGFR, an Eph receptor, a Tie receptor, c-Kit receptor, a Trk receptor, a FLT3 receptor, the c-Met oncogene, or their family members and their isoforms, and wherein the resulting fusion protein has detectable binding activity for ligands from each of its receptor substituents.

44. A DNA sequence encoding a chimeric ligand binding protein comprising portions of at least two receptors fused to each other in a single polypeptide sequence, wherein the receptors are selected from the group of receptors consisting of ErbB, an Axl receptor, FGFR, PDGFR, an Eph receptor, a Tie receptor, c-Kit receptor, a Trk receptor, a FLT3 receptor, the c-Met oncogene, or their family members and their isoforms, and wherein the resulting fusion protein has detectable binding activity for ligands from each of its receptor substituents.

ErbB4 Chimeric trap designs (domains not drawn to scale)

Fig. 1

Erb4(LI-SI)-Axl(Ig1-Ig2)-IgGFc

ErbB4 – LI	ErbB4 – SI	Axl-Ig1	Axl-Ig2	IgG-Fc

Axl(Ig1-Ig2)-Erb4(LI-SI)-IgGFc

Axl-Ig1	Axl-Ig2	ErbB4 – LI	ErbB4 – SI	IgG-Fc

Fig. 2

Erb4(LI-SI)-FGFR(Ig2-Ig3)-IgGFc

ErbB4 – LI	ErbB4 – SI	FGFR1-Ig2(D2)	FGFR1-Ig3(D3)	IgG-Fc

FGFR(Ig2-Ig3)-Erb4(LI-SI)-IgGFc

FGFR1-Ig2(D2)	FGFR1-Ig3(D3)	ErbB4 – LI	ErbB4 – SI	IgG-Fc

Fig. 3

Erb4(LI-SI)-PDGFRα(Ig1-Ig3)-IgGFc

ErbB4 – LI	ErbB4 – SI	PDGFRα – Ig1	PDGFRα – Ig2	PDGFRα – Ig3	IgG-Fc

PDGFRα(Ig1-Ig3)-Erb4(LI-SI)-IgGFc

PDGFRα – Ig1	PDGFRα – Ig2	PDGFRα – Ig3	ErbB4 – LI	ErbB4 – SI	IgG-Fc

ErbB4 Chimeric trap designs (domains not drawn to scale)
Fig. 4
Erb4(LI-SI)-EphB2(Ig1)-IgGFc
ErbB4 - LI
ErbB4 - SI
EphB2 - Ig1
IgG-Fc
EphB2(Ig1)-Erb4(LI-SI)-IgGFc
EphB2 - Ig1
ErbB4 - LI
ErbB4 - SI
IgG-Fc
Fig. 5
Erb4(LI-SI)-Tie2(Ig1-Ig2)-IgGFc
ErbB4 - LI
ErbB4 - SI
Tie2 - Ig1
Tie2- Ig2
IgG-Fc
Tie2(Ig1-Ig2)-Erb4(LI-SI)-IgGFc
Tie2 - Ig1
Tie2- Ig2
ErbB4 - LI
ErbB4 - SI
IgG-Fc
Fig. 6
Erb4(LI-SI)-cKit(Ig1-Ig3)-IgGFc
ErbB4 - LI
ErbB4 - SI
c-Kit-Ig1
c-Kit-Ig2
c-Kit-Ig3
IgG-Fc
cKit(Ig1-Ig3)-Erb4(LI-SI)-IgGFc
c-Kit-Ig1
c-Kit-Ig2
c-Kit-Ig3
ErbB4 - LI
ErbB4 - SI
IgG-Fc

ErbB4 Chimeric trap designs (domains not drawn to scale)

Fig. 7

Erb4(LI-SI)-TrkA(d5)-IgGFc

ErbB4 - LI	ErbB4 - SI	TrkA-d5(Ig)	IgG-Fc

TrkA(d5)-Erb4(LI-SI)-IgGFc

TrkA-d5(Ig)	ErbB4 - LI	ErbB4 - SI	IgG-Fc

Fig. 8

Erb4(LI-SI)-FLT3(Ig1-Ig3)-IgGFc

ErbB4 - LI	ErbB4 - SI	FLT3-Ig1	FLT3-Ig2	FLT3-Ig3	IgG-Fc

FLT3(Ig1-Ig3)-Erb4(LI-SI)-IgGFc

FLT3-Ig1	FLT3-Ig2	FLT3-Ig3	ErbB4 - LI	ErbB4 - SI	IgG-Fc

Fig. 9

Erb4(LI-SI)-cMet(519)-IgGFc

ErbB4 - LI	ErbB4 - SI	C-Met - 519	IgG-Fc

cMet(519)-Erb4(LI-SI)-IgGFc

C-Met - 519	ErbB4 - LI	ErbB4 - SI	IgG-Fc

ErbB1 Chimeric trap designs (domains not drawn to scale)

Fig. 10

ErbB1(ΔSI-LII-ΔSII)-Axl(Ig1-Ig2)-IgGFc

ErbB1-ΔSI	ErbB1-LII	ErbB1-ΔSII	Axl-Ig1	Axl-Ig2	IgG-Fc

Axl(Ig1-Ig2)-ErbB1(ΔSI-LII-ΔSII)-IgGFc

Axl-Ig1	Axl-Ig2	ErbB1-ΔSI	ErbB1-LII	ErbB1-ΔSII	IgG-Fc

Fig. 11

ErbB1(ΔSI-LII-ΔSII)-FGFR1(Ig2-Ig3)-IgGFc

ErbB1 - ΔSI	ErbB1 - LII	ErbB1 - ΔSII	FGFR1 - Ig2(D2)	FGFR1 - Ig3(D3)	IgG-Fc

FGFR1(Ig2-Ig3)-ErbB1(ΔSI-LII-ΔSII)-IgGFc

FGFR1 - Ig2(D2)	FGFR1 - Ig3(D3)	ErbB1-ΔSI	ErbB1-LII	ErbB1-ΔSII	IgG-Fc

Fig. 12

ErbB1(ΔSI-LII-ΔSII)-PDGFRα(Ig1-Ig3)-IgGFc

ErbB1-ΔSI	ErbB1 - LII	ErbB1-ΔSII	PDGFRα - Ig1	PDGFRα - Ig2	PDGFRα - Ig3	IgG-Fc

PDGFRα(Ig1-Ig3)-ErbB1(ΔSI-LII-ΔSII)-IgGFc

PDGFRα - Ig1	PDGFRα - Ig2	PDGFRα - Ig3	ErbB1-ΔSI	ErbB1-LII	ErbB1-ΔSII	IgG-Fc

ErbB1 Chimeric trap designs (domains not drawn to scale)

Fig. 13

ErbB1(ΔSI-LII-ΔSII)-EphB2(Ig1)-IgGFc

ErbB1-ΔSI	ErbB1 - LII	ErbB1-ΔSII	EphB2 - Ig1	IgG-Fc

EphB2(Ig1)-ErbB1(ΔSI-LII-ΔSII)-IgGFc

EphB2 - Ig1	ErbB1-ΔSI	ErbB1 - LII	ErbB1-ΔSII	IgG-Fc

Fig. 14

ErbB1(ΔSI-LII-ΔSII)-Tie2(Ig1-Ig2)-IgGFc

ErbB1-ΔSI	ErbB1-LII	ErbB1-ΔSII	Tie2 - Ig1	Tie2 - Ig2	IgG-Fc

Tie2(Ig1-Ig2)-ErbB1(ΔSI-LII-ΔSII)-IgGFc

Tie2 - Ig1	Tie2 - Ig2	ErbB1-ΔSI	ErbB1-LII	ErbB1-ΔSII	IgG-Fc

Fig. 15

ErbB1(ΔSI-LII-ΔSII)-cKit(Ig1-Ig3)-IgGFc

ErbB1-ΔSI	ErbB1-LII	ErbB1-ΔSII	c-Kit-Ig1	c-Kit-Ig2	c-Kit-Ig3	IgG-Fc

cKit(Ig1-Ig3)-ErbB1(ΔSI-LII-ΔSII)-IgGFc

c-Kit-Ig1	c-Kit-Ig2	c-Kit-Ig3	ErbB1-ΔSI	ErbB1-LII	ErbB1-ΔSII	IgG-Fc

ErbB1 Chimeric trap designs (domains not drawn to scale)

Fig. 16

ErbB1(ΔSI-LII-ΔSII)-TrkA(d5)-IgGFc

ErbB1 - ΔSI	ErbB1 - LII	ErbB1-ΔSII	TrkA-d5(Ig)	IgG-Fc

TrkA(d5)-ErbB1(ΔSI-LII-ΔSII)-IgGFc

TrkA-d5(Ig)	ErbB1 -ΔSI	ErbB1 - LII	ErbB1-ΔSII	IgG-Fc

Fig. 17

ErbB1(ΔSI-LII-ΔSII)-FLT3(Ig1-Ig3)-IgGFc

ErbB1 - ΔSI	ErbB1 - LII	ErbB1 - ΔSII	FLT3 - Ig1	FLT3 - Ig2	FLT3 - Ig3	IgG-Fc

FLT3(Ig1-Ig3)-ErbB1(ΔSI-LII-ΔSII)-IgGFc

FLT3 - Ig1	FLT3 - Ig2	FLT3 - Ig3	ErbB1 - ΔSI	ErbB1 - LII	ErbB1 - ΔSII	IgG-Fc

Fig. 18

ErbB1(ΔSI-LII-ΔSII)-cMet(519)-IgGFc

ErbB1 -ΔSI	ErbB1-LII	ErbB1 -ΔSII	c-Met - 519	IgG-Fc

cMet(519)-ErbB1(SI-LII-SII)-IgGFc

c-Met - 519	ErbB1 -ΔSI	ErbB1-LII	ErbB1-ΔSII	IgG-Fc