EGFR AND C-MET FIBRONECTIN TYPE III DOMAIN BINDING MOLECULES

FIELD OF THE INVENTION

The present invention relates to monospecific or bispecific EGFR and/or c-Met binding molecules and methods of making and using the molecules.

BACKGROUND OF THE INVENTION

Epidermal growth factor receptor (EGFR, ErbBl or HER1) is a transmembrane glycoprotein of 170 kDa that is encoded by the c-erbBl proto-oncogene. EGFR is a member of the human epidermal growth factor receptor (HER) family of receptor tyrosine kinases (RTK) which includes HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). EGFR signaling is initiated by ligand binding followed by induction of conformational change, homodimerization or heterodimerization of the receptor with other ErbB family members, and trans-autophosphorylation of the receptor (Ferguson *et al.,* Annu Rev Biophys, 37: 353-73, 2008), which initiates a signal transduction cascades that ultimately affects a wide variety of cellular functions, including cell proliferation and survival. Increases in expression or kinase activity of EGFR have been linked with a range of human cancers, making EGFR an attractive target for therapeutic intervention (Mendelsohn *et al.,* Oncogene 19: 6550-6565, 2000; Grünwald *et al.,* J Natl Cancer Inst 95: 851-67, 2003; Mendelsohn *et al.,* Semin Oncol 33: 369-85, 2006). Increases in both the EGFR gene copy number and protein expression have been associated with favorable responses to the EGFR tyrosine kinase inhibitor, IRESSA™ (gefitinib), in non-small cell lung cancer (Hirsch *et al.,* Ann Oncol 18:752-60, 2007).

EGFR therapies include both small molecules and anti-EGFR antibodies, approved for treatment of colorectal cancer, pancreatic cancer, head and neck cancer, and non-small cell lung cancer (NSCLC) (Baselga and Arteaga, J Clin Oncol 23:2445-2459 (20005; Gill *et al.,* J Biol Chem, 259:7755-7760, 1984; Goldstein *et al.,* Clin Cancer Res, 1:131 1-1318; 1995; Prewett *et al.,* Clin Cancer Res, 4:2957-2966,1998).

Efficacy of anti-EGFR therapies may depend on tumor type and EFGR mutation/ amplification status in the tumor. Side effects of current therapeutics may include skin toxicity (De Roock *et al.,* Lancet Oncol 11 :753-762, 2010; Linardou *et al.,* Nat Rev Clin Oncol, 6: 352-366, 2009; Li and Perez-Soler, Targ Oncol 4: 107-119, 2009). EGFR tyrosine kinase inhibitors (TKI) are commonly used as 2nd line therapies for non small cell

lung cancer (NSCLC), but often stop working within twelve months due to resistance pathways (Riely *et al.,* Clin Cancer Res 12: 839-44, 2006).

c-Met encodes a tyrosine kinase receptor. It was first identified as a proto-oncogene in 1984 after it was found that treatment with a carcinogen resulted in a constitutively active fusion protein TPR-MET (Cooper *et al.,* Nature 311:29-33, 1984). Activation of c-Met by its ligand hepatocyte growth factor (HGF) stimulates a plethora of cell processes including growth, motility, invasion, metastasis, epithelial-mesenchymal transition, angiogenesis/wound healing, and tissue regeneration (Christensen *et al.,* Cancer Lett 225:1-26, 2005; Peters and Adjei, Nat Rev Clin Oncol 9:314-26, 2012). c-Met is synthesized as a single chain protein that is proteolytically cleaved into a 50 kDa alpha- and 140 kDa beta-subunit linked by a disulphide bond (Ma *et al.,* Cancer and Metastasis Reviews, 22: 309-325, 2003). c-Met is structurally similar to other membrane receptors such as Ron and. The exact stoichiometry of HGF:c-Met binding is unclear, but it is generally believed that two HGF molecules bind to two c-Met molecules leading to receptor dimerization and autophosphorylation at tyrosines 1230, 1234, and 1235 (Stamos *et al.,* The EMBO Journal 23: 2325-2335, 2004). Ligand-independent c-Met autophosphorylation can also occur due to gene amplification, mutation or receptor over-expression.

c-Met is frequently amplified, mutated or over-expressed in many types of cancer including gastric, lung, colon, breast, bladder, head and neck, ovarian, prostate, thyroid, pancreatic, and CNS cancers. Missense mutations typically localized to the kinase domain are commonly found in hereditary papillary renal carcinomas (PRCC) and in 13% of sporadic PRCCs (Schmidt *et al.,* Oncogene 18: 2343-2350, 1999). c-Met mutations localized to the semaphorin or juxtamembrane domains of c-Met are frequently found in gastric, head and neck, liver, ovarian, NSCLC and thyroid cancers (Ma *et al.,* Cancer and Metastasis Reviews, 22: 309-325, 2003; Sakakura *et al.,* Chromosomes and Cancer, 1999. 24:299-305) . c-Met amplification has been detected in brain, colorectal, gastric, and lung cancers, often correlating with disease progression (Ma *et al.,* Cancer and Metastasis Reviews, 22: 309-325, 2003). Up to 4% and 20% of non-small cell lung cancer (NSCLC) and gastric cancers, respectively, exhibit c-Met amplification (Sakakura *et al.,* Chromosomes and Cancer, 1999. 24:299-305: Sierra and Tsao, Therapeutic Advances in Medical Oncology, 3:S21-35, 2011). Even in the absence of gene amplification, c-Met overexpression is frequently observed in lung cancer (Ichimura *et al.,* Jpn J Cancer Res, 87:1063-9, 1996). Moreover, in clinical samples, nearly half of lung adenocarcinomas exhibited high levels of c-Met and HGF, both of which correlated with enhanced tumor

growth rate, metastasis and poor prognosis (Sierra and Tsao, Therapeutic Advances in Medical Oncology, 3:S21-35, 2011; Siegfried et al., Ann Thorac Surg 66: 1915-8, 1998).

Nearly 60% of all tumors that become resistant to EGFR tyrosine kinase inhibitors increase c-Met expression, amplify c-Met, or increase its only known ligand, HGF (Turke *et al.,* Cancer Cell, 17:77-88, 2010), suggesting the existence of a compensatory pathway for EGFR through c-Met. c-Met amplification was first identified in cultured cells that became resistant to gefinitib, an EGFR kinase inhibitor, and exhibited enhanced survival through the Her3 pathway (Engelman *et al*., Science, 316:1039-43, 2007). This was further validated in clinical samples where nine of 43 patients with acquired resistance to either erlotinib or gefitinib exhibited c-Met amplification, compared to only two of 62 untreated patients. Four of the nine treated patients also acquired the EGFR activating mutation, T790M, demonstrating simultaneous resistance pathways (Beat *et al.,* Proc Natl Acad Sci U S A, 104:20932-7, 2007).

The individual roles of both EGFR and c-Met in cancer is well established, making these targets attractive for combination therapy. Both receptors signal through the same survival and anti-apoptotic pathways (ERK and AKT); thus, inhibiting the pair in combination may limit the potential for compensatory pathway activation thereby improving overall efficacy. Combination therapies targeting EGFR and c-Met are tested in clinical trials with Tarceva® (erlotinib) in combination with anti-c-Met monovalent antibody for NSCL (Spigel *et al.,* 2011 ASCO Annual Meeting Proceedings 2011, Journal of Clinical Oncology: Chicago, IL. p. 7505) and Tarceva (erlotinib) in combination with ARQ-197, a small molecule inhibitor of c-Met (Adjei *et al.,* Oncologist, 16:788-99, 2011). Combination therapies or bispecific anti-EGFR/c-Met molecules have been disclosed for example in: Int. Pat. Publ. No. WO2008/127710, U.S. Pat. Publ. No. US2009/0042906, Int. Pat. Publ. No. WO2009/111691, Int. Pat. Publ. No. WO2009/126834, Int. Pat. Publ. No. WO2010/039248, Int. Pat. Publ. No. WO2010/115551.

Current small molecule and large molecule therapeutic approaches to antagonize EGFR and/or c-Met signaling pathways for therapy may be sub-optimal due to possible lack of specificity, potential off-target activity and dose-limiting toxicity that may be encountered with small molecule inhibitors. Typical bivalent antibodies may result in clustering of membrane bound receptors and unwanted activation of the downstream signaling pathways. Monovalent antibodies (half arms) pose significant complexity and cost to the manufacturing process.

Accordingly, the need exists for additional monospecific and bispecific EGFR and/or c-Met inhibitors for both therapeutic and diagnostic purpose.

SUMMARY OF THE INVENTION

The invention provides an isolated bispecific FN3 domain containing molecule comprising a first fibronectin type III (FN3) domain and a second FN3 domain, wherein the first FN3 domain specifically binds epidermal growth factor receptor (EGFR) and blocks binding of epidermal growth factor (EGF) to EGFR, and the second FN3 domain specifically binds hepatocyte growth factor receptor (c-Met), and blocks binding of hepatocyte growth factor (HGF) to c-Met.

The invention also provides an isolated bispecific FN3 domain containing molecule comprising a first fibronectin type III (FN3) domain and a second FN3 domain wherein the first FN3 domain comprises an amino acid sequence at least 87% identical to the amino acid sequence of SEQ ID NO: 27, and the second FN3 domain comprises an amino acid sequence at least 83% identical to the amino acid sequence of SEQ ID NO: 41.

The invention also provides bispecific EGFR/c-Met binding and monospecific EGFR or c-Met binding FN3 domain containing molecules having certain sequences.

The invention also provides an isolated fibronectin type III (FN3) domain that specifically binds epidermal growth factor receptor (EGFR) and blocks binding of epidermal growth factor (EGF) to EGFR, wherein the FN3 domain is isolated from a library designed based on the Tencon amino acid sequence of SEQ ID NO: 1.

The invention also provides an isolated fibronectin type III (FN3) domain that specifically binds hepatocyte growth factor receptor (c-Met) and blocks binding of hepatocyte growth factor (HGF) to c-Met.

The invention also provides an isolated polynucleotide encoding the molecule of the invention. Another aspect of the invention is a vector comprising the polynucleotide of the invention.

The invention also provides a host cell comprising the vector of the invention

The invention also provides a method of producing a bispecific molecule, comprising culturing the isolated host cell of the invention under conditions such that the bispecific molecule is expressed, and purifying the bispecific molecule.

The invention also provides a pharmaceutical composition comprising the molecule of the invention and a pharmaceutically acceptable carrier.

The invention also provides a method of treating a subject having cancer, comprising administering a therapeutically effective amount of the bispecific EGFR/c-Met

FN3 domain containing molecule or the EGFR or c-Met binding FN3 domain to a patient in need thereof for a time sufficient to treat cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A and 1B. Amino acid alignment of the EGFR-binding FN3 domains. The BC and FG loops are boxed at residues 22-28 and 75-86 of SEQ ID NO: 18. Some variants include thermal stability improving L17A, N46K and E86I substitutions (residue numbering according to Tencon SEQ ID NO: 1). P54AR4-83v2 (SEQ ID NO: 27) paratope residues are underlined (D23, F27, Y28, V77, G85 in SEQ ID NO: 27).

Figure 2. Sequence alignment of the Tencon27 scaffold (SEQ ID NO: 99) and a TCL14 library (SEQ ID NO: 100) having randomized C-CD-F-FG alternative surface. The loop residues are boxed. Loops and strands are indicated above the sequences.

Figure 3. Sequence alignment of the c-Met-binding FN3 domains. The C loop and the CD strand and the F loop and the FG strand are boxed and span residues 29-43 and 65-81. P114AR7P95-A3 (SEQ ID NO: 41) paratope residues are underlined (R34S, F38S, M72S and I79S).

Figure 4. Inhibition of c-Met phosphorylation in H292 cells pre-treated with monospecific or bispecific FN3 domain containing molecules and stimulated with HGF is shown. Substantial increase in the potency of the bispecific EGFR/c-Met molecule (ECB1) was observed when compared to a monospecific c-Met-binding FN3 domain (P114AR5P74-A5, shown as A5 in the Figure) on its own or in combination with an EGFR-binding FN3 domain (P54AR4-83v2, shown as 83v2 in the Figure).

Figure 5. Inhibition of EGFR and c-Met phosphorylation in cells pre-treated with monospecific or bispecific FN3 domain containing molecules. In cell lines expressing high levels of EGFR, NCI-H292 (Figure 5A) and H596 Figure 5(B), anti-EGFR monospecific and bispecific FN3 domain containing molecules are equally potent at decreasing EGFR phosphorylation. In cell lines expressing low levels of EGFR relative to c-Met, H441 (Figure 5C), bispecific EGFR/c-Met molecules improve the potency for inhibition of EGFR phosphorylation compared to the monospecific EGFR-binding FN3 domain alone. In cell lines with low levels of c-Met, relative to EGFR, H292 (Figure 5D) and H596 (Figure 5E), inhibition of c-Met phosphorylation is significantly potentiated with bispecific EGFR/c-Met molecule, compared to monospecific c-Met-binding FN3 domain only. Molecules used in the study were: bispecific ECB5 (shown as 17-A3 in the Figure), monospecific EGFR-binding FN3 domain P53A1R5-17 (shown as “17” in the

Figure), bispecific EGFR/c-Met molecule ECB3 (shown as 83-H9 in the Figure), and monospecific c-Met binding FN3 domain P114AR7P93-H9 (shown as H9 in the Figure).

Figure 6. Pharmacodynamic signaling in tumors isolated from mice dosed with bispecific EGFR/c-Met molecules for 6h or 72h. All molecules significantly reduced c-Met, EGFR and ERK phosphorylation at both 6h and 72h, the degree if inhibition was dependent on the affinity of the FN3 domains to EGFR and/or c-Met. Bispecific molecules were generated by joining EGFR-binding FN3 domain with a high ("83" in the Figure is p54AR4-83v2) or medium ("17v2" in the Figure is P53A1R5-17v2) affinity to a c-Met-binding FN3 domain with high ("A3" in the Figure is P114AR7P94-A3) or medium ("A5" in the Figure is P114AR5P74-A5) affinity.

Figure 7: Plasma (top) and tumor (bottom) accumulation of bispecific EGFR/cMet molecules of variable affinities linked to an albumin binding domain (ABD) are shown 6h (left) and 72h (right) after IP dosing. Six hours after dosing, tumor accumulation is maximal in mice dosed with a bispecific molecule harboring a medium affinity EGFR-binding FN3 domain (17v2) or high affinity EGFR binding domain (83v2). The bispecific molecules incorporated high or medium affinity EGFR or c-Met binding FN3 domains as follows: 83v2-A5-ABD (ECB18; high/medium for EGFR/cMet) 83v2-A3-ABD (ECB38; high/high) 17v2-A5 (ECB28; medium/medium) 17v2-A3-ABD (ECB39; medium/high). In the figure, 83v2 refers to p54AR4-83v2; 17v2 refers to p53A1R5-17v2; A3 refers to p114AR7P94-A3 and A5 refers to p114AR5P74-A5.

Figure 8. H292-HGF tumor xenografts were implanted into SCID beige mice. When tumors reached an average volume of approximately 80 mm^3, mice were dosed three times per week with bispecific EGFR/c-Met molecules (25 mg/kg) or PBS vehicle. All bispecific molecules reduced tumor growth, the tumor growth inhibition (TGI) being dependent on the affinities of the molecules for c-Met and EGFR. (high EGFR-high cMet refers to p54AR4-83v2-p114AR7P94-A3 (ECB38); high EGFR-med cMet refers to p54AR4-83v2-p114AR5P74-A5 (ECB18); med EGFR-high cMet refers to p53A1R5-17v2-p114AR7P94-A3 (ECB39); med EGFR-med-cMet refers to p53A1R5-17-p114AR5P74-A 5 (ECB28)).

Figure 9. H292-HGF tumor xenografts were implanted into SCID beige mice and they were treated with different therapies. The anti-tumor activity of the therapies is shown. (bispecific EGFR/c-Met molecule refers to p54AR4-83v2-p114AR7P94-A3-ABD (ECB38); the other therapies are crizotinib, erlotinib, cetuximab, and the combination of crizotinib and erlotinib).

DETAILED DESCRIPTION OF THE INVENTION

The term "fibronectin type III (FN3) domain" (FN3 domain) as used herein refers to a domain occurring frequently in proteins including fibronectins, tenascin, intracellular cytoskeletal proteins, cytokine receptors and prokaryotic enzymes (Bork and Doolittle, Proc Nat Acad Sci USA 89:8990-8994, 1992; Meinke *et al*., J Bacteriol 175:1910-1918, 1993; Watanabe *et al.,* J Biol Chem 265:15659-15665, 1990). Exemplary FN3 domains are the 15 different FN3 domains present in human tenascin C, the 15 different FN3 domains present in human fibronectin (FN), and non-natural synthetic FN3 domains as described for example in U.S. Pat. Publ. No. 2010/0216708. Individual FN3 domains are referred to by domain number and protein name, e.g., the 3rd FN3 domain of tenascin (TN3), or the 10th FN3 domain of fibronectin (FN10).

The term "substituting" or "substituted" or 'mutating" or "mutated" as used herein refers to altering, deleting of inserting one or more amino acids or nucleotides in a polypeptide or polynucleotide sequence to generate a variant of that sequence.

The term "randomizing" or "randomized" or "diversified" or "diversifying" as used herein refers to making at least one substitution, insertion or deletion in a polynucleotide or polypeptide sequence.

"Variant" as used herein refers to a polypeptide or a polynucleotide that differs from a reference polypeptide or a reference polynucleotide by one or more modifications for example, substitutions, insertions or deletions.

The term "specifically binds" or "specific binding" as used herein refers to the ability of the FN3 domain of the invention to bind to a predetermined antigen with a dissociation constant (K_D) of about $1x10^{-6}$ M or less, for example about $1x10^{-7}$ M or less, about $1x10^{-8}$ M or less, about $1x10^{-9}$ M or less, about $1x10^{-10}$ M or less, about $1x10^{-11}$ M or less, about $1x10^{-12}$ M or less, or about $1x10^{-13}$ M or less. Typically the FN3 domain of the invention binds to a predetermined antigen (i.e. EGFR or c-Met) with a K_D that is at least ten fold less than its K_D for a nonspecific antigen (for example BSA or casein) as measured by surface plasmon resonance using for example a Proteon Instrument (BioRad). Thus, a bispecific EGFR/c-Met FN3 domain containing molecule of the invention specifically binds to each EGFR and c-Met with a binding affinity (K_D) of at least $1x10^{-6}$ M or less for both EGFR and c-Met. The isolated FN3 domain of the invention that specifically binds to a predetermined antigen may, however, have cross-reactivity to other

related antigens, for example to the same predetermined antigen from other species (homologs).

The term “library” refers to a collection of variants. The library may be composed of polypeptide or polynucleotide variants.

The term "stability" as used herein refers to the ability of a molecule to maintain a folded state under physiological conditions such that it retains at least one of its normal functional activities, for example, binding to a predetermined antigen such as EGFR or c-Met.

“Epidermal growth factor receptor” or “EGFR” as used here refers to the human EGFR (also known as HER-1 or Erb-B1 (Ullrich *et al.,* Nature 309:418-425, 1984) having the sequence shown in SEQ ID NO: 73 and in GenBank accession number NP_005219, as well as naturally-occurring variants thereof. Such variants include the well known EGFRvIII and other alternatively spliced variants (e.g., as identified by SwissProt Accession numbers P00533-1 (wild type; identical to SEA ID NO: 73 and NP_005219), P00533-2 (F404L/L405S),, P00533-3 (628-705: CTGPGLEGCP...GEAPNQALLR →PGNESLKAML...SVIITASSCH and 706-1210 deleted), P00533-4 (C628S and 629-1210 deleted), variants Q98, R266, K521, I674, G962, and P988 (Livingston *et al.,* NIEHS-SNPs, environmental genome project, NIEHS ES15478), T790M, L858R/T790M and del(E746, A750).

“EGFR ligand” as used herein encompasses all (e.g., physiological) ligands for EGFR, including EGF, TGF-α, heparin binding EGF (HB-EGF), amphiregulin (AR), and epiregulin (EPI).

“Epidermal growth factor” (EGF) as used herein refers to the well known 53 amino acid human EGF having an amino acid sequence shown in SEQ ID NO: 74.

“Hepatocyte growth factor receptor” or “c-Met” as used herein refers to the human c-Met having the amino acid sequence shown in SEQ ID NO: 101 or in GenBank Accession No: NP_001120972 and natural variants thereof.

“Hepatocyte growth factor” (HGF) as used herein refers to the well known human HGF having the amino acid sequence shown in SEQ ID NO: 102 which is cleaved to form a dimer of an alpha and beta chain linked by a disulfide bond.

“Blocks binding” or “inhibits binding”, as used herein interchangeably refers to the ability of the FN3 domains of the invention of the bispecific EGFR/c-Met FN3 domain containing molecule to block or inhibit binding of the EGFR ligand such as EGF to EGFR and/or HGF to c-Met, and encompass both partial and complete blocking/inhibition. The blocking/inhibition of EGFR ligand such as EGF to EGFR and/or HGF to c-Met by the

FN3 domain or the bispecific EGFR/c-Met FN3 domain containing molecule of the invention reduces partially or completely the normal level of EGFR signaling and/or c-Met signaling when compared to the EGFR ligand binding to EGFR and/or HGF binding to c-Met without blocking or inhibition. The FN3 domain or the bispecific EGFR/c-Met FN3 domain containing molecule of the invention "blocks binding" of the EGFR ligand such as EGF to EGFR and/or HGF to c-Met when the inhibition is at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% . Inhibition of binding can be measured using well known methods, for example by measuring inhibition of binding of biotinylated EGF on EGFR expressing A431 cells exposed to the FN3 domain or the bispecific EGFR/c-Met FN3 domain containing molecule of the invention using FACS, and using methods described herein, or measuring inhibition of binding of biotinylated HGF on c-Met extracellular domain using well known methods and methods described herein.

The term "EGFR signaling" refers to signal transduction induced by EGFR ligand binding to EGFR resulting in autophosphorylation of at least one tyrosine residue in the EGFR. An exemplary EGFR ligand is EGF.

"Neutralizes EGFR signaling" as used herein refers to the ability of the FN3 domain of the invention to inhibit EGFR signaling induced by EGFR ligand such as EGF by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% .

The term "c-Met signaling" refers to signal transduction induced by HGF binding to c-Met resulting in autophosphorylation of at least one tyrosine residue in the c-Met. Typically at least one tyrosine residue at positions 1230, 1234, 1235 or 1349 is autophosphorylated upon HGF binding.

"Neutralizes c-Met signaling" as used herein refers to the ability of the FN3 domain of the invention to inhibit c-Met signaling induced by HGF by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% .

"Overexpress", "overexpressed" and "overexpressing" as used herein interchangeably refer to a cancer or malignant cell that has measurably higher levels of EGFR and/or c-Met on the surface compared to a normal cell of the same tissue type. Such overexpression may be caused by gene amplification or by increased transcription or translation. EGFR and/or c-Met expression and overexpression can be measured using well know assays using for example ELISA, immunofluorescence, flow cytometry or radioimmunoassay on live or lysed cells. Alternatively, or additionally, levels of EGFR

and/or c-Met-encoding nucleic acid molecules may be measured in the cell for example using fluorescent *in situ* hybridization, Southern blotting, or PCR techniques. EGFR and/or c-Met is overexpressed when the level of EGFR and/or c-Met on the surface of the cell is at least 1.5-fold higher when compared to the normal cell.

"Tencon" as used herein refers to the synthetic fibronectin type III (FN3) domain having the sequence shown in SEQ ID NO: 1 and described in U.S. Pat. Publ. No. US2010/0216708.

A "cancer cell" or a "tumor cell" as used herein refers to a cancerous, pre-cancerous or transformed cell, either *in vivo*, *ex vivo*, and in tissue culture, that has spontaneous or induced phenotypic changes that do not necessarily involve the uptake of new genetic material. Although transformation can arise from infection with a transforming virus and incorporation of new genomic nucleic acid, or uptake of exogenous nucleic acid, it can also arise spontaneously or following exposure to a carcinogen, thereby mutating an endogenous gene. Transformation/cancer is exemplified by, e.g., morphological changes, immortalization of cells, aberrant growth control, foci formation, proliferation, malignancy, tumor specific markers levels, invasiveness, tumor growth or suppression in suitable animal hosts such as nude mice, and the like, *in vitro*, *in vivo*, and *ex vivo* (Freshney, Culture of Animal Cells: A Manual of Basic Technique (3rd ed. 1994)).

The term "vector" means a polynucleotide capable of being duplicated within a biological system or that can be moved between such systems. Vector polynucleotides typically contain elements, such as origins of replication, polyadenylation signal or selection markers that function to facilitate the duplication or maintenance of these polynucleotides in a biological system. Examples of such biological systems may include a cell, virus, animal, plant, and reconstituted biological systems utilizing biological components capable of duplicating a vector. The polynucleotide comprising a vector may be DNA or RNA molecules or a hybrid of these.

The term "expression vector" means a vector that can be utilized in a biological system or in a reconstituted biological system to direct the translation of a polypeptide encoded by a polynucleotide sequence present in the expression vector.

The term "polynucleotide" means a molecule comprising a chain of nucleotides covalently linked by a sugar-phosphate backbone or other equivalent covalent chemistry. Double and single-stranded DNAs and RNAs are typical examples of polynucleotides.

The term "polypeptide" or "protein" means a molecule that comprises at least two amino acid residues linked by a peptide bond to form a polypeptide. Small polypeptides of less than about 50 amino acids may be referred to as "peptides".

The term "bispecific EGFR/c-Met molecule" or "bispecific EGFR/c-Met FN3 domain containing molecule" as used herein refers to a molecule comprising an EGFR binding FN3 domain and a distinct c-Met binding FN3 domain that are covalently linked together either directly or via a linker. An exemplary bispecific EGFR/c-Met binding molecule comprises a first FN3 domain specifically binding EGFR and a second FN3 domain specifically binding c-Met.

"Valent" as used herein refers to the presence of a specified number of binding sites specific for an antigen in a molecule. As such, the terms "monovalent", "bivalent", "tetravalent", and "hexavalent" refer to the presence of one, two, four and six binding sites, respectively, specific for an antigen in a molecule.

"Mixture" as used herein refers to a sample or preparation of two or more FN3 domains not covalently linked together. A mixture may consist of two or more identical FN3 domains or distinct FN3 domains.

Compositions of matter

The present invention provides monospecific and bispecific EGFR and/or c-Met binding FN3 domain containing molecules. The present invention provides polynucleotides encoding the FN3 domains of the invention or complementary nucleic acids thereof, vectors, host cells, and methods of making and using them.

Monospecific EGFR binding molecules

The present invention provides fibronectin type III (FN3) domains that bind specifically to epidermal growth factor receptor (EGFR) and block binding of epidermal growth factor (EGF) to EGFR, and thus can be widely used in therapeutic and diagnostic applications. The present invention provides polynucleotides encoding the FN3 domains of the invention or complementary nucleic acids thereof, vectors, host cells, and methods of making and using them.

The FN3 domains of the invention bind EGFR with high affinity and inhibit EGFR signaling, and may provide a benefit in terms of specificity and reduced off-target toxicity when compared to small molecule EGFR inhibitors, and improved tissue penetration when compared to conventional antibody therapeutics.

The invention also provides an isolated fibronectin type III (FN3) domain that specifically binds epidermal growth factor receptor (EGFR) and blocks binding of epidermal growth factor (EGF) to EGFR.

The FN3 domains of the invention described herein may block EGF binding to the EGFR with an IC_{50} value of less than about $1x10^{-7}$ M, less than about $1x10^{-8}$ M, less than about $1x10^{-9}$ M, less than about $1x10^{-10}$ M, less than about $1x10^{-11}$ M, or less than about $1x10^{-12}$ M in a competition assay employing A431 cells and detecting amount of fluorescence from bound biotinylated EGF using streptavidin-phycoerythrin conjugate at 600 nM on A431 cells incubated with or without the FN3 domains of the invention. Exemplary FN3 domains may block EGF binding to the EGFR with an IC_{50} value between about $1x10^{-9}$ M to about $1x10^{-7}$ M, such as EGFR binding FN3 domains having the amino acid sequence of SEQ ID NOs: 18-29, 107-110, or 122-137. The FN3 domains of the invention may block EGF binding to the EGFR by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% when compared to binding of EGF to the EGFR in the absence of the FN3 domains of the invention using the same assay conditions.

The FN3 domain of the invention described herein may inhibit EGFR signaling by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% when compared to the level of signaling in the absence of the FN3 domains of the invention using the same assay conditions.

Binding of a ligand such as EGF to EGFR stimulates receptor dimerization, autophosphorylation, activation of the receptor's internal, cytoplasmic tyrosine kinase domain, and initiation of multiple signal transduction and transactivation pathways involved in regulation of DNA synthesis (gene activation) and cell cycle progression or division. Inhibition of EGFR signaling may result in inhibition in one or more EGFR downstream signaling pathways and therefore neutralizing EGFR may have various effects, including inhibition of cell proliferation and differentiation, angiogenesis, cell motility and metastasis.

EGFR signaling may be measured using various well know methods, for example measuring the autophosphorylation of the receptor at any of the tyrosines Y1068, Y1148, and Y1173 (Downward *et al.,* Nature 311:483-5, 1984) and/or phosphorylation of natural or synthetic substrates. Phosphorylation can be detected using well known methods such as an ELISA assay or a western plot using a phosphotyrosine specific antibody. Exemplary

assays can be found in Panek *et al.,* J Pharmacol Exp Thera 283:1433-44, 1997 and Batley *et al.,* Life Sci 62:143-50, 1998, and assays described herein.

In some embodiments described herein, the FN3 domain of the invention inhibits EGF-induced EGFR phosphorylation at EGFR residue position Tyrosine 1173 with an IC_{50} value of less than about $2.5x10^{-6}$ M, for example less than about $1x10^{-6}$ M, less than about $1x10^{-7}$ M, less than about $1x10^{-8}$ M, less than about $1x10^{-9}$ M, less than about $1x10^{-10}$ M, less than about $1x10^{-11}$ M, or less than about $1x10^{-12}$ M when measured in A431 cells using 50 ng/mL human EGF.

In some embodiments described herein, the FN3 domain of the invention inhibits EGF- induced EGFR phosphorylation at EGFR residue position Tyrosine 1173 with an IC_{50} value between about 1.8×10^{-8} M to about 2.5×10^{-6} M when measured in A431 cells using 50 ng/mL human EGF. Such exemplary FN3 domains are those having the amino acid sequence of SEQ ID NOs: 18-29, 107-110, or 122-137.

In some embodiments described herein, the FN3 domain of the invention binds human EGFR with a dissociation constant (K_D) of less than about $1x10^{-8}$ M, for example less than about $1x10^{-9}$ M, less than about $1x10^{-10}$ M, less than about $1x10^{-11}$ M, less than about $1x10^{-12}$ M, or less than about $1x10^{-13}$ M as determined by surface plasmon resonance or the Kinexa method, as practiced by those of skill in the art. In some embodiments, the FN3 domain of the invention binds human EGFR with a K_D of between about $2x10^{-10}$ to about $1x10^{-8}$ M. The affinity of a FN3 domain for EGFR can be determined experimentally using any suitable method. (See, for example, Berzofsky, *et al.*, "Antibody-Antigen Interactions," In *Fundamental Immunology*, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kuby, Janis *Immunology*, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular FN3 domain-antigen interaction can vary if measured under different conditions (e.g., osmolarity, pH). Thus, measurements of affinity and other antigen-binding parameters (e.g., K_D, K_{on}, K_{off}) are preferably made with standardized solutions of protein scaffold and antigen, and a standardized buffer, such as the buffer described herein.

Exemplary FN3 domains of the invention that bind EGFR include FN3 domains of SEQ ID NOs: 18-29, 107-110, or 122-137.

In some embodiments described herein, the FN3 domain that specifically binds EGFR comprises an amino acid sequence at least 87% identical to the amino acid sequence of SEQ ID NO: 27.

In some embodiments described herein, the FN3 domain that specifically binds EGFR comprises

an FG loop comprising the sequence HNVYKDTNX$_9$RGL (SEQ ID NO: 179) or the sequence LGSYVFEHDVML (SEQ ID NO: 180), wherein X$_9$ is M or I; and

a BC loop comprising the sequence X$_1$X$_2$X$_3$X$_4$X$_5$X$_6$X$_7$X$_8$ (SEQ ID NO: 181), wherein

X$_1$ is A, T, G or D;

X$_2$ is A, D, Y or W;

X$_3$ is P, D or N;

X$_4$ is L or absent;

X$_5$ is D, H, R, G, Y or W;

X$_6$ is G, D or A;

X$_7$ is A, F, G, H or D; and

X$_8$ is Y, F or L.

The FN3 domains of the invention that specifically bind EGFR and inhibit autophosphorylation of EGFR as described herein may comprise as a structural feature an FG loop comprising the sequence HNVYKDTNX$_9$RGL (SEQ ID NO: 179) or the sequence LGSYVFEHDVML (SEQ ID NO: 180), wherein X$_9$ is M or I. Such FN3 domains may further comprise a BC loop of 8 or 9 amino acids in length and defined by the sequence X$_1$X$_2$X$_3$X$_4$X$_5$X$_6$X$_7$X$_8$ (SEQ ID NO: 181), and inhibit EGFR autophosphorylation with an IC$_{50}$ value of less than about 2.5x10^{-6} M, or with an IC$_{50}$ value of between about 1.8x10^{-8} M to about 2.5x10^{-6} M when measured in A431 cells using 50 ng/mL human EGF.

The FN3 domains of the invention that specifically bind EGFR and inhibit autophosphorylation of EGFR as described herein further comprise the sequence of

LPAPKNLVVSEVTEDSLRLSWX$_1$X$_2$X$_3$X$_4$X$_5$X$_6$X$_7$X$_8$DSFLIQYQESEKVGEAINLTVP GSERSYDLTGLKPGTEYTVSIYGVHNVYKDTNX$_9$RGLPLSAEFTT (SEQ ID NO: 182), or the sequence

LPAPKNLVVSEVTEDSLRLSWX$_1$X$_2$X$_3$X$_4$X$_5$X$_6$X$_7$X$_8$DSFLIQYQESEKVGEAINLTVP GSERSYDLTGLKPGTEYTVSIYGVLGSYVFEHDVMLPLSAEFTT (SEQ ID NO: 183),

wherein

X$_1$ is A, T, G or D;

X$_2$ is A, D, Y or W;

X$_3$ is P, D or N;

X_4 is L or absent;

X_5 is D, H, R, G, Y or W;

X_6 is G, D or A;

X_7 is A, F, G, H or D;

X_8 is Y, F or L; and

X_9 is M or I

The EGFR binding FN3 domains as described herein can be generated and tested for their ability to inhibit EGFR autophosphorylation using well known methods and methods described herein.

The invention also provides an isolated FN3 domain that specifically binds EGFR, wherein the FN3 domain comprises the sequence shown in SEQ ID NOs: 18-29, 107-110, 122-137 or 194-211.

In some embodiments described herein, the EGFR binding FN3 domains comprise an initiator methionine (Met) linked to the N-terminus or a cysteine (Cys) linked to a C-terminus of a particular FN3 domain, for example to facilitate expression and/or conjugation of half-life extending molecules.

The invention also provides an isolated fibronectin type III (FN3) domain that specifically binds EGFR and blocks binding of EGF to the EGFR, wherein the FN3 domain is isolated from a library designed based on Tencon sequence of SEQ ID NO: 1.

The invention also provides an isolated fibronectin type III (FN3) domain that specifically binds EGFR and blocks binding of EGF to the EGFR, wherein the FN3 domain binds EGFR with one or more amino acid residues corresponding to residues D23, F27, Y28, V77 and G85 of P54AR4-83v2 (SEQ ID NO: 27).

Amino acid residues contributing to FN3 domain binding to EGFR can be identified using methods such as mutagenesis and evaluating of binding residues/surface by crystal structure. Substitutions at residues D23, F27, Y28, V77, G85 in EGFR binding FN3 domain P54AR4-83v2 (SEQ ID NO: 27) reduced EGFR binding to the FN3 domain by greater than 100-fold. EGFR-binding FN3 domains P54AR4-48, P54AR4-81, P53A1R5-17v2, P54AR4-83v22 and P54AR4-83v23 share these residues and can be expected to bind to EGFR with the same paratope residues as P54AR4-83v2. Other EGFR binding FN3 domains can be created by holding positions D23, F27, Y28, V77, G85 constant while changing the amino acids located at the other positions of the BC and FG loops (positions 24, 25, 75, 76, 78, 79, 80, 81, 82, 83, 84, and 86). These changes can be done by design of specific amino acids at specific positions or by incorporation of these

positions into a library that replaces these sites with random amino acids. New FN3 domains designed in such a way can be used to screen for or select for optimized properties such as EGFR binding, solubility, stability, immunogenicity or serum half-life.

Monospecific c-Met binding molecules

The present invention also provides fibronectin type III (FN3) domains that bind specifically to hepatocyte growth factor receptor (c-Met) and block binding of hepatocyte growth factor (HGF) to c-Met, and thus can be widely used in therapeutic and diagnostic applications. The present invention provides polynucleotides encoding the FN3 domains of the invention or complementary nucleic acids thereof, vectors, host cells, and methods of making and using them.

The FN3 domains of the invention described herein bind c-Met with high affinity and inhibit c-Met signaling, and may provide a benefit in terms of specificity and reduced off-target toxicity when compared to small molecule c-Met inhibitors, and improved tissue penetration when compared to conventional antibody therapeutics. The FN3 domains of the invention are monovalent, therefore preventing unwanted receptor clustering and activation that may occur with other bivalent molecules.

The invention also provides isolated fibronectin type III (FN3) domain that specifically binds hepatocyte growth factor receptor (c-Met) and blocks binding of hepatocyte growth factor (HGF) to c-Met.

The FN3 domains of the invention described herein may block HGF binding to c-Met with an IC_{50} value of less than about $1x10^{-7}$ M, less than about $1x10^{-8}$ M, less than about $1x10^{-9}$ M, less than about $1x10^{-10}$ M, less than about $1x10^{-11}$ M, or less than about $1x10^{-12}$ M in an assay detecting inhibition of binding of biotinylated HGF to c-Met-Fc fusion protein in the presence of the FN3 domains of the invention. Exemplary FN3 domains my block HGF binding to the c-Met with an IC_{50} value between about $2x10^{-10}$ M to about $6x10^{-8}$ M. The FN3 domains of the invention may block HGF binding to c-Met by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% when compared to binding of HGF to c-Met in the absence of the FN3 domains of the invention using the same assay conditions.

The FN3 domain of the invention described herein may inhibit c-Met signaling by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% when compared to the level of signaling in the absence of FN3 domains of the invention using the same assay conditions.

Binding of HGF to c-Met stimulates receptor dimerization, autophosphorylation, activation of the receptor's internal, cytoplasmic tyrosine kinase domain, and initiation of multiple signal transduction and transactivation pathways involved in regulation of DNA synthesis (gene activation) and cell cycle progression or division. Inhibition of c-Met signaling may result in inhibition of one or more c-Met downstream signaling pathways and therefore neutralizing c-Met may have various effects, including inhibition of cell proliferation and differentiation, angiogenesis, cell motility and metastasis.

c-Met signaling may be measured using various well know methods, for example measuring the autophosphorylation of the receptor on at least one tyrosine residues Y1230, Y1234, Y1235 or Y1349, and/or phosphorylation of natural or synthetic substrates. Phosphorylation can be detected, for example, using an antibody specific for phosphotyrosine in an ELISA assay or on a western blot. Assays for tyrosine kinase activity (Panek *et al.,* J Pharmacol Exp Thera 283:1433-44, 1997; Batley *et al.,* Life Sci 62:143-50, 1998), and assays described herein.

In some embodiments described herein, the FN3 domain of the invention inhibits HGF-induced c-Met phosphorylation at c-Met residue position 1349 with an IC_{50} value of less than about $1x10^{-6}$ M, less than about $1x10^{-7}$ M, less than about $1x10^{-8}$ M, less than about $1x10^{-9}$ M, less than about $1x10^{-10}$ M, less than about $1x10^{-11}$ M, or less than about $1x10^{-12}$ M when measured in NCI-H441 cells using 100 ng/mL recombinant human HGF.

In some embodiments described herein, the FN3 domain of the invention inhibits HGF-induced c-Met phosphorylation at c-Met tyrosine Y1349 with an IC_{50} value between about $4x10^{-9}$ M to about 1 $x10^{-6}$ M when measured in NCI-H441 cells using 100 ng/mL recombinant human HGF.

In some embodiments described herein, the FN3 domain of the invention binds human c-Met with an dissociation constant (K_D) of equal to or less than about $1x10^{-7}$ M, $1x10^{-8}$ M, $1x10^{-9}$ M, $1x10^{-10}$ M, $1x10^{-11}$ M, $1x10^{-12}$ M, $1x10^{-13}$ M, $1x10^{-14}$ M, or $1x10^{-15}$ M as determined by surface plasmon resonance or the Kinexa method, as practiced by those of skill in the art. I some embodiments, the FN3 domain of the invention binds human c-Met with a K_D of between about $3x10^{-10}$ M to about $5x10^{-8}$ M. The affinity of a FN3 domain for c-Met can be determined experimentally using any suitable method. (See, for example, Berzofsky, *et al.*, "Antibody-Antigen Interactions," In *Fundamental Immunology*, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kuby, Janis *Immunology*, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular FN3 domain-antigen interaction can vary if measured under different conditions (e.g., osmolarity, pH). Thus, measurements of affinity and other

antigen-binding parameters (e.g., K_D, K_{on}, K_{off}) are preferably made with standardized solutions of protein scaffold and antigen, and a standardized buffer, such as the buffer described herein.

Exemplary FN3 domains of the invention that bind c-Met include FN3 domains having the amino acid sequence of SEQ ID NOs: 32-49, 111-114 or 212-223.

In some embodiments described herein, the FN3 domain that specifically binds c-Met comprises an amino acid sequence at least 83% identical to the amino acid sequence of SEQ ID NO: 41.

In some embodiments described herein, the FN3 domain that specifically binds c-Met comprises

a C strand and a CD loop comprising the sequence $DSFX_{10}IRYX_{11}E$ $X_{12}X_{13}X_{14}X_{15}GX_{16}$ (SEQ ID NO: 184), wherein

X_{10} is W, F or V;

X_{11} is D, F or L;

X_{12} is V, F or L;

X_{13} is V, L or T;

X_{14} is V, R, G, L, T or S;

X_{15} is G, S, A, T or K; and

X_{16} is E or D; and

a F strand and a FG loop comprising the sequence $TEYX_{17}VX_{18}IX_{19}X_{20}V$ $KGGX_{21}X_{22}SX_{23}$ (SEQ ID NO: 185), wherein

X_{17} is Y, W, I, V, G or A;

X_{18} is N, T, Q or G;

X_{19} is L, M, N or I;

X_{20} is G or S;

X_{21} is S, L, G, Y, T, R, H or K;

X_{22} is I, V or L; and

X_{23} is V, T, H, I, P, Y or L.

The FN3 domains of the invention that specifically bind c-Met and inhibit autophosphorylation of c-Met described herein further comprises the sequence: LPAPKNLVVSRVTEDSARLSWTAPDAAF $DSFX_{10}IRYX_{11}E$ $X_{12}X_{13}X_{14}X_{15}GX_{16}$ AIVLTVPGSERSYDLTGLKPGTEY$X_{17}VX_{18}IX_{19}X_{20}VKGGX_{21}X_{22}SX_{23}$PLSAEFTT (SEQ ID NO: 186),

wherein

X_{10} is W, F or V; and

X_{11} is D, F or L;

X_{12} is V, F or L;

X_{13} is V, L or T;

X_{14} is V, R, G, L, T or S;

X_{15} is G, S, A, T or K;

X_{16} is E or D;

X_{17} is Y, W, I, V, G or A;

X_{18} is N, T, Q or G;

X_{19} is L, M, N or I;

X_{20} is G or S;

X_{21} is S, L, G, Y, T, R, H or K;

X_{22} is I, V or L; and

X_{23} is V, T, H, I, P, Y or L.

The invention also provides an isolated FN3 domain that specifically binds c-Met, wherein the FN3 domain comprises the sequence shown in SEQ ID NOs: 32-49 or 111-114.

The invention also provides an isolated fibronectin type III (FN3) domain that specifically binds c-Met and blocks binding of HGF to the c-Met, wherein the FN3 domain is isolated from a library designed based on Tencon sequence of SEQ ID NO: 1.

The invention also provides an isolated fibronectin type III (FN3) domain that specifically binds c-Met and blocks binding of HGF to c-Met, wherein the FN3 domain binds c-Met with one or more amino acid residues corresponding to residues R34, F38, M72 and I79 in P114AR7P95-A3 (SEQ ID NO: 41).

Amino acid residues contributing to FN3 domain binding to c-Met can be identified using methods such as mutagenesis and evaluating of binding residues/surface by crystal structure. Substitutions at residues R34S, F38S, M72S and I79S in the c-Met-binding FN3 domain P114AR7P95-A3 (SEQ ID NO: 27) reduced c-Met binding to the FN3 domain by greater than 100-fold. c-Met-binding FN3 domains molecules P114AR7P92-F3, P114AR7P95-D3, P114AR7P95-F10 and P114AR7P95-H8 share these residues and can be expected to bind to c-Met with the same paratope residues as P114AR7P95-A3. Other c-Met binding FN3 domains can be created by holding positions R34S, F38S, M72S and I79S constant while changing the amino acids located at the other positions of the C-strand, F-strand, CD-Loop and/or FG-loops (positions 32, 36, 39, 40, 68, 70, 78, and 81). These changes can be done by design of specific amino acids at specific positions or by incorporation of these positions into a library that replaces these

sites with random amino acids. New FN3 domains designed in such a way can be used to screen for or select for optimized properties such as c-Met binding, solubility, stability, immunogenicity, or serum half-life.

Isolation of EGFR or c-Met binding FN3 domains from a library based on Tencon sequence

Tencon (SEQ ID NO: 1) is a non-naturally occurring fibronectin type III (FN3) domain designed from a consensus sequence of fifteen FN3 domains from human tenascin-C (Jacobs *et al.,* Protein Engineering, Design, and Selection, 25:107-117, 2012; U.S. Pat. Publ. No. 2010/0216708). The crystal structure of Tencon shows six surface-exposed loops that connect seven beta-strands as is characteristic to the FN3 domains, the beta-strands referred to as A, B, C, D, E, F, and G, and the loops referred to as AB, BC, CD, DE, EF, and FG loops (Bork and Doolittle, Proc Natl Acad Sci USA 89:8990-8992, 1992; U.S. Pat. No. 6,673,901). These loops, or selected residues within each loop, can be randomized in order to construct libraries of fibronectin type III (FN3) domains that can be used to select novel molecules that bind EGFR or c-Met. Table 1 shows positions and sequences of each loop and beta-strand in Tencon (SEQ ID NO: 1).

Library designed based on Tencon sequence may thus have randomized FG loop, or randomized BC and FG loops, such as libraries TCL1 or TCL2 as described below. The Tencon BC loop is 7 amino acids long, thus 1, 2, 3, 4, 5, 6 or 7 amino acids may be randomized in the library diversified at the BC loop and designed based on Tencon sequence. The Tencon FG loop is 7 amino acids long, thus 1, 2, 3, 4, 5, 6 or 7 amino acids may be randomized in the library diversified at the FG loop and designed based on Tencon sequence. Further diversity at loops in the Tencon libraries may be achieved by insertion and/or deletions of residues at loops. For example, the FG and/or BC loops may be extended by 1-22 amino acids, or decreased by 1-3 amino acids. The FG loop in Tencon is 7 amino acids long, whereas the corresponding loop in antibody heavy chains ranges from 4-28 residues. To provide maximum diversity, the FG loop may be diversified in sequence as well as in length to correspond to the antibody CDR3 length range of 4-28 residues. For example, the FG loop can further be diversified in length by extending the loop by additional 1, 2, 3, 4 or 5 amino acids.

Library designed based on Tencon sequence may also have randomized alternative surfaces that form on a side of the FN3 domain and comprise two or more beta strands, and at least one loop. One such alternative surface is formed by amino acids in the C and the F beta-strands and the CD and the FG loops (a C-CD-F-FG surface). A library design

based on Tencon alternative C-CD-F-FG surface and is shown in Figure 1 and detailed generation of such libraries is described in U.S. Pat. Publ. No. US2013/0226834. Library designed based on Tencon sequence also includes libraries designed based on Tencon variants, such as Tencon variants having substitutions at residues positions 11, 14, 17, 37, 46, 73, or 86 (residue numbering corresponding to SEQ ID NO: 1), and which variants display improve thermal stability. Exemplary Tencon variants are described in US Pat. Publ. No. 2011/0274623, and include Tencon27 (SEQ ID NO: 99) having substitutions E11R, L17A, N46V and E86I when compared to Tencon of SEQ ID NO: 1.

Table 1.

FN3 domain	Tencon (SEQ ID NO: 1)
A strand	1-12
AB loop	13-16
B strand	17-21
BC loop	22-28
C strand	29-37
CD loop	38-43
D strand	44-50
DE loop	51-54
E strand	55-59
EF loop	60-64
F strand	65-74
FG loop	75-81
G strand	82-89

Tencon and other FN3 sequence based libraries can be randomized at chosen residue positions using a random or defined set of amino acids. For example, variants in the library having random substitutions can be generated using NNK codons, which encode all 20 naturally occurring amino acids. In other diversification schemes, DVK codons can be used to encode amino acids Ala, Trp, Tyr, Lys, Thr, Asn, Lys, Ser, Arg,

Asp, Glu, Gly, and Cys. Alternatively, NNS codons can be used to give rise to all 20 amino acid residues and simultaneously reducing the frequency of stop codons. Libraries of FN3 domains with biased amino acid distribution at positions to be diversified can be synthesized for example using Slonomics® technology (http:_//www_sloning_com). This technology uses a library of pre-made double stranded triplets that act as universal building blocks sufficient for thousands of gene synthesis processes. The triplet library represents all possible sequence combinations necessary to build any desired DNA molecule. The codon designations are according to the well known IUB code.

The FN3 domains specifically binding EGFR or c-Met of the invention as described herein can be isolated by producing the FN3 library such as the Tencon library using *cis* display to ligate DNA fragments encoding the scaffold proteins to a DNA fragment encoding RepA to generate a pool of protein-DNA complexes formed after *in vitro* translation wherein each protein is stably associated with the DNA that encodes it (U.S. Pat. No. 7,842,476; Odegrip *et al.,* Proc Natl Acad Sci U S A 101, 2806-2810, 2004), and assaying the library for specific binding to EGFR and/or c-Met by any method known in the art and described in the Example. Exemplary well known methods which can be used are ELISA, sandwich immunoassays, and competitive and non-competitive assays (see, e.g., Ausubel *et al.,* eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York). The identified FN3 domains specifically binding EGFR or c-Met are further characterized for their ability to block EGFR ligand such as EGF binding to EGFR, or HGF binding to c-Met, and for their ability to inhibit EGFR and/or c-Met signaling using methods described herein.

The FN3 domains specifically binding to EGFR or c-Met of the invention as describd herein can be generated using any FN3 domain as a template to generate a library and screening the library for molecules specifically binding EGFR or c-Met using methods provided within. Exemplar FN3 domains that can be used are the 3rd FN3 domain of tenascin C (TN3) (SEQ ID NO: 75), Fibcon (SEQ ID NO: 76), and the 10th FN3 domain of fibronectin (FN10) (SEQ ID NO: 77). Standard cloning and expression techniques are used to clone the libraries into a vector or synthesize double stranded cDNA cassettes of the library, to express, or to translate the libraries *in vitro*. For example ribosome display (Hanes and Pluckthun, Proc Natl Acad Sci USA, 94, 4937-4942, 1997), mRNA display (Roberts and Szostak*, Proc Natl Acad Sci USA,* 94, 12297-12302, 1997), or other cell-free systems (U.S. Pat. No. 5,643,768) can be used. The libraries of the FN3 domain variants may be expressed as fusion proteins displayed on the surface for example of any suitable bacteriophage. Methods for displaying fusion polypeptides on the surface of a bacteriophage are well known

(U.S. Pat. Publ. No. 2011/0118144; Int. Pat. Publ. No. WO2009/085462; U.S. Pat. No. 6,969,108; U.S. Pat. No. 6,172,197; U.S. Pat. No. 5,223,409; U.S. Pat. No. 6,582,915; U.S. Pat. No. 6,472,147).

The FN3 domains specifically binding EGFR or c-Met of the invention as described herein can be modified to improve their properties such as improve thermal stability and reversibility of thermal folding and unfolding. Several methods have been applied to increase the apparent thermal stability of proteins and enzymes, including rational design based on comparison to highly similar thermostable sequences, design of stabilizing disulfide bridges, mutations to increase alpha-helix propensity, engineering of salt bridges, alteration of the surface charge of the protein, directed evolution, and composition of consensus sequences (Lehmann and Wyss, Curr Opin Biotechnol, 12, 371-375, 2001). High thermal stability may increase the yield of the expressed protein, improve solubility or activity, decrease immunogenicity, and minimize the need of a cold chain in manufacturing. Residues that can be substituted to improve thermal stability of Tencon (SEQ ID NO: 1) are residue positions 11, 14, 17, 37, 46, 73, or 86, and are described in US Pat. Publ. No. 2011/0274623. Substitutions corresponding to these residues can be incorporated to the FN3 domains or the bispecific FN3 domain containing molecules of the invention.

The invention also provides an isolated FN3 domain that specifically binds EGFR and blocks binding of EGF to EGFR, comprising the sequence shown in SEQ ID NOs: 18-29, 107-110, 122-137, further comprising substitutions at one or more residue positions corresponding to positions 11, 14, 17, 37, 46, 73, and 86 in Tencon (SEQ ID NO: 1).

The invention also provides an isolated FN3 domain that specifically binds c-Met and blocks binding of HGF to c-Met, comprising the sequence shown in SEQ ID NOs: 32-49 or 111-114, further comprising substitutions at one or more residue positions corresponding to positions 11, 14, 17, 37, 46, 73, and 86 in Tencon (SEQ ID NO: 1).

Exemplary substitutions are substitutions E11N, E14P, L17A, E37P, N46V, G73Y and E86I (numbering according to SEQ ID NO: 1).

In some embodiments, the FN3 domains of the invention comprise substitutions corresponding to substitutions L17A, N46V, and E86I in Tencon (SEQ ID NO: 1).

The FN3 domains specifically binding EGFR as described herein (Figure 1) have an extended FG loop when compared to Tencon (SEQ ID NO: 1). Therefore, the residues corresponding to residues 11, 14, 17, 37, 46, 73, and 86 in Tencon (SEQ ID NO: 1) are residues 11, 14, 17, 37, 46, 73 and 91 in EGFR FN3 domains shown in Figure 1A and 1B

except for the FN3 domain of SEQ ID NO: 24, wherein the corresponding residues are residues 11, 14, 17, 38, 74, and 92 due to an insertion of one amino acid in the BC loop.

The invention also provides an isolated FN3 domain that specifically binds EGFR and blocks binding of EGF to EGFR comprising the amino acid sequence shown in SEQ ID NOs: 18-29, 107-110, 122-137 or 194-211, optionally having one, two or three substitutions corresponding to substitutions L17A, N46V and E86I in Tencon (SEQ ID NO: 1).

The invention also provides an isolated FN3 domain that specifically binds c-Met and blocks binding of HGF to c-Met comprising the amino acid sequence shown in SEQ ID NOs: 32-49, 111-114 or 212-223, optionally having one, two or three substitutions corresponding to substitutions L17A, N46V, and E86I in Tencon (SEQ ID NO: 1).

Measurement of protein stability and protein lability can be viewed as the same or different aspects of protein integrity. Proteins are sensitive or "labile" to denaturation caused by heat, by ultraviolet or ionizing radiation, changes in the ambient osmolarity and pH if in liquid solution, mechanical shear force imposed by small pore-size filtration, ultraviolet radiation, ionizing radiation, such as by gamma irradiation, chemical or heat dehydration, or any other action or force that may cause protein structure disruption. The stability of the molecule can be determined using standard methods. For example, the stability of a molecule can be determined by measuring the thermal melting ("TM") temperature, the temperature in ° Celsius (°C) at which half of the molecules become unfolded, using standard methods. Typically, the higher the TM, the more stable the molecule. In addition to heat, the chemical environment also changes the ability of the protein to maintain a particular three dimensional structure.

In some embodiments described herein, the FN3 domains binding EGFR or c-Met of the invention exhibit increased stability by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% or more compared to the same domain prior to engineering measured by the increase in the TM.

Chemical denaturation can likewise be measured by a variety of methods. Chemical denaturants include guanidinium hydrochloride, guanidinium thiocyanate, urea, acetone, organic solvents (DMF, benzene, acetonitrile), salts (ammonium sulfate, lithium bromide, lithium chloride, sodium bromide, calcium chloride, sodium chloride); reducing agents (e.g. dithiothreitol, beta-mercaptoethanol, dinitrothiobenzene, and hydrides, such as sodium borohydride), non-ionic and ionic detergents, acids (e.g. hydrochloric acid (HCl), acetic acid (CH_3COOH), halogenated acetic acids), hydrophobic molecules (e.g. phosopholipids), and targeted denaturants. Quantitation of the extent of denaturation can

rely on loss of a functional property, such as ability to bind a target molecule, or by physiochemical properties, such as tendency to aggregation, exposure of formerly solvent inaccessible residues, or disruption or formation of disulfide bonds.

In some embodiments described herein, the FN3 domain of the invention binding EGFR or c-Met exhibit increased stability by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% or more compared to the same scaffold prior to engineering, measured by using guanidinium hydrochloride as a chemical denaturant. Increased stability can be measured as a function of decreased tryptophan fluorescence upon treatment with increasing concentrations of guanidine hydrochloride using well known methods.

The FN3 domains of the invention described herein may be generated as monomers, dimers, or multimers, for example, as a means to increase the valency and thus the avidity of target molecule binding, or to generate bi- or multispecific scaffolds simultaneously binding two or more different target molecules. The dimers and multimers may be generated by linking monospecific, bi- or multispecific protein scaffolds, for example, by the inclusion of an amino acid linker, for example a linker containing poly-glycine, glycine and serine, or alanine and proline. Exemplary linker include $(GS)_2$, (SEQ ID NO: 78), $(GGGS)_2$ (SEQ ID NO: 224), $(GGGGS)_5$ (SEQ ID NO: 79), $(AP)_2$ (SEQ ID NO: 80), $(AP)_5$ (SEQ ID NO: 81), $(AP)_{10}$ (SEQ ID NO: 82), $(AP)_{20}$ (SEQ ID NO: 83) and $A(EAAAK)_5AAA$ (SEQ ID NO: 84). The dimers and multimers may be linked to each other in a N-to C-direction. The use of naturally occurring as well as artificial peptide linkers to connect polypeptides into novel linked fusion polypeptides is well known in the literature (Hallewell *et al., J Biol Chem* 264, 5260-5268, 1989; Alfthan *et al., Protein Eng.* 8, 725-731, 1995; Robinson & Sauer, *Biochemistry* 35, 109-116, 1996; U.S. Pat. No. 5,856,456).

Bispecific EGFR/c/Met binding molecules

The bispecific EGFR/c-Met FN3 domain containing molecules of the invention described herein may provide a benefit in terms of specificity and reduced off-target toxicity when compared to small molecule EGFR inhibitors, and improved tissue penetration when compared to conventional antibody therapeutics. The present invention is based at least in part on the surprising finding that the bispecific EGFR/c-Met FN3 domain containing molecules of the invention provide a significantly improved synergistic inhibitory effect when compared to a mixture of EGFR-binding and c-Met-binding FN3

domains. The molecules may be tailored to specific affinity towards both EGFR and c-Met to maximize tumor penetration and retention. The bispecific EGFR/c-Met FN3 domain containing molecules of the invention provide more efficient inhibition of EGFR and/or c-Met signaling pathways and inhibit tumor growth more efficiently than cetuximab (Eribtux®)

The invention also provides an isolated bispecific FN3 domain containing molecule comprising a first fibronectin type III (FN3) domain and a second FN3 domain, wherein the first FN3 domain specifically binds epidermal growth factor receptor (EGFR) and blocks binding of epidermal growth factor (EGF) to EGFR, and the second FN3 domain specifically binds hepatocyte growth factor receptor (c-Met) and blocks binding of hepatocyte growth factor (HGF) to c-Met.

The bispecific EGFR/c-Met FN3 domain containing molecules of the invention described herein can be generated by covalently linking any EGFR-binding FN3 domain and any c-Met-binding FN3 domain of the invention directly or via a linker. Therefore, the first FN3 domain of the bispecific molecule may have characteristics as described above for the EGFR-binding FN3 domains, and the second FN3 domain of the bispecific molecule may have characteristics as described above for the c-Met-binding FN3 domains.

In some embodiments described herein, the first FN3 domain of the bispecific EGFR/c-Met FN3 domain containing molecule inhibits EGF-induced EGFR phosphorylation at EGFR residue Tyrosine 1173 with an IC_{50} value of less than about $2.5x10^{-6}$ M when measured in A431 cells using 50 ng/mL human EGF, and the second FN3 domain of the bispecific EGFR/c-Met FN3 domain containing molecule inhibits HGF- induced c-Met phosphorylation at c-Met residue Tyrosine 1349 with an IC_{50} value of less than about $1.5x10^{-6}$ M when measured in NCI-H441 cells using 100 ng/mL human HGF.

In some embodiments described herein, the first FN3 domain of the bispecific EGFR/c-Met FN3 domain containing molecule inhibits EGF-induced EGFR phosphorylation at EGFR residue Tyrosine 1173 with an IC_{50} value of between about 1.8 x 10^{-8} M to about $2.5x10^{-6}$ M when measured in NCI-H292 cells using 50 ng/mL human EGF, and the second FN3 domain of the bispecific EGFR/c-Met FN3 domain containing molecule inhibits HGF- induced c-Met phosphorylation at c-Met residue Tyrosine 1349 with an IC_{50} value between about $4x10^{-9}$ M to about $1.5x10^{-6}$ M when measured in NCI-H441 cells using 100 ng/mL human HGF.

In some embodiments described herein, the first FN3 domain of the bispecific EGFR/c-Met FN3 domain containing molecule binds human EGFR with a dissociation

constant (K_D) of less than about $1x10^{-8}$ M, and the second FN3 domain of the bispecific EGFR/c-Met FN3 domain containing molecule binds human c-Met with a K_D of less than about 5 $x10^{-8}$ M.

In the bispecific molecule binding both EGFR and c-Met as described herein, the first FN3 domain binds human EGFR with a K_D of between about $2x10^{-10}$ to about $1x10^{-8}$ M, and the second FN3 domain binds human c-Met with a K_D of between about $3x10^{-10}$ to about 5 $x10^{-8}$ M.

The affinity of the bispecific EGFR/c-Met molecule for EGFR and c-Met can be determined as described in Example 3 and Example 5 for the monospecific molecules.

The first FN3 domain in the bispecific EGFR/c-Met molecule of the invention may block EGF binding to EGFR with an IC_{50} value of between about $1x10^{-9}$ M to about $1.5x10^{-7}$ M in an assay employing A431 cells and detecting the amount of fluorescence from bound biotinylated EGF using streptavidin-phycoerythrin conjugate at 600 nM on A431 cells incubated with or without the first FN3 domain. The first FN3 domain in the bispecific EGFR/c-Met molecule of the invention may block EGF binding to the EGFR by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% when compared to binding of EGF to EGFR in the absence of the first FN3 domains using the same assay conditions.

The second FN3 domain in the bispecific EGFR/c-Met molecule of the invention may block HGF binding to c-Met with an IC_{50} value of between about $2x10^{-10}$ M to about $6x10^{-8}$ M in an assay detecting inhibition of binding of biotinylated HGF to c-Met-Fc fusion protein in the presence of the second FN3 domain. The second FN3 domain in the bispecific EGFR/c-Met molecule may block HGF binding to c-Met by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% when compared to binding of HGF to c-Met in the absence of the second FN3 domain using the same assay conditions.

The bispecific EGFR/c-Met molecule of the invention described herein may inhibit EGFR and/or c-Met signaling by at least 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% when compared to the level of signaling in the absence of the bispecific EGFR/c-Met molecule of the invention using the same assay conditions.

EGFR and c-Met signaling may be measured using various well know methods as described above for the monospecific molecules.

The bispecific EGFR/c-Met molecules of the invention as described herein comprising the first FN3 domain specifically binding EGFR and the second FN3 domain

specifically binding c-Met provide a significantly increased synergistic inhibition of EGFR and c/Met signaling and tumor cell proliferation when compared to the synergistic inhibition observed by a mixture of the first and the second FN3 domain. Synergistic inhibition can be assessed for example by measuring inhibition of ERK phosphorylation by the bispecific EGFR/c-Met FN3 domain containing molecules and by a mixture of two monospecific molecules, one binding EGFR and the other c-Met. The bispecific EGFR/c-Met molecules of the invention may inhibit ERK phosphorylation with an at least about 100 fold smaller, for example at least 500, 1000, 5000 or 10,000 fold smaller IC_{50} value when compared to the IC_{50} value for a mixture of two monospecific FN3 domains, indicating at least 100 fold increased potency for the bispecific EGFR/c-Met FN3 domain containing molecules when compared to the mixture of two monospecific FN3 domains. Exemplary bispecific EGFR-c-Met FN3 domain containing molecules may inhibit ERK phosphorylation with and IC_{50} value of about $5x10^{-9}$ M or less. ERK phosphorylation can be measured using standard methods and methods described herein.

The bispecific EGFR/c-Met FN3 domain containing molecule of the invention as described herein may inhibit H292 cell proliferation with an IC_{50} value that is at least 30-fold less when compared to the IC_{50} value of inhibition of H292 cell growth with a mixture of the first FN3 domain and the second FN3, wherein the cell proliferation is induced with medium containing 10% FBS supplemented with 7.5 ng/mL HGF. The bispecific molecule of the invention as described herein may inhibit tumor cell proliferation with an IC_{50} value that is about 30, 40, 50, 60, 70, 80, 90, 100, 150, 200, 300, 400, 500, 600, 700, 800, or about 1000 fold less when compared to the IC_{50} value of inhibition of tumor cell proliferation with a mixture of the first FN3 domain and the second FN3 domain. Inhibition of tumor cell proliferation can be measured using standard methods and methods described herein.

In some embodiments described herein, the bispecific EGFR/c-Met FN3 domain containing molecule binds EGFR with one or more amino acid residues corresponding to residues D23, F27, Y28, V77 and G85 of P54AR4-83v2 (SEQ ID NO: 27).

In some embodiments described herein, the bispecific EGFR/c-Met FN3 domain containing molecule binds c-Met with one or more amino acid residues corresponding to residues R34, F38, M72 and I79 in P114AR7P95-A3 (SEQ ID NO: 41).

Paratope residues in the bispecific molecules can be identified by mutagenesis studies or from co-crystal structures of the FN3 domain and EGFR or c-Met. Mutagenesis studies may be employed by for example using alanine scanning, and the resulting variants may be tested for their binding to EGFR or c-Met using standard methods. Typically

paratope residues are those residues that when mutagenized, result in variants with reduced or abolished binding to EGFR or c-Met. EGFR-binding FN3 domains with substitutions at amino acid residue positions corresponding to residues D23, F27, Y28, V77 and G85 of P54AR4-83v2 (SEQ ID NO: 27), when substituted, reduce EGFR binding at least 100-fold when compared to the wild type P54AR4-83v2. Bispecific molecules ECB1, ECB2, ECB3, ECB4, ECB5, ECB6, ECB7, ECB15, ECB17, ECB60, ECB37, ECB94, ECB95, ECB96, ECB97, ECB91, ECB18, ECB28, ECB38, ECB39, ECB168 and ECB176 have D, F, Y, V and G at residue positions corresponding to residues D23, F27, Y28, V77 and G85 of P54AR4-83v2 and expected to bind to EGFR with these residues. c-Met binding FN3 domains with substitutions at amino acid residue positions corresponding to residues R34, F38, M72 and I79 of P114AR7P95-A3 (SEQ ID NO: 41), when substituted, abolish or reduce c-Met binding at least 100-fold when compared to the wild type P114AR7P95-A3. Bispecific molecules ECB2, ECB5, ECB15, ECB60, ECB38 and ECB39 have R, F, M and I at residue positions corresponding to residues R34, F38, M72 and I79 of P114AR7P95-A3 (SEQ ID NO: 41) and expected to bind to c-Met with these residues.

The invention also provides a bispecific FN3 domain containing molecule comprising a first fibronectin type III (FN3) domain and a second FN3 domain, wherein the first FN3 domain specifically binds epidermal growth factor receptor (EGFR) and blocks binding of epidermal growth factor (EGF) to EGFR, and the second FN3 domain specifically binds hepatocyte growth factor receptor (c-Met), and blocks binding of hepatocyte growth factor (HGF) to c-Met, wherein

the first FN3 domain comprises

an FG loop comprising the sequence HNVYKDTNX$_9$RGL (SEQ ID NO: 179) or the sequence LGSYVFEHDVML (SEQ ID NO: 180), wherein X$_9$ is M or I; and

a BC loop comprising the sequence X$_1$X$_2$X$_3$X$_4$X$_5$X$_6$X$_7$X$_8$ (SEQ ID NO: 181), wherein

X$_1$ is A, T, G or D;

X$_2$ is A, D, Y or W;

X$_3$ is P, D or N;

X$_4$ is L or absent;

X$_5$ is D, H, R, G, Y or W;

X$_6$ is G, D or A;

X$_7$ is A, F, G, H or D; and

X_8 is Y, F or L; and

the second FN3 domain comprises

a C strand and a CD loop comprising the sequence DSFX_{10}IRYX_{11}E $X_{12}X_{13}X_{14}X_{15}GX_{16}$ (SEQ ID NO: 184), wherein

X_{10} is W, F or V;

X_{11} is D, F or L;

X_{12} is V, F or L;

X_{13} is V, L or T;

X_{14} is V, R, G, L, T or S;

X_{15} is G, S, A, T or K; and

X_{16} is E or D; and

a F strand and a FG loop comprising the sequence TEYX_{17}VX_{18}I$X_{19}X_{20}$V KGG$X_{21}X_{22}SX_{23}$ (SEQ ID NO: 185), wherein

X_{17} is Y, W, I, V, G or A;

X_{18} is N, T, Q or G;

X_{19} is L, M, N or I;

X_{20} is G or S;

X_{21} is S, L, G, Y, T, R, H or K;

X_{22} is I, V or L; and

X_{23} is V, T, H, I, P, Y or L.

In some other embodiments described herein, the bispecific molecule comprises the first FN3 domain that binds EGFR comprising the sequence:

LPAPKNLVVSEVTEDSLRLSW$X_1X_2X_3X_4X_5X_6X_7X_8$DSFLIQYQESEKVGEAINLTVP GSERSYDLTGLKPGTEYTVSIYGVHNVYKDTNX_9RGL PLSAEFTT (SEQ ID NO: 182), or the sequence

LPAPKNLVVSEVTEDSLRLSW$X_1X_2X_3X_4X_5X_6X_7X_8$ DSFLIQYQESEKVGEAINLTVP GSERSYDLTGLKPGTEYTVSIYGV LGSYVFEHDVMLPLSAEFTT (SEQ ID NO: 183),

wherein in the SEQ ID NOs: 182 and 183;

X_1 is A, T, G or D;

X_2 is A, D, Y or W;

X_3 is P, D or N;

X_4 is L or absent;

X_5 is D, H, R, G, Y or W;

X_6 is G, D or A;

X_7 is A, F, G, H or D;

X_8 is Y, F or L; and

X_9 is M or I.

In some other embodiments described herein, the bispecific molecule comprises the second FN3 domain that binds c-Met comprising the sequence LPAPKNLVVSRVTEDSARLSWTAPDAAF DSFX_{10}IRYX_{11}E $X_{12}X_{13}X_{14}X_{15}$GX_{16} AIVLTVPGSERSYDLTGLKPG TEYX_{17}VX_{18}I$X_{19}X_{20}$VKGG$X_{21}X_{22}$SX_{23}PLSAEFTT (SEQ ID NO: 186),

wherein

X_{10} is W, F or V; and

X_{11} is D, F or L;

X_{12} is V, F or L;

X_{13} is V, L or T;

X_{14} is V, R, G, L, T or S;

X_{15} is G, S, A, T or K;

X_{16} is E or D;

X_{17} is Y, W, I, V, G or A;

X_{18} is N, T, Q or G;

X_{19} is L, M, N or I;

X_{20} is G or S;

X_{21} is S, L, G, Y, T, R, H or K;

X_{22} is I, V or L; and

X_{23} is V, T, H, I, P, Y or L.

Exemplary bispecific EGFR/c-Met FN3 domain containing molecules comprise the amino acid sequences shown in SEQ ID NOs: 50-72, 106, 118-121, 138-165, 170-178 or 190-193.

The bispecific EGFR/c-Met molecules of the invention as described herein comprise certain structural characteristics associated with their functional characteristics, such as inhibition of EGFR autophosphorylation, such as the FG loop of the first FN3 domain that binds EGFR comprising the sequence HNVYKDTNX_9RGL (SEQ ID NO: 179) or the sequence LGSYVFEHDVML (SEQ ID NO: 180), wherein X_9 is M or I.

In some embodiments described herein, the bispecific EGFR/c-Met FN3 domain containing molecules of the invention

inhibit EGF-induced EGFR phosphorylation at EGFR residues Tyrosine 1173 with an IC_{50} value of less than about $8x10^{-7}$ M when measured in H292 cells using 50 ng/mL human EGF;

inhibit HGF-induced c-Met phosphorylation at c-Met residue Tyrosine 1349 with and IC_{50} value of less than about $8.4x10^{-7}$ M when measured in NCI-H441 cells using 100 ng/mL human HGF;

inhibit HGF-induced NCI-H292 cell proliferation with an IC_{50} value of less than about $9.5x10^{-6}$M wherein the cell proliferation is induced with 10% FBS containing 7.5 ng HGF;

bind EGFR with a K_D of less than about $2.0x10^{-8}$ M; or

bind c-Met with a K_D of less than about $2.0x10^{-8}$ M; wherein the K_D is measured using surface plasmon resonance as described in Example 3 or Example 5.

In another embodiment, the bispecific EGFR/c-Met FN3 domain containing molecules of the invention

inhibit EGF-induced EGFR phosphorylation at EGFR residues Tyrosine 1173 with and IC_{50} of between about $4.2x10^{-9}$ M and $8x10^{-7}$ M when measured in H292 cells using 50 ng/mL human EGF;

inhibit HGF-induced c-Met phosphorylation at c-Met residues Tyrosine 1349 with and IC_{50} value of between about $2.4x10^{-8}$ M to about $8.4x10^{-7}$ M when measured in NCI-H441 cells using 100 ng/mL human HGF;

inhibit HGF-induced NCI-H292 cell proliferation with an IC_{50} value between about $2.3x10^{-8}$ M to about $9.5x10^{-6}$M wherein the cell proliferation is induced with 10% FBS containing 7.5 ng HGF;

bind EGFR with a K_D of between about $2x10^{-10}$ M to about $2.0x10^{-8}$ M; or

bind c-Met with a K_D of between about $1x10^{-9}$ M to about $2.0x10^{-8}$ M, wherein the K_D is measured using surface plasmon resonance as described in Example 3 or Example 5.

In some embodiments described herein, the bispecific EGFR/c-Met molecules comprise the EGFR-binding FN3 domain comprising the sequence LPAPKNLVVSEVTEDSLRLSWX$_1$X$_2$X$_3$X$_4$X$_5$X$_6$X$_7$X$_8$DSFLIQYQESEKVGEAINLTVP GSERSYDLTGLKPGTEYTVSIYGV HNVYKDTNX$_9$RGL PLSAEFTT (SEQ ID NO: 182), wherein

X_1 is D;

X_2 is D;

X_3 is P;

X_4 is absent;

X_5 is H or W;

X_6 is A;

X_7 is F

X_8 is Y; and

X_9 is M or I; and

the c-Met-binding FN3 domain comprising the sequence LPAPKNLVVSRVTEDSARLSWTAPDAAF DSFX_{10}IRYX_{11}E $X_{12}X_{13}X_{14}X_{15}GX_{16}$ AIVLTVPGSERSYDLTGLKPG TEYX_{17}VX_{18}I$X_{19}X_{20}$VKGG$X_{21}X_{22}S X_{23}$ PLSAEFTT (SEQ ID NO: 186),

wherein

X_{10} is W;

X_{11} is F;

X_{12} is F;

X_{13} is V or L;

X_{14} is G or S;

X_{15} is S or K;

X_{16} is E or D;

X_{17} is V;

X_{18} is N;

X_{19} is L or M;

X_{20} is G or S;

X_{21} is S or K;

X_{22} is I; and

X_{23} is P.

Exemplary bispecific EGFR/c-Met molecules are those having the sequence shown in SEQ ID NOs: 57, 61, 62, 63, 64, 65, 66, 67, 68 or 190-193.

The bispecific molecules of the invention as described herein may further comprise substitutions at one or more residue positions in the first FN3 domain and/or the second FN3 domain corresponding to positions 11, 14, 17, 37, 46, 73 and 86 in Tencon (SEQ ID NO: 1) as described above, and a substitution at position 29. Exemplary substitutions are substitutions E11N, E14P, L17A, E37P, N46V, G73Y, E86I and D29E (numbering according to SEQ ID NO: 1). Skilled in the art will appreciate that other

amino acids can be used for substitutions, such as amino acids within a family of amino acids that are related in their side chains as described *infra.*. The generated variants can be tested for their stability and binding to EGFR and/or c-Met using methods herein.

In some embodiments described herein, the bispecific EGFR/c-Met FN3 domain containing molecule comprises the first FN3 domain that binds specifically EGFR and the second FN3 domain that binds specifically c-Met, wherein the first FN3 domain comprises the sequence:

LPAPKNLVVSX$_{24}$VTX$_{25}$DSX$_{26}$RLSWDDPX$_{27}$AFYX$_{28}$SFLIQYQX$_{29}$SEKVGEAIX$_{30}$LT VPGSERSYDLTGLKPGTEYTVSIYX$_{31}$VHNVYKDTNX$_{32}$RGLPLSAX$_{33}$FTT (SEQ ID NO: 187), wherein

X$_{24}$ is E, N or R;

X$_{25}$ is E or P;

X$_{26}$ is L or A;

X$_{27}$ is H or W;

X$_{28}$ is E or D;

X$_{29}$ is E or P;

X$_{30}$ is N or V;

X$_{31}$ is G or Y;

X$_{32}$ is M or I; and

X$_{33}$ is E or I;

and the second FN3 domain comprises the sequence:

LPAPKNLVVSX$_{34}$VTX$_{35}$DSX$_{36}$RLSWTAPDAAFDSFWIRYFX$_{37}$FX$_{38}$X$_{39}$X$_{40}$GX$_{41}$AIX$_{42}$ LTVPGSERSYDLTGLKPGTEYVVNIX$_{43}$X$_{44}$VKGGX$_{45}$ISPPLSAX$_{46}$FTT (SEQ ID NO: 188); wherein

X$_{34}$ is E, N or R;

X$_{35}$ is E or P;

X$_{36}$ is L or A;

X$_{37}$ is E or P;

X$_{38}$ is V or L;

X$_{39}$ is G or S;

X$_{40}$ is S or K;

X$_{41}$ is E or D;

X$_{42}$ is N or V;

X$_{43}$ is L or M;

X$_{44}$ is G or S;

X_{45} is S or K; and

X_{46} is E or I.

In some embodiments described herein, the bispecific EGFR/c-Met FN3 domain containing molecule comprises the first FN3 domain comprising an amino acid sequence at least 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of SEQ ID NO: 27, and the second FN3 domain comprising an amino acid sequence at least 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to the amino acid sequence of SEQ ID NO: 41.

The bispecific EGFR/c-Met FN3 domain containing molecules of the invention as described herein may be tailored to a specific affinity towards EGFR and c-Met to maximize tumor accumulation.

The invention also provides an isolated bispecific FN3 domain containing molecule comprising a first fibronectin type III (FN3) domain and a second FN3 domain, wherein the first FN3 domain specifically binds epidermal growth factor receptor (EGFR) and blocks binding of epidermal growth factor (EGF) to EGFR, and the second FN3 domain specifically binds hepatocyte growth factor receptor (c-Met), and blocks binding of hepatocyte growth factor (HGF) to c-Met, wherein the first FN3 domain and the second FN3 domain is isolated from a library designed based on Tencon sequence of SEQ ID NO: 1.

The bispecific EGFR/c-Met FN3 domain containing molecule of the inventionas described herein can be generated by covalently coupling the EGFR-binding FN3 domain and the c-Met binding FN3 domain of the invention using well known methods. The FN3 domains may be linked via a linker, for example a linker containing poly-glycine, glycine and serine, or alanine and proline. Exemplary linker include $(GS)_2$, (SEQ ID NO: 78), (GGGS)2 (SEQ ID NO: 224), $(GGGGS)_5$ (SEQ ID NO: 79), $(AP)_2$ (SEQ ID NO: 80), $(AP)_5$ (SEQ ID NO: 81), $(AP)_{10}$ (SEQ ID NO: 82), $(AP)_{20}$ (SEQ ID NO: 83), $A(EAAAK)_5AAA$ (SEQ ID NO: 84). The use of naturally occurring as well as artificial peptide linkers to connect polypeptides into novel linked fusion polypeptides is well known in the literature (Hallewell *et al., J Biol Chem* 264, 5260-5268, 1989; Alfthan *et al., Protein Eng.* 8, 725-731, 1995; Robinson & Sauer, *Biochemistry* 35, 109-116, 1996; U.S. Pat. No. 5,856,456). The bispecific EGFR/c-Met molecules of the invention as described herein may be linked together from a C-terminus of the first FN3 domain to the N-terminus of the second FN3 domain, or from the C-terminus of the second FN3 domain to the N-terminus of the first FN3 domain. Any EGFR-binding FN3 domain may be

covalently linked to a c-Met-binding FN3 domain. Exemplary EGFR-binding FN3 domains are domains having the amino acid sequence shown in SEQ ID NOs: 18-29, 107-110, 122-137 or 194-211, and exemplary c-Met binding FN3 domains are domains having the amino acid sequence shown in SEQ ID NOs: 32-49, 111-114 or 212-223. The EGFR-binding FN3 domains to be coupled to a bispecific molecule may additionally comprise an initiator methionine (Met) at their N-terminus.

Variants of the bispecific EGFR/c-Met FN3 domain containing molecules as described herein are within the scope of the invention. For example, substitutions can be made in the bispecific EGFR/c-Met FN3 domain containing molecule as long as the resulting variant retains similar selectivity and potency towards EGFR and c-Met when compared to the parent molecule. Exemplary modifications are for example conservative substitutions that will result in variants with similar characteristics to those of the parent molecules. Conservative substitutions are those that take place within a family of amino acids that are related in their side chains. Genetically encoded amino acids can be divided into four families: (1) acidic (aspartate, glutamate); (2) basic (lysine, arginine, histidine); (3) nonpolar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan); and (4) uncharged polar (glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine). Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids. Alternatively, the amino acid repertoire can be grouped as (1) acidic (aspartate, glutamate); (2) basic (lysine, arginine histidine), (3) aliphatic (glycine, alanine, valine, leucine, isoleucine, serine, threonine), with serine and threonine optionally be grouped separately as aliphatic-hydroxyl; (4) aromatic (phenylalanine, tyrosine, tryptophan); (5) amide (asparagine, glutamine); and (6) sulfur-containing (cysteine and methionine) (Stryer (ed.), Biochemistry, 2nd ed, WH Freeman and Co., 1981). Non-conservative substitutions can be made to the bispecific EGFR/c-Met FN3 domain containing molecule that involves substitutions of amino acid residues between different classes of amino acids to improve properties of the bispecific molecules. Whether a change in the amino acid sequence of a polypeptide or fragment thereof results in a functional homolog can be readily determined by assessing the ability of the modified polypeptide or fragment to produce a response in a fashion similar to the unmodified polypeptide or fragment using the assays described herein. Peptides, polypeptides or proteins in which more than one replacement has taken place can readily be tested in the same manner.

The bispecific EGFR/c-Met FN3 domain containing molecules of the invention as described herein may be generated as dimers or multimers, for example, as a means to

increase the valency and thus the avidity of target molecule binding. The multimers may be generated by linking one or more EGFR-binding FN3 domain and one or more c-Met-binding FN3 domain to form molecules comprising at least three individual FN3 domains that are at least bispecific for either EGFR or c-Met, for example by the inclusion of an amino acid linker using well known methods.

The invention also provides a bispecific FN3 domain containing molecule comprising a first fibronectin type III (FN3) domain and a second FN3 domain, wherein the first FN3 domain specifically binds epidermal growth factor receptor (EGFR) and blocks binding of epidermal growth factor (EGF) to EGFR, and the second FN3 domain specifically binds hepatocyte growth factor receptor (c-Met), and blocks binding of hepatocyte growth factor (HGF) to c-Met comprising the amino acid sequence shown in SEQ ID NOs: 50-72, 106, 118-121, 138-165, 170-179 or 190-193.

Half-life extending moieties

The bispecific EGFR/c-Met FN3 domain containing molecules or the monospecific EGFR or c-Met binding FN3 domains of the invention as described herein may incorporate other subunits for example via covalent interaction. In one aspect of the invention, the bispecific EGFR/c-Met FN3 domain containing molecules of the invention further comprise a half-life extending moiety. Exemplary half-life extending moieties are albumin, albumin variants, albumin-binding proteins and/or domains, transferrin and fragments and analogues thereof, and Fc regions. An exemplary albumin-binding domain is shown in SEQ ID NO: 117 and an exemplary albumin variant is shown in SEQ ID NO: 189.

All or a portion of an antibody constant region may be attached to the molecules of the invention to impart antibody-like properties, especially those properties associated with the Fc region, such as Fc effector functions such as C1q binding, complement dependent cytotoxicity (CDC), Fc receptor binding, antibody-dependent cell-mediated cytotoxicity (ADCC), phagocytosis, down regulation of cell surface receptors (e.g., B cell receptor; BCR), and can be further modified by modifying residues in the Fc responsible for these activities (for review; see Strohl, *Curr Opin Biotechnol.* 20, 685-691, 2009).

Additional moieties may be incorporated into the bispecific molecules of the invention such as polyethylene glycol (PEG) molecules, such as PEG5000 or PEG20,000, fatty acids and fatty acid esters of different chain lengths, for example laurate, myristate, stearate, arachidate, behenate, oleate, arachidonate, octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like, polylysine, octane, carbohydrates

(dextran, cellulose, oligo- or polysaccharides) for desired properties. These moieties may be direct fusions with the protein scaffold coding sequences and may be generated by standard cloning and expression techniques. Alternatively, well known chemical coupling methods may be used to attach the moieties to recombinantly produced molecules of the invention.

A pegyl moiety may for example be added to the bispecific or monospecific molecules of the invention by incorporating a cysteine residue to the C-terminus of the molecule and attaching a pegyl group to the cysteine using well known methods. Exemplary bispecific molecules with the C-terminal cysteine are those having the amino acid sequence shown in SEQ IN NO: 170-178.

Monospecific and bispecific molecules of the invention as described herein incorporating additional moieties may be compared for functionality by several well known assays. For example, altered properties of monospecific and/or bispecific molecules due to incorporation of Fc domains and/or Fc domain variants may be assayed in Fc receptor binding assays using soluble forms of the receptors, such as the FcγRI, FcγRII, FcγRIII or FcRn receptors, or using well known cell-based assays measuring for example ADCC or CDC, or evaluating pharmacokinetic properties of the molecules of the invention in *in vivo* models.

Polynucleotides, vectors, host cells

The invention provides for nucleic acids encoding the EGFR-binding or c-Met binding FN3 domains or the bispecific EGFR/c-Met FN3 domain containing molecules of the invention as isolated polynucleotides or as portions of expression vectors or as portions of linear DNA sequences, including linear DNA sequences used for *in vitro* transcription/translation, vectors compatible with prokaryotic, eukaryotic or filamentous phage expression, secretion and/or display of the compositions or directed mutagens thereof. Certain exemplary polynucleotides are disclosed herein, however, other polynucleotides which, given the degeneracy of the genetic code or codon preferences in a given expression system, encode the EGFR-binding or c-Met binding FN3 domains or the bispecific EGFR/c-Met FN3 domain containing molecules of the invention are also within the scope of the invention.

The invention also provides an isolated polynucleotide encoding the FN3 domain specifically binding EGFR having the amino acid sequence of SEQ ID NOs: 18-29, 107-110, 122-137 or 194-211.

The invention also provides an isolated polynucleotide encoding the FN3 domain specifically binding c-Met having the amino acid sequence of the sequence shown in SEQ ID NOs: 32-49, 111-114 or 212-223.

The invention also provides an isolated polynucleotide encoding the bispecific EGFR/-c-Met FN3 domain containing molecule having the amino acid sequence of SEQ ID NOs: 50-72, 106, 118-121, 138-165, 170-179 or 190-193.

The invention also provides an isolated polynucleotide comprising the polynucleotide sequence of SEQ ID NOs: 97, 98, 103, 104, 115, 116 or 166-169.

The polynucleotides of the invention as described herein may be produced by chemical synthesis such as solid phase polynucleotide synthesis on an automated polynucleotide synthesizer and assembled into complete single or double stranded molecules. Alternatively, the polynucleotides of the invention may be produced by other techniques such a PCR followed by routine cloning. Techniques for producing or obtaining polynucleotides of a given known sequence are well known in the art.

The polynucleotides of the invention as described herein may comprise at least one non-coding sequence, such as a promoter or enhancer sequence, intron, polyadenylation signal, a *cis* sequence facilitating RepA binding, and the like. The polynucleotide sequences may also comprise additional sequences encoding additional amino acids that encode for example a marker or a tag sequence such as a histidine tag or an HA tag to facilitate purification or detection of the protein, a signal sequence, a fusion protein partner such as RepA, Fc or bacteriophage coat protein such as pIX or pIII.

The invention also provides a vector comprising at least one polynucleotide of the invention. Such vectors may be plasmid vectors, viral vectors, vectors for baculovirus expression, transposon based vectors or any other vector suitable for introduction of the polynucleotides of the invention into a given organism or genetic background by any means. Such vectors may be expression vectors comprising nucleic acid sequence elements that can control, regulate, cause or permit expression of a polypeptide encoded by such a vector. Such elements may comprise transcriptional enhancer binding sites, RNA polymerase initiation sites, ribosome binding sites, and other sites that facilitate the expression of encoded polypeptides in a given expression system. Such expression systems may be cell-based, or cell-free systems well known in the art.

The invention also provides a host cell comprising the vector of the invention. A monospecific EGFR-binding or c-Met binding FN3 domain or the bispecific EGFR/c-Met FN3 domain containing molecule of the invention can be optionally produced by a cell line, a mixed cell line, an immortalized cell or clonal population of immortalized cells, as

well known in the art. See, e.g., Ausubel, *et al.,* ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, *et al.,* Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, Antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, *et al.,* eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan *et al.,* Current Protocols in Protein Science, John Wiley & Sons, NY, NY, (1997-2001).

The host cell chosen for expression may be of mammalian origin or may be selected from COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, He G2, SP2/0, HeLa, myeloma, lymphoma, yeast, insect or plant cells, or any derivative, immortalized or transformed cell thereof. Alternatively, the host cell may be selected from a species or organism incapable of glycosylating polypeptides, e.g. a prokaryotic cell or organism, such as BL21, BL21(DE3), BL21-GOLD(DE3), XL1-Blue, JM109, HMS174, HMS174(DE3), and any of the natural or engineered *E. coli spp, Klebsiella spp.,* or *Pseudomonas spp* strains.

Another embodiment of the invention is a method of producing the isolated FN3 domain specifically binding EGFR or c-Met of the invention or the isolated bispecific EGFR/c-Met FN3 domain containing molecule of the invention, comprising culturing the isolated host cell of the invention under conditions such that the isolated FN3 domain specifically binding EGFR or c-Met or the isolated bispecific EGFR/c-Met FN3 domain containing molecule is expressed, and purifying the domain or molecule.

The FN3 domain specifically binding EGFR or c-Met or the isolated bispecific EGFR/c-Met FN3 domain containing molecule of the invention can be purified from recombinant cell cultures by well-known methods, for example by protein A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography, or high performance liquid chromatography (HPLC).

Uses of bispecific EGFR/c-Met FN3 domain containing molecules and EGFR-binding or c-Met binding FN3 domains of the invention

The bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR binding FN3 domains or the c-Met binding FN3 domains of the invention as described herein may be used to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of human disease or specific pathologies in cells, tissues, organs,

fluid, or, generally, a host. The methods of the invention may be used to treat an animal patient belonging to any classification. Examples of such animals include mammals such as humans, rodents, dogs, cats and farm animals.

One aspect of the invention is a method for inhibiting growth or proliferation of cells that express EGFR and/or c-Met, comprising contacting the cells with the isolated bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention.

Another aspect of the invention is a method for inhibiting growth or metastasis of EGFR and/or c-Met -expressing tumor or cancer cells in a subject comprising administering to the subject an effective amount of the isolated bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention so that the growth or metastasis of EGFR- and/or c-Met-expressing tumor or cancer cell is inhibited.

Another aspect of the invention is a method of treating a subject having cancer, comprising administering a therapeutically effective amount of the isolated bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain, or the c-Met binding FN3 domain of the invention to a patient in need thereof for a time sufficient to treat the cancer.

The bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention may be used for treatment of any disease or disorder characterized by abnormal activation or production of EGFR, c-Met, EGF or other EGFR ligand or HGF, or disorder related to EGFR or c-Met expression, which may or may not involve malignancy or cancer, where abnormal activation and/or production of EGFR, c-Met, EGF or other EGFR ligand, or HGF is occurring in cells or tissues of a subject having, or predisposed to, the disease or disorder. The bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention may be used for treatment of tumors, including cancers and benign tumors. Cancers that are amenable to treatment by the bispecific molecules of the invention include those that overexpress EGFR and/or c-Met, cancers associated with elevated EGFR activity and/or expression levels (such as, for example, an EGFR activating mutation, an EGFR gene amplification, or ligand mediated EGFR activation) and elevated c-Met activity and/or expression levels (such as, for example, a c-Met activating mutation, a c-Met gene amplification, or HGF mediated c-Met activation.

Exemplary EGFR activating mutations that may be associated with cancer include point mutations, deletion mutations, insertion mutations, inversions or gene amplifications that lead to an increase in at least one biological activity of EGFR, such as elevated tyrosine kinase activity, formation of receptor homodimers and heterodimers, enhanced ligand binding etc. Mutations can be located in any portion of an EGFR gene or regulatory region associated with an EGFR gene and include mutations in exon 18, 19, 20 or 21 or mutations in the kinase domain. Exemplary activating EGFR mutations are G719A, L861X (X being any amino acid), L858R, E746K, L747S, E749Q, A750P, A755V, V765M, , L858P or T790M substitutions, deletion of E746-A750, deletion of R748-P753, insertion of Ala between M766 and A767, insertion of SVA (Ser, Val, Ala) between S768 and V769, and insertion of NS (Asn, Ser) between P772 and H773. Other examples of EGFR activating mutations are known in the art (see e.g., U.S. Pat. Publ. No. US2005/0272083). Information about EGFR and other ErbB receptors including receptor homo- and hetero-dimers, receptor ligands, autophosphorylation sites, and signaling molecules involved in ErbB mediated signaling is known in the art (see e.g., Hynes and Lane, Nature Reviews Cancer 5: 341-354, 2005).

Exemplary c-Met activating mutations include point mutations, deletion mutations, insertion mutations, inversions or gene amplifications that lead to an increase in at least one biological activity of a c-Met protein, such as elevated tyrosine kinase activity, formation of receptor homodimers and heterodimers, enhanced ligand binding etc. Mutations can be located in any portion of the c-Met gene or regulatory regions associated with the gene, such as mutations in the kinase domain of c-Met. Exemplary c-Met activating mutations are mutations at residue positions N375, V13, V923, R175, V136, L229, S323, R988, S1058/T1010 and E168. Methods for detecting EGFR and c-Met mutations or gene amplifications are well known.

Exemplary cancers that are amenable to treatment by the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention include epithelial cell cancers, breast cancer, ovarian cancer, lung cancer, non-small cell lung cancer (NSCLC), lung adenocarcinoma, colorectal cancer, anal cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancer, ovarian cancer, pancreatic cancer, skin cancer, oral cancer, esophageal cancer, vaginal cancer, cervical cancer, cancer of the spleen, testicular cancer, gastric cancer, cancer of the thymus, colon cancer, thyroid cancer, liver cancer, or sporadic or hereditary papillary renal carcinoma (PRCC).

The FN3 domains that specifically bind c-Met and block binding of HGF to c-Met of the invention may be for treatment of tumors, including cancers and benign tumors. Cancers that are amenable to treatment by the c-Met binding FN3 domains of the invention include those that overexpress c-Met. Exemplary cancers that are amenable to treatment by the FN3 domains of the invention include epithelial cell cancers, breast cancer, ovarian cancer, lung cancer, colorectal cancer, anal cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancer, ovarian cancer, pancreatic cancer, skin cancer, oral cancer, esophageal cancer, vaginal cancer, cervical cancer, cancer of the spleen, testicular cancer, and cancer of the thymus.

The FN3 domains that specifically bind EGFR and blocks binding of EGF to the EGFR of the invention may be used for treatment of tumors, including cancers and benign tumors. Cancers that are amenable to treatment by the FN3 domains of the invention include those that overexpress EGFR or variants. Exemplary cancers that are amenable to treatment by the FN3 domains of the invention include epithelial cell cancers, breast cancer, ovarian cancer, lung cancer, colorectal cancer, anal cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancer, ovarian cancer, pancreatic cancer, skin cancer, oral cancer, esophageal cancer, vaginal cancer, cervical cancer, cancer of the spleen, testicular cancer, and cancer of the thymus.

In some methods described herein, the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention may be used to treat a subject with a cancer that is resistant or has acquired resistance to treatment with one or more EGFR inhibitors. Exemplary EGFR inhibitors for which cancer may acquire resistance are anti-EGFR antibodies cetuximab (Erbitux®), pantinumumab (Vectibix®), matuzumab, nimotuzumab, small molecule EGFR inhibitors Tarceva® (erlotinib), IRESSA (gefitinib), EKB-569 (pelitinib, irreversible EGFR TKI), pan-ErbB and other receptor tyrosine kinase inhibitors lapatinib (EGFR and HER2 inhibitor), pelitinib (EGFR and HER2 inhibitor),vandetanib (ZD6474, ZACTIMA™,EGFR, VEGFR2 and RET TKI), PF00299804 (dacomitinib, irreversible pan-ErbB TKI) , CI-1033 (irreversible pan-erbB TKI), afatinib (BIBW2992, irreversible pan-ErbB TKI), AV-412 (dual EGFR and ErbB2 inhibitor)EXEL-7647 (EGFR, ErbB2, GEVGR and EphB4 inhibitor), CO-1686 (irreversible mutant-selective EGFR TKI), AZD9291 (irreversible mutant-selective EGFR TKI),and HKI-272 (neratinib, irreversible EGFR/ErbB2 inhibitor). The methods described herein may be used to treat cancer that is resistant or has acquired resistance to treatment with gefitinib, erlotinib, afatinib, CO-1686, AZD9291 and/or cetuximab. Exemplary bispecific EGFR/c-Met FN3 domain

containing molecules, the EGFR binding FN3 domains or the c-Met binding FN3 domains that can be used are those described herein having amino acid sequences shown in SEQ ID NOs: 18-29, 107-110, 122-137, 194-211, 32-49, 111-114, 212-223, 50-72, 106, 118-121, 138-165, 170-178 or 190-193.

Another aspect of the invention is a method of treating a subject having cancer, comprising administering a therapeutically effective amount of the bispecific EGFR/c-Met FN3 domain containing molecule, the FN3 domain that specifically bind c-Met or the FN3 domain that specifically bind EGFR to a patient in need thereof for a time sufficient to treat the cancer, wherein the subject is resistant or has acquired resistant to treatment with erlotinib, gefitinib, afatinib, CO-1686 (CAS number: 1374640-70-6), AZD9291 or cetuximab.

Various qualitative and/or quantitative methods may be used to determine if a subject is resistant, has developed or is susceptible to developing a resistance to treatment with an EGFR inhibitor. Symptoms that may be associated with resistance to an EGFR inhibitor include, for example, a decline or plateau of the well-being of the patient, an increase in the size of a tumor, arrested or slowed decline in growth of a tumor, and/or the spread of cancerous cells in the body from one location to other organs, tissues or cells. Re-establishment or worsening of various symptoms associated with cancer may also be an indication that a subject has developed or is susceptible to developing resistance to EGFR inhibitors, such as anorexia, cognitive dysfunction, depression, dyspnea, fatigue, hormonal disturbances, neutropenia, pain, peripheral neuropathy, and sexual dysfunction. The symptoms associated with cancer may vary according to the type of cancer. For example, symptoms associated with cervical cancer may include abnormal bleeding, unusual heavy vaginal discharge, pelvic pain that is not related to the normal menstrual cycle, bladder pain or pain during urination, and bleeding between regular menstrual periods, after sexual intercourse, douching, or pelvic exam. Symptoms associated with lung cancer may include persistent cough, coughing up blood, shortness of breath, wheezing chest pain, loss of appetite, losing weight without trying and fatigue. Symptoms for liver cancer may includeloss of appetite and weight, abdominal pain, especially in the upper right part of abdomen that may extend into the back and shoulder, nausea and vomiting, general weakness and fatigue, an enlarged liver, abdominal swelling (ascites), and a yellow discoloration of the skin and the whites of eyes (jaundice). One skilled in oncology may readily identify symptoms associated with a particular cancer type.

Others means to determine if a subject has developed a resistance to an EGFR inhibitor include examining EGFR phosphorylation, ERK1/2 phosphorylation and/or AKT phosphorylation in cancer cells, where increased phosphorylation may be indicative that the subject has developed or is susceptible to developing resistance to an EGFR inhibitor. Methods of determining EGFR, ERK1/2 and/or AKT phosphorylation are well known and described herein. Identification of a subject who has developed a resistance to an EGFR inhibitor may involve detection of elevated c-Met expression levels or elevated c-Met activity, for example, arising from increased levels of circulating HGF, an activating mutation of the c-Met gene or a c-Met gene amplification.

Another embodiment of the invention is a method of treating NSCLC in a patient having an NSCLC tumor or tumor metastasis having an activating EGFR mutation or EGFR gene amplification, comprising administering to the patient a therapeutically effective amount of the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention.

The bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention can be used to treat non-small cell lung cancer (NSCLC), which includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. In some embodiments, cells of the NSCLC have an epithelial phenotype. In some embodiments, the NSCLC has acquired resistance to treatment with one or more EGFR inhibitors.

In NSCLC, specific mutations in the EGFR gene are associated with high response rates (70-80%) to EGFR tyrosine kinase inhibitors (EGFR-TKIs). A 5 amino acid deletion in exon 19 or the point mutation L858R in EGFR are associated with EGFR-TKI sensitivity (Nakata and Gotoh, Expert Opin Ther Targets 16 :771-781, 2012). These mutations result in a ligand-independent activation of the EGFR kinase activity. Activating EGFR mutations occur in 10-30% of NSCLC patients and are significantly more common in East Asians, women, never smokers, and patients with adenocarcinoma histology (Janne and Johnson Clin Cancer Res 12(14 Suppl): 4416s-4420s, 2006). EGFR gene amplification is also strongly correlated with response after EGFR-TKI treatment (Cappuzzo *et al.,* J Natl Cancer Inst 97:643-55, 2005).

Although the majority of NSCLC patients with EGFR mutations initially respond to EGFR TKI therapy, virtually all acquire resistance that prevents a durable response. 50-60% of patients acquire resistance due to a second-site point mutation in the kinase domain of EGFR (T790M). Nearly 60% of all tumors that become resistant to EGFR

tyrosine kinase inhibitors increase c-Met expression, amplify the c-Met gene, or increase its only known ligand, HGF (Turke *et al.,* Cancer Cell, 17:77-88, 2010).

Another embodiments of the invention is a method of treating patient having cancer, comprising administering a therapeutically effective amount of the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention to a patient in need thereof for a time sufficient to treat the cancer, wherein the cancer is associated with an EGFR activating mutation, an EGFR gene amplification, a c-Met activating mutation or a c-Met gene amplification.

In some embodiments the EGFR activating mutation is G719A, G719X (X being any amino acid), L861X (X being any amino acid), L858R, E746K, L747S, E749Q, A750P, A755V, V765M, L858P or T790M substitution, deletion of E746-A750, deletion of R748-P753, insertion of Ala (A) between M766 and A767, insertion of Ser, Val and Ala (SVA) between S768 and V769, and insertion of Asn and Ser (NS) between P772 and H773.

Another embodiments of the invention is a method of treating patient having cancer, comprising administering a therapeutically effective amount of the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention to a patient in need thereof for a time sufficient to treat the cancer, wherein the cancer is associated with an EGFR mutation L858R, T790M or deletion of residues E746-A750 (del(E746, A750)), EGFR amplification or c-Met amplification.

In some embodiments, the cancer is associated with wild type EGFR and wild type c-Met.

In some embodiments, the cancer is associated with wild type EGFR and c-Met amplification.

In some embodiments, the cancer is associated with EGFR L858R and T790M mutations and wild type c-Met.

In some embodiments, the cancer is associated with EGFR deletion del (E764, A750) and wild type c-Met.

In some embodiments, the cancer is associated with EGFR deletion del(E764, A750) and c-Met amplification.

In some embodiments, the cancer is associated with EGFR deletion del(E764, A750), EGFR amplification and c-Met amplification.

In some embodiments, the patient has a NSCLC associated with EGFR L858R and T790M mutations and wild type c-Met.

In some embodiments, the patient has a NSCLC associated with EGFR amplification and wild type c-Met.

In some embodiments, the patient has a NSCLC associated with EGFR amplification and c-Met amplification.

In some embodiments, the patient has a NSCLC associated with EGFR deletion del(E764, A750) and wild type c-Met.

In some embodiments, the patient has a NSCLC associated with EGFR deletion del(E764, A750) and c-Met amplification. Amplification of EGFR or c-Met may be evaluated by standard methods, for example by determining the copy number of the EGFR or c-Met gene by southern blotting, FISH, or comparative genomic hybridization (CGH)

The terms "treat" or "treatment" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the development or spread of cancer. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount of the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention to elicit a desired response in the individual. Exemplary indicators of an effective EGFR/c-Met therapeutic that may decline or abate in association with resistance include, for example, improved well-being of the patient, decrease or shrinkage of the size of a tumor, arrested or slowed

growth of a tumor, and/or absence of metastasis of cancer cells to other locations in the body.

Administration/ Pharmaceutical Compositions

The invention provides for pharmaceutical compositions the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR binding FN3 domain or the c-Met binding FN3 domain of the invention and a pharmaceutically acceptable carrier. For therapeutic use, the bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR-binding FN3 domains or the c-Met-binding FN3 domains of the invention may be prepared as pharmaceutical compositions containing an effective amount of the domain or molecule as an active ingredient in a pharmaceutically acceptable carrier. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the active compound is administered. Such vehicles can be 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. For example, 0.4% saline and 0.3% glycine can be used. These solutions are sterile and generally free of particulate matter. They may be sterilized by conventional, well-known sterilization techniques (*e.g.*, filtration). The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, stabilizing, thickening, lubricating and coloring agents, etc. The concentration of the molecules of the invention in such pharmaceutical formulation can vary widely, *i.e.*, from less than about 0.5%, usually at least about 1% to as much as 15 or 20% by weight and will be selected primarily based on required dose, fluid volumes, viscosities, etc., according to the particular mode of administration selected. Suitable vehicles and formulations, inclusive of other human proteins, e.g., human serum albumin, are described, for example, in e.g. Remington: The Science and Practice of Pharmacy, 21st Edition, Troy, D.B. ed., Lipincott Williams and Wilkins, Philadelphia, PA 2006, Part 5, Pharmaceutical Manufacturing pp 691-1092, See especially pp. 958-989.

The mode of administration for therapeutic use of the bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR binding FN3 domains or the c-Met binding FN3 domains of the invention may be any suitable route that delivers the agent to the host, such as parenteral administration, e.g., intradermal, intramuscular, intraperitoneal, intravenous or subcutaneous, pulmonary; transmucosal (oral, intranasal, intravaginal, rectal), using a formulation in a tablet, capsule, solution, powder, gel, particle; and contained in a syringe,

an implanted device, osmotic pump, cartridge, micropump; or other means appreciated by the skilled artisan, as well known in the art. Site specific administration may be achieved by for example intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracerebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intracardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravascular, intravesical, intralesional, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery.

Thus, a pharmaceutical composition of the invention for intramuscular injection could be prepared to contain 1 ml sterile buffered water, and between about 1 ng to about 100 mg, *e.g*. about 50 ng to about 30 mg or more preferably, about 5 mg to about 25 mg, of the FN3 domain of the invention.

The bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR binding FN3 domains or the c-Met binding FN3 domains of the invention may be administered to a patient by any suitable route, for example parentally by intravenous (IV) infusion or bolus injection, intramuscularly or subcutaneously or intraperitoneally. IV infusion can be given over as little as 15 minutes, but more often for 30 minutes, 60 minutes, 90 minutes or even 2 or 3 hours. The bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR binding FN3 domains or the c-Met binding FN3 domains of the invention may also be injected directly into the site of disease (e.g., the tumor itself). The dose given to a patient having a cancer is sufficient to alleviate or at least partially arrest the disease being treated ("therapeutically effective amount") and may be sometimes 0.1 to 10 mg/kg body weight, for example 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 mg/kg, but may even higher, for example 15, 20, 30, 40, 50, 60, 70, 80, 90 or 100 mg/kg. A fixed unit dose may also be given, for example, 50, 100, 200, 500 or 1000 mg, or the dose may be based on the patient's surface area, e.g., 400, 300, 250, 200, or 100 mg/m^2. Usually between 1 and 8 doses, (e.g., 1, 2, 3, 4, 5, 6, 7 or 8) may be administered to treat cancer, but 10, 12, 20 or more doses may be given. Administration of the bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR binding FN3 domains or the c-Met binding FN3 domains of the invention may be repeated after one day, two days, three days, four days, five days, six days, one week, two weeks, three weeks, one month, five weeks, six weeks, seven weeks, two months, three months, four months, five months, six months or longer. Repeated courses of treatment are also possible, as is chronic administration. The repeated administration may be at the same dose or at a different dose.

For example, a pharmaceutical composition of the bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR binding FN3 domains or the c-Met binding FN3 domains of the invention for intravenous infusion may be made up to contain about 200 ml of sterile Ringer's solution, and about 8 mg to about 2400 mg, about 400 mg to about 1600 mg, or about 400 mg to about 800 mg of the bispecific EGFR/c-Met antibody for administration to a 80 kg patient. Methods for preparing parenterally administrable compositions are well known and are described in more detail in, for example, "Remington's Pharmaceutical Science", 15th ed., Mack Publishing Company, Easton, PA.

The bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR-binding FN3 domains or the c-Met-binding FN3 domains of the invention can be lyophilized for storage and reconstituted in a suitable carrier prior to use. This technique has been shown to be effective with conventional protein preparations and art-known lyophilization and reconstitution techniques can be employed.

The bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR-binding FN3 domains or the c-Met-binding FN3 domains of the invention may be administered to a subject in a single dose or the administration may be repeated, e.g. after one day, two days, three days, five days, six days, one week, two weeks, three weeks, one month, five weeks, six weeks, seven weeks, two months or three months. The repeated administration can be at the same dose or at a different dose. The administration can be repeated once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times, or more.

The bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR-binding FN3 domains or the c-Met-binding FN3 domains of the invention may be administered in combination with a second therapeutic agent simultaneously, sequentially or separately. The second therapeutic agent may be a chemotherapeutic agent, an anti-angiogenic agent, or a cytotoxic drug. When used for treating cancer, the bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR-binding FN3 domains or the c-Met-binding FN3 domains may be used in combination with conventional cancer therapies, such as surgery, radiotherapy, chemotherapy or combinations thereof. Exemplary agents that can be used in combination with the FN3 domains of the invention are antagonists of HER2, HER3, HER4, VEGF, and protein tyrosine kinase inhibitors such as Iressa® (gefitinib) and Tarceva (erlotinib).

The bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR-binding FN3 domains or the c-Met-binding FN3 domainmay be administered together with any one or more of the chemotherapeutic drugs or other anti-cancer therapeutics known to

those of skill in the art. Chemotherapeutic agents are chemical compounds useful in the treatment of cancer and include growth inhibitory agents or other cytotoxic agents and include alkylating agents, anti-metabolites, anti-microtubule inhibitors, topoisomerase inhibitors, receptor tyrosine kinase inhibitors, angiogenesis inhibitors and the like. Examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethylenethiophosphaoramide and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabicin, carminomycin, carzinophilin, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-FU; folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogues such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogues such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfornithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone; mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK®; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2′,2′-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside (“Ara-C”); cyclophosphamide; thiotepa; members of taxoid or taxane family, such as paclitaxel (TAXOL®docetaxel (TAXOTERE®) and analogues thereof; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate;

platinum analogues such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine; navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoic acid; esperamicins; capecitabine; inhibitors of receptor tyrosine kinases and/or angiogenesis, including sorafenib (NEXAVAR®), sunitinib (SUTENT®), pazopanib (VOTRIENT™), toceranib (PALLADIA™), vandetanib (ZACTIMA™), cediranib (RECENTIN®), regorafenib (BAY 73-4506), axitinib (AG013736), lestaurtinib (CEP-701), erlotinib (TARCEVA®), gefitinib (IRESSA™), BIBW 2992 (TOVOK™), lapatinib (TYKERB®), neratinib (HKI-272), and the like, and pharmaceutically acceptable salts, acids or derivatives of any of the above. Also included in this definition are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (FARESTON®); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; and pharmaceutically acceptable salts, acids or derivatives of any of the above. Other conventional cytotoxic chemical compounds as those disclosed in Wiemann et al., 1985, in *Medical Oncology* (Calabresi et aL, eds.), Chapter 10, McMillan Publishing, are also applicable to the methods of the present invention.

Exemplary agents that may be used in combination with the bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR-binding FN3 domains or the c-Met-binding FN3 domaininclude tyrosine kinase inhibitors and targeted anti-cancer therapies such as Iressa® (gefitinib) and

Tarceva (erlotinib) and other antagonists of HER2, HER3, HER4 or VEGF. Exemplary HER2 antagonists include CP-724-714, HERCEPTIN™ (trastuzumab), OMNITARG™ (pertuzumab), TAK-165, lapatinib (EGFR and HER2 inhibitor), and GW-282974, . Exemplary HER3 antagonists include anti-Her3 antibodies (see e.g., U.S. Pat. Publ. No. US2004/0197332). Exemplary HER4 antagonists include anti-HER4 siRNAs (see e.g., Maatta *et al.,* Mol Biol Cell 17: 67-79, 2006,. An exemplary VEGF antagonist is Bevacizumab (Avastin™).

When a small molecule is used in combination with the bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR-binding FN3 domains or the c-Met-binding FN3 domains of the invention, it is typically administered more often, preferably once a day, but 2, 3, 4 or more times per day is also possible, as is every two days, weekly or at some other interval. Small molecule drugs are often taken orally but parenteral

administration is also possible, e.g., by IV infusion or bolus injection or subcutaneously or intramuscularly. Doses of small molecule drugs may typically be from 10 to 1000 mg, or about 100, 150, 200 or 250 mg.

When the bispecific EGFR/c-Met FN3 domain containing molecules, the EGFR-binding FN3 domains or the c-Met-binding FN3 domains of the invention is administered in combination with a second therapeutic agent, the combination may take place over any convenient timeframe. For example, the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR-binding FN3 domain or the c-Met-binding FN3 domain of the invention and the second therapeutic agent may be administered to a patient on the same day, and even in the same intravenous infusion. However, the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR-binding FN3 domain or the c-Met-binding FN3 domain of the invention and the second therapeutic agent may also be administered on alternating days or alternating weeks, fortnights or months, and so on. In some methods, the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR-binding FN3 domain or the c-Met-binding FN3 domain of the invention and the second therapeutic agent are administered with sufficient proximity in time that they are simultaneously present (e.g., in the serum) at detectable levels in the patient being treated. In some methods, an entire course of treatment of the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR-binding FN3 domain or the c-Met-binding FN3 domain of the invention consisting of a number of doses over a time period is followed or preceded by a course of treatment of the second therapeutic agent also consisting of a number of doses. In some methods, treatment with the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR-binding FN3 domain or the c-Met-binding FN3 domain of the invention administered second is begun if the patient has resistance or develops resistance to the second therapeutic agent administered initially. The patient may receive only a single course or multiple courses of treatment with one or both the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR-binding FN3 domain or the c-Met-binding FN3 domain of the invention and the second therapeutic agent. A recovery period of 1, 2 or several days or weeks may be used between administration of the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR-binding FN3 domain or the c-Met-binding FN3 domain of the invention and the second therapeutic agent. When a suitable treatment regiment has already been established for the second therapeutic agent, that regimen may be used in combination with the bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR-binding FN3 domain or the c-Met-

binding FN3 domain of the invention. For example, Tarceva® (erlotinib) is taken as a 100 mg or 150 mg pill once a day, and Iressa® (gefitinib) is taken as 250 mg tablet daily.

The bispecific EGFR/c-Met FN3 domain containing molecule, the EGFR-binding FN3 domain or the c-Met-binding FN3 domain of the invention, optionally in combination with the second therapeutic agent may be administered together with any form of radiation therapy including external beam radiation, intensity modulated radiation therapy (IMRT) and any form of radiosurgery including Gamma Knife, Cyberknife, Linac, and interstitial radiation (e.g. implanted radioactive seeds, GliaSite balloon), and/or with surgery. Combination with radiation therapy can be especially appropriate for head and neck cancer and brain tumors.

While having described the invention in general terms, the embodiments of the invention will be further disclosed in the following examples that should not be construed as limiting the scope of the claims.

EXAMPLE 1. Construction of Tencon libraries

Tencon (SEQ ID NO: 1) is an immunoglobulin-like scaffold, fibronectin type III (FN3) domain, designed from a consensus sequence of fifteen FN3 domains from human tenascin-C (Jacobs *et al.,* Protein Engineering, Design, and Selection, 25:107-117, 2012; U.S. Pat. Publ. No. 2010/0216708). The crystal structure of Tencon shows six surface-exposed loops that connect seven beta-strands. These loops, or selected residues within each loop, can be randomized in order to construct libraries of fibronectin type III (FN3) domains that can be used to select novel molecules that bind to specific targets.

Tencon:

LPAPKNLVVSEVTEDSLRLSWTAPDAAFDSFLIQYQESEKVGEAINLTVPGSERSYDLTGLK
PGTEYTVSIYGVKGGHRSNPLSAEFTT (SEQ ID NO 1):

Construction of TCL1 library

A library designed to randomize only the FG loop of Tencon (SEQ ID NO: 1), TCL1, was constructed for use with the *cis*-display system (Jacobs *et al.,* Protein Engineering, Design, and Selection, 25:107-117, 2012). In this system, a single-strand DNA incorporating sequences for a Tac promoter, Tencon library coding sequence, RepA coding sequence, cis-element, and ori element is produced. Upon expression in an *in vitro* transcription/translation system, a complex is produced of the Tencon-RepA fusion protein bound in *cis* to the DNA from which it is encoded. Complexes that bind to a target

molecule are then isolated and amplified by polymerase chain reaction (PCR), as described below.

Construction of the TCL1 library for use with *cis*-display was achieved by successive rounds of PCR to produce the final linear, double-stranded DNA molecules in two halves; the 5' fragment contains the promoter and Tencon sequences, while the 3' fragment contains the *repA* gene and the cis- and ori elements. These two halves are combined by restriction digest in order to produce the entire construct. The TCL1 library was designed to incorporate random amino acids only in the FG loop of Tencon, KGGHRSN (SEQ ID NO: 86). NNS codons were used in the construction of this library, resulting in the possible incorporation of all 20 amino acids and one stop codon into the FG loop. The TCL1 library contains six separate sub-libraries, each having a different randomized FG loop length, from 7 to 12 residues, in order to further increase diversity. Design of tencon-based libraries are shown in Table 2.

Table 2.

Library	BC Loop Design	FG Loop Design
WT Tencon	TAPDAAFD*	KGGHRSN**
TCL1	TAPDAAFD*	XXXXXXX
		XXXXXXXX
		XXXXXXXXX
		XXXXXXXXXX
		XXXXXXXXXXX
		XXXXXXXXXXXX
TCL2	########	#####S##

*TAPDAAFD: residues 22-28 of SEQ ID NO: 1;

**KGGHRSN: SEQ ID NO: 86

X refers to degenerate amino acids encoded by NNS codons.

refers to the "designed distribution of amino acids" described in the text.

To construct the TCL1 library, successive rounds of PCR were performed to append the Tac promoter, build degeneracy into the FG loop, and add necessary restriction sites for final assembly. First, a DNA sequence containing the promoter sequence and Tencon sequence 5' of the FG loop was generated by PCR in two steps. DNA corresponding to the full Tencon gene sequence was used as a PCR template with primers POP2220 (SEQID NO: 2) and TC5'toFG (SEQID NO: 3). The resulting PCR product from this reaction was used as a template for the next round of PCR amplification with primers 130mer (SEQID NO: 4) and Tc5'toFG to complete the appending of the 5' and promoter sequences to Tencon. Next, diversity was introduced into the FG loop by amplifying the DNA product produced in the first step with forward primer POP2222 (SEQID NO: 5), and reverse primers TCF7 (SEQID NO: 6), TCF8 (SEQID NO: 7), TCF9 (SEQID NO: 8), TCF10 (SEQID NO: 9), TCF11 (SEQID N NO: 10), or TCF12 (SEQID NO: 11), which contain degenerate nucleotides. At least eight 100 μL PCR reactions were performed for each sub-library to minimize PCR cycles and maximize the diversity of the library. At least 5 μg of this PCR product were gel-purified and used in a subsequent PCR step, with primers POP2222 (SEQ ID NO: 5) and POP2234 (SEQID NO: 12), resulting in the attachment of a 6xHis tag and NotI restriction site to the 3' end of the Tencon sequence. This PCR reaction was carried out using only fifteen PCR cycles and at least 500 ng of template DNA. The resulting PCR product was gel-purified, digested with NotI restriction enzyme, and purified by Qiagen column.

The 3' fragment of the library is a constant DNA sequence containing elements for display, including a PspOMI restriction site, the coding region of the *repA* gene, and the cis- and ori elements. PCR reactions were performed using a plasmid (pCR4Blunt) (Invitrogen) containing this DNA fragment with M13 Forward and M13 Reverse primers. The resulting PCR products were digested by PspOMI overnight and gel-purified. To ligate the 5' portion of library DNA to the 3' DNA containing the *repA* gene, 2 pmol of 5' DNA were ligated to an equal molar amount of 3' *repA* DNA in the presence of NotI and PspOMI enzymes and T4 ligase. After overnight ligation at 37°C, a small portion of the ligated DNA was run on a gel to check ligation efficiency. The ligated library product was split into twelve PCR amplifications and a 12-cycle PCR reaction was run with primer pair POP2250 (SEQID NO: 13) and DidLigRev (SEQID NO: 14). The DNA yield for each sub-library of TCL1 library ranged from 32-34 μg.

To assess the quality of the library, a small portion of the working library was amplified with primers Tcon5new2 (SEQID NO: 15) and Tcon6 (SEQID NO: 16), and

was cloned into a modified pET vector via ligase-independent cloning. The plasmid DNA was transformed into BL21-GOLD (DE3) competent cells (Stratagene) and 96 randomly picked colonies were sequenced using a T7 promoter primer. No duplicate sequences were found. Overall, approximately 70-85% of clones had a complete promoter and Tencon coding sequence without frame-shift mutation. The functional sequence rate, which excludes clones with STOP codons, was between 59% and 80%.

Construction of TCL2 Library

TCL2 library was constructed in which both the BC and the FG loops of Tencon were randomized and the distribution of amino acids at each position was strictly controlled. Table 3 shows the amino acid distribution at desired loop positions in the TCL2 library. The designed amino acid distribution had two aims. First, the library was biased toward residues that were predicted to be structurally important for Tencon folding and stability based on analysis of the Tencon crystal structure and/or from homology modeling. For example, position 29 was fixed to be only a subset of hydrophobic amino acids, as this residue was buried in the hydrophobic core of the Tencon fold. A second layer of design included biasing the amino acid distribution toward that of residues preferentially found in the heavy chain HCDR3 of antibodies, to efficiently produce high-affinity binders (Birtalan *et al.,* J Mol Biol 377:1518-28, 2008; Olson *et al.,* Protein Sci 16:476-84, 2007). Towards this goal, the "designed distribution" of Table 3 refers to the distribution as follows: 6% alanine, 6% arginine, 3.9% asparagine, 7.5% aspartic acid, 2.5% glutamic acid, 1.5% glutamine, 15% glycine, 2.3% histidine, 2.5% isoleucine, 5% leucine, 1.5% lysine, 2.5% phenylalanine, 4% proline, 10% serine, 4.5% threonine, 4% tryptophan, 17.3% tyrosine, and 4% valine. This distribution is devoid of methionine, cysteine, and STOP codons.

Table 3.

Residue Position*	WT residues	Distribution in the TCL2 library
22	T	designed distribution
23	A	designed distribution
24	P	50% P + designed distribution
25	D	designed distribution

26	A	20% A + 20% G + designed distribution
27	A	designed distribution
28	F	20% F, 20% I, 20% L, 20% V, 20% Y
29	D	33% D, 33% E, 33% T
75	K	designed distribution
76	G	designed distribution
77	G	designed distribution
78	H	designed distribution
79	R	designed distribution
80	S	100% S
81	N	designed distribution
82	P	50% P + designed distribution

*residue numbering is based on Tencon sequence of SEQ ID NO: 1

The 5' fragment of the TCL2 library contained the promoter and the coding region of Tencon (SEQ ID NO: 1), which was chemically synthesized as a library pool (Sloning Biotechnology). This pool of DNA contained at least 1 x 10^{11} different members. At the end of the fragment, a BsaI restriction site was included in the design for ligation to *RepA*.

The 3' fragment of the library was a constant DNA sequence containing elements for display including a 6xHis tag, the coding region of the *repA* gene, and the cis-element. The DNA was prepared by PCR reaction using an existing DNA template (above), and primers LS1008 (SEQID NO: 17) and DidLigRev (SEQID NO: 14). To assemble the complete TCL2 library, a total of 1 μg of BsaI-digested 5' Tencon library DNA was ligated to 3.5 μg of the 3' fragment that was prepared by restriction digestion with the same enzyme. After overnight ligation, the DNA was purified by Qiagen column and the DNA was quantified by measuring absorbance at 260 nm. The ligated library product was amplified by a 12-cycle PCR reaction with primer pair POP2250 (SEQID NO: 13) and DidLigRev (SEQID NO: 14). A total of 72 reactions were performed, each containing 50 ng of ligated DNA products as a template. The total yield of TCL2 working library DNA was about 100 μg. A small portion of the working library was sub-cloned and sequenced, as described above for library TCL1. No duplicate sequences were found. About 80% of the sequences contained complete promoter and Tencon coding sequences with no frame-shift mutations.

Construction of TCL14 Library

The top (BC, DE, and FG) and the bottom (AB, CD, and EF) loops, e.g., the reported binding surfaces in the FN3 domains are separated by the beta-strands that form the center of the FN3 structure. Alternative surfaces residing on the two "sides" of the FN3 domains having different shapes than the surfaces formed by loops only are formed at one side of the FN3 domain by two anti-parallel beta-strands, the C and the F beta-strands, and the CD and FG loops, and is herein called the C-CD-F-FG surface.

A library randomizing an alternative surface of Tencon was generated by randomizing select surface exposed residues of the C and F strands, as well as portions of the CD and FG loops as shown in Figure 1. A Tencon variant, Tencon27 (SEQ ID NO: 99) having following substitutions when compared to Tencon (SEQ ID NO: 1) was used to generate the library; E11R L17A, N46V, E86I. A full description of the methods used to construct this library is described in US. Pat. Publ. No. US2013/0226834.

EXAMPLE 2: Selection of fibronectin type III (FN3) domains that bind EGFR and Inhibit EGF Binding

Library screening

Cis-display was used to select EGFR binding domains from the TCL1 and TCL2 libraries. A recombinant human extracellular domain of EGFR fused to an IgG1 Fc (R&D Systems) was biotinylated using standard methods and used for panning (residues 25-645 of full length EGFR of SEQ ID NO: 73). For *in vitro* transcription and translation (ITT), 2-6 μg of library DNA were incubated with 0.1 mM complete amino acids, 1X S30 premix components, and 30 μL of S30 extract (Promega) in a total volume of 100 μL and incubated at 30°C. After 1 hour, 450 μL of blocking solution (PBS pH 7.4, supplemented with 2% bovine serum albumin, 100 μg/mL herring sperm DNA, and 1 mg/mL heparin) were added and the reaction was incubated on ice for 15 minutes. EGFR-Fc:EGF complexes were assembled at molar ratios of 1:1 and 10:1 EGFR to EGF by mixing recombinant human EGF (R&D Systems) with biotinylated recombinant EGFR-Fc in blocking solution for 1 hour at room temperature. For binding, 500 μL of blocked ITT reactions were mixed with 100 μL of EGFR-Fc:EGF complexes and incubated for 1 hour at room temperature, after which bound complexes were pulled down with magnetic neutravidin or streptavidin beads (Seradyne). Unbound library members were removed by successive washes with PBST and PBS. After washing, DNA was eluted from the bound complexes by heating to

65°C for 10 minutes, amplified by PCR, and attached to a DNA fragment encoding RepA by restriction digestion and ligation for further rounds of panning. High affinity binders were isolated by successively lowering the concentration of target EGFR-Fc during each round from 200 nM to 50 nM and increasing the washing stringency. In rounds 4 and 5, unbound and weakly bound FN3 domains were removed by washing in the presence of a 10-fold molar excess of non-biotinylated EGFR-Fc overnight in PBS.

Following panning, selected FN3 domains were amplified by PCR using oligos Tcon5new2 (SEQID NO: 15) and Tcon6 (SEQID NO: 16), subcloned into a pET vector modified to include a ligase independent cloning site, and transformed into BL21-GOLD (DE3) (Stratagene) cells for soluble expression in *E. coli* using standard molecular biology techniques. A gene sequence encoding a C-terminal poly-histidine tag was added to each FN3 domain to enable purification and detection. Cultures were grown to an optical density of 0.6-0.8 in 2YT medium supplemented with 100 μg/mL carbenicillin in 1-mL 96-well blocks at 37°C before the addition of IPTG to 1 mM, at which point the temperature was reduced to 30°C. Cells were harvested approximately 16 hours later by centrifugation and frozen at -20°C. Cell lysis was achieved by incubating each pellet in 0.6 mL of BugBuster® HT lysis buffer (Novagen EMD Biosciences) with shaking at room temperature for 45 minutes.

Selection of FN3 domains that Bind EGFR on Cells

To assess the ability of different FN3 domains to bind EGFR in a more physiological context, their ability to bind A431 cells was measured. A431 cells (American Type Culture Collection, cat. #CRL-1555) over-express EGFR with ~2 x 10^6 receptors per cell. Cells were plated at 5,000/well in opaque black 96-well plates and allowed to attach overnight at 37°C, in a humidified 5% CO_2 atmosphere. FN3 domain-expressing bacterial lysates were diluted 1,000-fold into FACS stain buffer (Becton Dickinson) and incubated for 1 hour at room temperature in triplicate plates. Lysates were removed and cells were washed 3 times with 150 μL/well of FACS stain buffer. Cells were incubated with 50 μL/well of anti-penta His-Alexa488 antibody conjugate (Qiagen) diluted 1:100 in FACS stain buffer for 20 minutes at room temperature. Cells were washed 3 times with 150 μL/well of FACS stain buffer, after which wells were filled with 100 μL of FACS stain buffer and read for fluorescence at 488 nm using an Acumen eX3 reader. Bacterial lysates containing FN3 domains were screened for their ability to bind A431 cells (1320 crude bacterial lysates for TCL1 and TCL2 libraries) and 516 positive

clones were identified, where binding was ≥10-fold over the background signal. 300 lysates from the TCL14 library were screened for binding, resulting in 58 unique FN3 domain sequences that bind to EGFR.

Selection of FN3 domains that Inhibit EGF Binding to EGFR on Cells

To better characterize the mechanism of EGFR binding, the ability of various identified FN3 domain clones to bind EGFR in an EGF-competitive manner was measured using A431 cells and run in parallel with the A431 binding assay screen. A431 cells were plated at 5,000/well in opaque black 96-well plates and allowed to attach overnight at 37°C in a humidified 5% CO_2 atmosphere. Cells were incubated with 50 μL/well of 1:1,000 diluted bacterial lysate for 1 hour at room temperature in triplicate plates. Biotinylated EGF (Invitrogen, cat. #E-3477) was added to each well for a final concentration of 30 ng/mL and incubated for 10 minutes at room temperature. Cells were washed 3 times with 150 μL/well of FACS stain buffer. Cells were incubated with 50 μL/well of streptavidin-phycoerythrin conjugate (Invitrogen) diluted 1:100 in FACS stain buffer for 20 minutes at room temperature. Cells were washed 3 times with 150 μL/well of FACS stain buffer, after which wells were filled with 100 μL of FACS stain buffer and read for fluorescence at 600 nm using an Acumen eX3 reader.

Bacterial lysates containing the FN3 domains were screened in the EGF competition assay described above. 1320 crude bacterial lysates from TCL1 and TCL2 libraries were screened resulting in 451 positive clones that inhibited EGF binding by > 50%.

Expression and Purification of identified FN3 domains binding EGFR

His-tagged FN3 domains were purified from clarified *E. coli* lysates with His MultiTrap™ HP plates (GE Healthcare) and eluted in buffer containing 20 mM sodium phosphate, 500 mM sodium chloride, and 250 mM imidazole at pH 7.4. Purified samples were exchanged into PBS pH 7.4 for analysis using PD MultiTrap™ G-25 plates (GE Healthcare).

Size Exclusion Chromatography Analysis

Size exclusion chromatography was used to determine the aggregation state of the FN3 domains binding EGFR. Aliquots (10 μL) of each purified FN3 domain were injected onto a Superdex 75 5/150 column (GE Healthcare) at a flow rate of 0.3 mL/min in a mobile phase of PBS pH 7.4. Elution from the column was monitored by absorbance at 280 nm. FN3 domains that exhibited high levels of aggregation by SEC were excluded from further analysis.

Off-Rate of Selected EGFR-binding FN3 domains from EGFR-Fc

Select EGFR-binding FN3 domains were screened to identify those with slow off-rates (k_{off}) in binding to EGFR-Fc on a ProteOn XPR-36 instrument (Bio-Rad) to facilitate selection of high affinity binders. Goat anti-human Fc IgG (R&D systems), at a concentration of 5 μg/mL, was directly immobilized via amine coupling (at pH 5.0) on all 6 ligand channels in horizontal orientation on the chip with a flow rate of 30 μL/min in PBS containing 0.005% Tween-20. The immobilization densities averaged about 1500 Response Units (RU) with less than 5% variation among different channels. EGFR-Fc was captured on the anti-human Fc IgG surface to a density around 600 RU in vertical ligand orientation. All tested FN3 domains were normalized to a concentration of 1 μM and tested for their binding in horizontal orientation. All 6 analyte channels were used for the FN3 domains to maximize screening throughput. The dissociation phase was monitored for 10 minutes at a flow rate of 100 μL/min. The inter-spot binding signals were used as references to monitor non-specific binding between analytes and the immobilized IgG surface, and were subtracted from all binding responses. The processed binding data were locally fit to a 1:1 simple Langmuir binding model to extract the k_{off} for each FN3 domain binding to captured EGFR-Fc.

Inhibition of EGF-Stimulated EGFR Phosphorylation

Purified EGFR-binding FN3 domains were tested for their ability to inhibit EGF-stimulated phosphorylation of EGFR in A431 cells at a single concentration. EGFR phosphorylation was monitored using the EGFR phospho(Tyr1173) kit (Meso Scale Discovery). Cells were plated at 20,000/well in clear 96-well tissue culture-treated plates (Nunc) in 100 μL/well of RPMI medium (Gibco) containing GlutaMAX™ with 10% fetal

bovine serum (FBS) (Gibco) and allowed to attach overnight at 37°C in a humidified 5% CO_2 atmosphere. Culture medium was removed completely and cells were starved overnight in 100 μL/well of medium containing no FBS at 37°C in a humidified 5% CO_2 atmosphere. Cells were then treated with 100 μL/well of pre-warmed (37°C) starvation medium containing EGFR-binding FN3 domains at a concentration of 2 μM for 1 hour at 37°C in a humidified 5% CO_2 atmosphere. Controls were treated with starvation medium only. Cells were stimulated by the addition and gentle mixing of 100 μL/well of pre-warmed (37°C) starvation medium containing 100 ng/mL recombinant human EGF (R&D Systems, cat. #236-EG), for final concentrations of 50 ng/mL EGF and 1 μM EGFR-binding FN3 domain, and incubation at 37°C, 5% CO_2 for 15 minutes. One set of control wells was left un-stimulated as negative controls. Medium was completely removed and cells were lysed with 100 μL/well of Complete Lysis Buffer (Meso Scale Discovery) for 10 minutes at room temperature with shaking, as per the manufacturer's instructions. Assay plates configured for measuring EGFR phosphorylated on tyrosine 1173 (Meso Scale Discovery) were blocked with the provided blocking solution as per the manufacturer's instructions at room temperature for 1.5-2 hours. Plates were then washed 4 times with 200 μL/well of 1X Tris Wash Buffer (Meso Scale Discovery). Aliquots of cell lysate (30 μL/well) were transferred to assay plates, which were covered with plate sealing film (VWR) and incubated at room temperature with shaking for 1 hour. Assay plates were washed 4 times with 200 μL/well of Tris Wash Buffer, after which 25 μL of ice-cold Detection Antibody Solution (Meso Scale Discovery) were added to each well, being careful not to introduce bubbles. Plates were incubated at room temperature with shaking for 1 hour, followed by 4 washes with 200 μL/well of Tris Wash Buffer. Signals were detected by addition of 150 μL/well of Read Buffer (Meso Scale Discovery) and reading on a SECTOR® Imager 6000 instrument (Meso Scale Discovery) using manufacturer-installed assay-specific default settings. Percent inhibition of the EGF-stimulated positive control signal was calculated for each EGFR-binding FN3 domain.

Inhibition of EGF-stimulated EGFR phosphorylation was measured for 232 identified clones from the TCL1 and TCL2 libraries. 22 of these clones inhibited EGFR phosphorylation by $\geq$50% at 1 μM concentration. After removal of clones that either expressed poorly or were judged to be multimeric by size exclusion chromatography, nine clones were carried forward for further biological characterization. The BC and FG loop sequences of these clones are shown in Table 4. Eight of the nine selected clones had a common FG loop sequence (HNVYKDTNMRGL; SEQ ID NO: 95) and areas of significant similarity were seen between several clones in their BC loop sequences.

Table 4.

FN3 Domain		BC Loop		FG Loop	
Clone ID	SEQ ID NO:	Sequence	SEQ ID NO:	Sequence	SEQ ID NO:
P53A1R5-17	18	ADPHGFYD	87	HNVYKDTNMRGL	95
P54AR4-17	19	TYDRDGYD	88	HNVYKDTNMRGL	95
P54AR4-47	20	WDPFSFYD	89	HNVYKDTNMRGL	95
P54AR4-48	21	DDPRGFYE	90	HNVYKDTNMRGL	95
P54AR4-73	22	TWPYADLD	91	HNVYKDTNMRGL	95
P54AR4-74	23	GYNGDHFD	92	HNVYKDTNMRGL	95
P54AR4-81	24	DYDLGVYD	93	HNVYKDTNMRGL	95
P54AR4-83	25	DDPWDFYE	94	HNVYKDTNMRGL	95
P54CR4-31	26	TAPDAAFD	85	LGSYVFEHDVM	96

EXAMPLE 3: Characterization of EGFR-binding FN3 domains that Inhibit EGF Binding

Large-scale Expression, Purification, and Endotoxin Removal

The FN3 domains shown in Table 4 were scaled up to provide more material for detailed characterization. An overnight culture containing each EGFR-binding FN3 domain variant was used to inoculate 0.8 L of Terrific broth medium supplemented with 100 g/mL ampicillin at a 1/80 dilution of overnight culture into fresh medium, and incubated with shaking at 37°C. The culture was induced when the optical density at 600 nm reached ~1.2-1.5 by addition of IPTG to a final concentration of 1 mM and the temperature was reduced to 30°C. After 4 hours, cells were collected by centrifugation and the cell pellet was stored at -80°C until needed.

For cell lysis, the thawed pellet was resuspended in 1X BugBuster® supplemented with 25 U/mL Benzonase® (Sigma-Aldrich) and 1 kU/mL rLysozyme™ (Novagen EMD Biosciences) at a ratio of 5 mL of BugBuster® per gram of pellet. Lysis proceeded for 1 hour at room temperature with gentle agitation, followed by centrifugation at 56,000 x g for 50 minutes at 4°C. The supernatant was collected and filtered through a 0.2 μm filter, then loaded on to a 5-mL HisTrap FF column pre-equilibrated with Buffer A (50 mM Tris-HCl pH 7.5, 500 mM NaCl, 10 mM imidazole) using a GE Healthcare ÄKTAexplorer 100s chromatography system. The column was washed with 20 column volumes of Buffer A and further washed with 16 % Buffer B (50 mM Tris-HCl pH7.5, 500 mM NaCl, 250 mM imidazole) for 6 column volumes. The FN3 domains were eluted with 50% B for 10 column volumes, followed by a gradient from 50-100% B over 6 column volumes. Fractions containing the FN3 domain protein were pooled, concentrated using a Millipore 10K MWCO concentrator, and filtered before loading onto a HiLoad™ 16/60 Superdex™ 75 column (GE Healthcare) pre-equilibrated with PBS. The protein monomer peak eluting from the size exclusion column was retained.

Endotoxins were removed using a batch approach with ActiClean Etox resin (Sterogene Bioseparations). Prior to endotoxin removal, the resin was pre-treated with 1 N NaOH for 2 hours at 37°C (or overnight at 4°C) and washed extensively with PBS until the pH had stabilized to ~7 as measured with pH indicator paper. The purified protein was filtered through a 0.2 μm filter before adding to 1 mL of Etox resin at a ratio of 10 mL of protein to 1 mL of resin. The binding of endotoxin to resin was allowed to proceed at room temperature for at least 2 hours with gentle rotation. The resin was removed by centrifugation at 500 x g for 2 minutes and the protein supernatant was retained. Endotoxin levels were measured using EndoSafe®-PTS™ cartridges and analyzed on an EndoSafe®-MCS reader (Charles River). If endotoxin levels were above 5 EU/mg after the first Etox treatment, the above procedure was repeated until endotoxin levels were decreased to ≤ 5 EU/mg. In cases where the endotoxin level was above 5 EU/mg and stabilized after two consecutive treatments with Etox, anion exchange or hydrophobic interaction chromatography conditions were established for the protein to remove the remaining endotoxins.

Affinity Determination of Selected EGFR-binding FN3 domains to EGFR-Fc (EGFR-Fc Affinity)

Binding affinity of selected EGFR-binding FN3 domains to recombinant EGFR extracellular domain was further characterized by surface Plasmon resonance methods using a Proteon Instrument (BioRad). The assay set-up (chip preparation, EGFR-Fc capture) was similar to that described above for off-rate analysis. Selected EGFR binding FN3 domains were tested at 1 μM concentration in 3-fold dilution series in the horizontal orientation. A buffer sample was also injected to monitor the baseline stability. The dissociation phase for all concentrations of each EGFR-binding FN3 domain was monitored at a flow rate of 100 μL/min for 30 minutes (for those with k_{off} ~10^{-2} s^{-1} from off-rate screening), or 1 hour (for those with k_{off} ~10^{-3} s^{-1} or slower). Two sets of reference data were subtracted from the response data: 1) the inter-spot signals to correct for the non-specific interactions between the EGFR-binding FN3 domain and the immobilized IgG surface; 2) the buffer channel signals to correct for baseline drifting due to the dissociation of captured EGFR-Fc surface over time. The processed binding data at all concentrations for each FN3 domain were globally fit to a 1:1 simple Langmuir binding model to extract estimates of the kinetic (k_{on}, k_{off}) and affinity (K_D) constants. Table 5 shows the kinetic constants for each of the constructs, with the affinity varying from 200 pM to 9.6 nM.

Binding of Selected EGFR-binding FN3 domains to EGFR on Cells ("A431 Cell Binding Assay")

A431 cells were plated at 5,000/well in opaque black 96-well plates and allowed to attach overnight at 37°C, in a humidified 5% CO_2 atmosphere. Purified EGFR-binding FN3 domains (1.5 nM to 30 □M) were added to the cells (in 50 uL) for 1 hour at room temperature in triplicate plates. Supernatant was removed and cells were washed 3 times with 150 □L/well of FACS stain buffer. Cells were incubated with 50 □L/well of anti-penta His-Alexa488 antibody conjugate (Qiagen) diluted 1:100 in FACS stain buffer for 20 minutes at room temperature. Cells were washed 3 times with 150 □L/well of FACS stain buffer, after which wells were filled with 100 □L of FACS stain buffer and read for fluorescence at 488 nm using an Acumen eX3 reader. Data were plotted as raw fluorescence signal against the logarithm of the FN3 domain molar concentration and fitted to a sigmoidal dose-response curve with variable slope using GraphPad Prism 4 (GraphPad Software) to calculate EC_{50} values. Table 5 reports the EC_{50} for each of the constructs ranging from 2.2 nM to > 20 μM.

Inhibition of EGF Binding to EGFR on Cells using Selected EGFR-binding FN3 domains (A431 cell EGF competition assay)

A431 cells were plated at 5,000/well in opaque black 96-well plates and allowed to attach overnight at 37°C, in a humidified 5% CO_2 atmosphere. Purified EGFR-binding FN3 domains (1.5 nM to 30 μM) were added to the cells (50 μL/well) for 1 hour at room temperature in triplicate plates. Biotinylated EGF (Invitrogen, Cat #: E-3477) was added to each well to give a final concentration of 30 ng/mL and incubated for 10 minutes at room temperature. Cells were washed 3 times with 150 μL/well of FACS stain buffer. Cells were incubated with 50 μL/well of streptavidin-phycoerythrin conjugate (Invitrogen) diluted 1:100 in FACS stain buffer for 20 minutes at room temperature. Cells were washed 3 times with 150 μL/well of FACS stain buffer, after which wells were filled with 100 μL of FACS stain buffer and read for fluorescence at 600 nm using an Acumen eX3 reader. Data were plotted as the raw fluorescence signal against the logarithm of FN3 domain molar concentration and fitted to a sigmoidal dose-response curve with variable slope using GraphPad Prism 4 (GraphPad Software) to calculate IC_{50} values. Table 5 reports the IC_{50} values ranging from 1.8 nM to 121 nM.

Inhibition of EGF-Stimulated EGFR Phosphorylation (Phoshpo-EGRF assay)

Select FN3 domains that significantly inhibited EGF-stimulated EGFR phosphorylation were assessed more completely by measuring IC_{50} values for inhibition. Inhibition of EGF-stimulated EGFR phosphorylation was assessed at varying FN3 domain concentrations (0.5 nM to 10 μM) as described above in "inhibition of EGF stimulated EGFR phosphorylation". Data were plotted as electrochemiluminescence signal against the logarithm of the FN3 domain molar concentration and IC_{50} values were determined by fitting data to a sigmoidal dose response with variable slope using GraphPad Prism 4 (GraphPad Software). Table 5 shows the IC_{50} values which ranged from 18 nM to >2.5 μM.

Inhibition of Human Tumor Cell Growth (NCI-H292 growth and NCI-H322 growth assay)

Inhibition of EGFR-dependent cell growth was assessed by measuring viability of the EGFR over-expressing human tumor cell lines, NCI-H292 and NCI-H322 (American Type Culture Collection, cat. #CRL-1848 & #CRL-5806, respectively), following

Table 5.

FN3 Domain Clone ID	SEQ ID NO:	EGFR-Fc Affinity (nM)	A431 Cell Binding EC_{50} (nM)	A431 Cell EGF Competition IC_{50} (nM)	Phospho-EGFR IC_{50} (nM)	NCI-H292 Growth IC_{50} (nM)	NCI-H322 Growth IC_{50} (nM)
P53A1R5-17	18	1.89	4.0	9.8	>2500	86	65
P54AR4-17	19	9.62	16	21	184	ND	ND
P54AR4-47	20	2.51	8.6	7.1	295	44	39
P54AR4-48	21	7.78	12	9.8	170	ND	ND
P54AR4-73	22	0.197	9.4	4.6	141	83	73
P54AR4-74	23	ND	77	ND	ND	ND	ND
P54AR4-81	24	ND	84	121	ND	ND	ND
P54AR4-83	25	0.255	2.2	1.8	18	5.9	9.2
P54CR4-31	26	0.383	>20000	55	179	1150	>3073

exposure to EGFR-binding FN3 domains. Cells were plated at 500 cells/well (NCI-H292) or 1,000 cells/well (NCI-H322) in opaque white 96-well tissue culture-treated plates (Nunc) in 100□L/well of RPMI medium (Gibco) containing GlutaMAX™ and 10mM HEPES, supplemented with 10% heat inactivated fetal bovine serum (Gibco) and 1% penicillin/streptomycin (Gibco), and allowed to attach overnight at 37°C in a humidified 5% CO_2 atmosphere. Cells were treated by addition of 5□L/well of phosphate-buffered saline (PBS) containing a concentration range of EGFR-binding FN3 domains. Controls

were treated with 5 L/well of PBS only or 25 mM ethylenediaminetetraacetic acid in PBS. Cells were incubated at 37°C, 5% CO_2 for 120 hours. Viable cells were detected by addition of 75 L/well of CellTiter-Glo® reagent (Promega), followed by mixing on a plate shaker for 2 minutes, and incubation in the dark at room temperature for a further 10 minutes. Plates were read on a SpectraMax M5 plate reader (Molecular Devices) set to luminescence mode, with a read time of 0.5 seconds/well against a blank of medium only. Data were plotted as a percentage of PBS-treated cell growth against the logarithm of FN3 domain molar concentration. IC_{50} values were determined by fitting data to the equation for a sigmoidal dose response with variable slope using GraphPad Prism 4 (GraphPad Software). Table 5 shows IC_{50} values ranging from 5.9 nM to 1.15 μM and 9.2 nM to > 3.1 μM, using the NCI-H292 and NCI-H322 cells respectively. Table 5 shows the summary of biological properties of EGFR-binding FN3 domains for each assay.

EXAMPLE 4: Engineering of EGFR-Binding FN3 domains

A subset of the EGFR binding FN3 domains was engineered to increase the conformational stability of each molecule. The mutations L17A, N46V and E86I which have been shown to improve FN3 domain stability (described in US Pat. Publ. No. US2011/0274623) were incorporated into clones P54AR4-83, P54CR4-31, and P54AR4-37 by DNA synthesis. The new mutants, P54AR5-83v2, P54CR431-v2, and P54AR4-37v2 were expressed and purified as described above. Differential scanning calorimetry in PBS was used to assess the stability of each mutant in order to compare it to that of the corresponding parent molecule. Table 6 shows that each variant molecule was stabilized significantly, with an average increase in the T_m of 18.5°C.

Table 6.

FN3 domain Clone	SEQID NO:	T_m (°C)
P54AR4-83	25	50.6
P54AR4-83v2	27	69.8
P54CR4-31	26	60.9
P54CR4-31v2	28	78.9
P54AR4-37	22	45.9

P54AR4-37v2	29	64.2

EXAMPLE 5: Selection of fibronectin type III (FN3) domains that bind c-Met and Inhibit HGF Binding

Panning on human c-Met

The TCL14 library was screened against biotinylated-human c-Met extracellular domain (bt-c-Met) to identify FN3 domains capable of specifically binding c-Met. For selections, 3 µg of TCL14 library was *in vitro* transcribed and translated (IVTT) in *E. Coli* S30 Linear Extract (Promega, Madison, WI) and the expressed library blocked with Cis Block (2% BSA (Sigma-Aldrich, St. Louis, MO), 100 µg/ml Herring Sperm DNA (Promega), 1 mg/mL heparin (Sigma-Aldrich)). For selections, bt-c-Met was added at concentrations of 400 nM (Round 1), 200 nM (Rounds 2 and 3) and 100 nM (Rounds 4 and 5). Bound library members were recovered using neutravidin magnetic beads (Thermo Fisher, Rockford, IL) (Rounds 1, 3, and 5) or streptavidin magnetic beads (Promega) (Rounds 2 and 4) and unbound library members were removed by washing the beads 5-14 times with 500 uL PBS-T followed by 2 washes with 500 µL PBS.

Additional selection rounds were performed to identify FN3 domains molecules with improved affinities. Briefly, outputs from round 5 were prepared as described above and subjected to additional iterative rounds of selection with the following changes: incubation with bt-c-Met was decreased from 1 hour to 15 minutes and bead capture was decreased from 20 minutes to 15 minutes, bt-c-Met decreased to 25 nM (Rounds 6 and 7) or 2.5 nM (Rounds 8 and 9), and an additional 1 hour wash was performed in the presence of an excess of non-biotinylated c-Met. The goal of these changes was to simultaneously select for binders with a potentially faster on-rate and a slower off-rate yielding a substantially lower K_D.

Rounds 5, 7 and 9 outputs were PCR cloned into a modified pET15 vector (EMD Biosciences, Gibbstown, NJ) containing a ligase independent cloning site (pET15-LIC) using TCON6 (SEQID No. 30) and TCON5 E86I short (SEQID No. 31) primers, and the proteins were expressed as C-terminal His6-tagged proteins after transformations and IPTG induction (1 mM final, 30°C for 16 hours) using standard protocols. The cells were harvested by centrifugation and subsequently lysed with Bugbuster HT (EMD Biosciences) supplemented with 0.2 mg/mL Chicken Egg White Lysozyme (Sigma-

Aldrich). The bacterial lysates were clarified by centrifugation and the supernatants were transferred to new 96 deep-well plates.

Screening for FN3 domains that Inhibit HGF Binding to c-Met

FN3 domains present in *E. coli* lysates were screened for their ability to inhibit HGF binding to purified c-Met extracellular domain in a biochemical format. Recombinant human c-Met Fc chimera (0.5 µg/mL in PBS, 100 µL/well) was coated on 96-well White Maxisorp Plates (Nunc) and incubated overnight at 4°C. The plates were washed two times with 300 µl/well of Tris-buffered saline with 0.05% Tween 20 (TBS-T, Sigma-Aldrich) on a Biotek plate washer. Assay plates were blocked with StartingBlock T20 (200 µL/well, Thermo Fisher Scientific, Rockland, IL) for 1 hour at room temperature (RT) with shaking and again washed twice with 300 µl of TBS-T. FN3 domain lysates were diluted in StartingBlock T20 (from 1:10 to 1:100,000) using the Hamilton STARplus robotics system. Lysates (50 µL/well) were incubated on assay plates for 1 hour at RT with shaking. Without washing the plates, bt-HGF (1 µg/mL in StartingBlock T20, 50 µL/well, biotinylated) was added to the plate for 30 min at RT while shaking. Control wells containing Tencon27 lysates received either Starting Block T20 or diluted bt-HGF. Plates were then washed four times with 300 µl/well of TBS-T and incubated with 100 µl/well of Streptavidin-HRP (1:2000 in TBS-T, Jackson Immunoresearch, West Grove, PA) for 30-40 minutes at RT with shaking. Again the plates were washed four times with TBS-T. To develop signal, POD Chemiluminescence Substrate (50 µL/well, Roche Diagnostics, Indianapolis, IN), prepared according to manufacturer's instructions, was added to the plate and within approximately 3 minutes luminescence was read on the Molecular Devices M5 using SoftMax Pro. Percent inhibition was determined using the following calculation: $100-((RLU_{sample} - \text{Mean } RLU_{\text{No bt-HGF control}})/(\text{Mean } RLU_{\text{bt-HGF control}} - \text{Mean } RLU_{\text{No bt-HGF control}})*100)$. Percent inhibition values of 50% or greater were considered hits.

High-throughput Expression and Purification of FN3 domains

His-tagged FN3 domains were purified from clarified *E. coli* lysates with His MultiTrap™ HP plates (GE Healthcare) and eluted in buffer containing 20 mM sodium phosphate, 500 mM sodium chloride, and 250 mM imidazole at pH 7.4. Purified samples

were exchanged into PBS pH 7.4 for analysis using PD MultiTrap™ G-25 plates (GE Healthcare).

IC_{50} determination of Inhibition of HGF Binding to c-Met

Select FN3 domains were further characterized in the HGF competition assay. Dose response curves for purified FN3 domains were generated utilizing the assay described above (starting concentrations of 5 μM). Percent inhibition values were calculated. The data were plotted as % inhibition against the logarithm of FN3 domain molar concentrations and IC_{50} values were determined by fitting data to a sigmoidal dose response with variable slope using GraphPad Prism 4.

35 unique sequences were identified from Round 5 to exhibit activity at dilutions of 1:10, with IC_{50} values ranging from 0.5 to 1500 nM. Round 7 yielded 39 unique sequences with activity at dilutions of 1:100 and IC_{50} values ranging from 0.16 to 2.9 nM. 66 unique sequences were identified from Round 9, where hits were defined as being active at dilutions of 1:1000. IC_{50} values as low as 0.2 nM were observed in Round 9 (Table 8).

Affinity Determination of Selected c-Met-binding FN3 domains to c-Met -Fc (c-Met-Fc Affinity)

Affinities were determined fro select c-Met binding FN3 domains according to the protocol described for determination of affinities to EGFR binding FN3 domaisn in Example 3 except that c-Met-Fc fusion protein was used in the experiments.

EXAMPLE 6: Characterization of FN3 domains that Bind c-Met and Inhibit HGF Binding

FN3 domains were expressed and purified as described above in Example 2. Size exclusion chromatography and kinetic analysis was done as described above in Examples 1 and 2, respectively. Table 7 shows the sequences of the C-strand, CD loop, F-strand, and FG loop, and a SEQ ID NO: for the entire amino acid sequence for each domain.

Table 7.

Clone		C loop	CD strand	F loop	FG strand
Name	SEQ ID NO:				
P114AR5P74-A5	32	FDSFWIRYDE	VVVGGE	TEYYVNILGV	KGGSISV
P114AR5P75-E9	33	FDSFFIRYDE	FLRSGE	TEYWVTILGV	KGGLVST
P114AR7P92-F3	34	FDSFWIRYFE	FLGSGE	TEYIVNIMGV	KGGSISH
P114AR7P92-F6	35	FDSFWIRYFE	FLGSGE	TEYVVNILGV	KGGGLSV
P114AR7P92-G8	36	FDSFVIRYFE	FLGSGE	TEYVVQILGV	KGGYISI
P114AR7P92-H5	37	FDSFWIRYLE	FLLGGE	TEYVVQIMGV	KGGTVSP
P114AR7P93-D11	38	FDSFWIRYFE	FLGSGE	TEYVVGINGV	KGGYISY
P114AR7P93-G8	39	FDSFWIRYFE	FLGSGE	TEYGVTINGV	KGGRVST
P114AR7P93-H9	40	FDSFWIRYFE	FLGSGE	TEYVVQIIGV	KGGHISL
P114AR7P94-A3	41	FDSFWIRYFE	FLGSGE	TEYVVNIMGV	KGGKISP
P114AR7P94-E5	42	FDSFWIRYFE	FLGSGE	TEYAVNIMGV	KGGRVSV
P114AR7P95-B9	43	FDSFWIRYFE	FLGSGE	TEYVVQILGV	KGGSISV
P114AR7P95-D3	44	FDSFWIRYFE	FLGSGE	TEYVVNIMGV	KGGSISY
P114AR7P95-D4	45	FDSFWIRYFE	FLGSGE	TEYVVQILGV	KGGYISI
P114AR7P95-E3	46	FDSFWIRYFE	FLGSGE	TEYVVQIMGV	KGGTVSP
P114AR7P95-F10	47	FDSFWIRYFE	FTTAGE	TEYVVNIMGV	KGGSISP
P114AR7P95-G7	48	FDSFWIRYFE	LLSTGE	TEYVVNIMGV	KGGSISP
P114AR7P95-H8	49	FDSFWIRYFE	FVSKGE	TEYVVNIMGV	KGGSISP

C loop residues correspond to residues 28-37 of indicated SEQ ID NO:

CD strand residues correspond to residues 38-43 of indicated SEQ ID NO:

F loop residues correspond to residues 65-74 of indicated SEQ ID NO:

FG strand residues correspond to residues 75-81 of indicated SEQ ID NO:

Binding of Selected c-Met-binding FN3 domains to c-Met on Cells ("H441 Cell Binding Assay")

NCI-H441 cells (Cat # HTB-174, American Type Culture Collection, Manassas, VA) were plated at 20,000 cells per well in Poly-D-lysine coated black clear bottom 96-well plates (BD Biosciences, San Jose, CA) and allowed to attach overnight at 37°C, 5% CO_2. Purified FN3 domains (50 µL/well; 0 to 1000 nM) were added to the cells for 1 hour at 4°C in duplicate plates. Supernatant was removed and cells were washed three times with FACS stain buffer (150 µL/well, BD Biosciences, cat # 554657). Cells were

incubated with biotinylated-anti HIS antibody (diluted 1:160 in FACS stain buffer, 50 µL/well, R&D Systems, cat # BAM050) for 30 minutes at 4°C. Cells were washed three times with FACS stain buffer (150 µL/well), after which wells were incubated with anti mouse IgG1-Alexa 488 conjugated antibody (diluted 1:80 in FACS stain buffer, 50 µL/well, Life Technologies, cat # A21121) for 30 minutes at 4°C. Cells were washed three times with FACS stain buffer (150 µL/well) and left in FACS stain buffer (50 µL/well). Total fluorescence was determined using an Acumen eX3 reader. Data were plotted as raw fluorescence signal against the logarithm of the FN3 domain molar concentration and fitted to a sigmoidal dose-response curve with variable slope using GraphPad Prism 4 (GraphPad Software) to calculate EC_{50} values. FN3 domains were found to exhibit a range of binding activities, with EC_{50} values between 1.4 nM and 22.0 nM, as shown in Table 8.

Inhibition of HGF-Stimulated c-Met Phosphorylation

Purified FN3 domains were tested for their ability to inhibit HGF-stimulated phosphorylation of c-Met in NCI-H441, using the c-Met phospho(Tyr1349) kit from Meso Scale Discovery (Gaithersburg, MD). Cells were plated at 20,000/well in clear 96-well tissue culture-treated plates in 100 µL/well of RPMI medium (containing Glutamax and HEPES, Life Technologies) with 10% fetal bovine serum (FBS; Life Technologies) and allowed to attach overnight at 37°C, 5% CO_2. Culture medium was removed completely and cells were starved overnight in serum-free RPMI medium (100 µL/well) at 37°C, 5% CO_2. Cells were then replenished with fresh serum-free RPMI medium (100 µL/well) containing FN3 domains at a concentration of 20 µM and below for 1 hour at 37°C, 5% CO_2. Controls were treated with medium only. Cells were stimulated with 100 ng/mL recombinant human HGF (100 µL/well, R&D Systems cat # 294-HGN) and incubated at 37°C, 5% CO_2 for 15 minutes. One set of control wells was left un-stimulated as negative controls. Medium was then completely removed and cells were lysed with Complete Lysis Buffer (50 µL/well, Meso Scale Discovery) for 10 minutes at RT with shaking, as per manufacturer's instructions. Assay plates configured for measuring phosphorylated c-Met were blocked with the provided blocking solution as per the manufacturer's instructions at room temperature for 1 hour. Plates were then washed three times with Tris Wash Buffer (200 µL/well, Meso Scale Discovery). Cell lysates (30 µL/well) were transferred to assay plates, and incubated at RT with shaking for 1 hour. Assay plates were then washed four times with Tris Wash Buffer, after which ice-cold Detection

Antibody Solution (25 µL/well, Meso Scale Discovery) was added to each well for 1hr at RT with shaking. Plates were again rinsed four times with Tris Wash Buffer. Signals were detected by addition of 150 Read Buffer (150 µL/well, Meso Scale Discovery) and reading on a SECTOR® Imager 6000 instrument (Meso Scale Discovery) using manufacturer-installed assay-specific default settings. Data were plotted as electrochemiluminescence signal against the logarithm of FN3 domain molar concentration and IC_{50} values were determined by fitting data to a sigmoidal dose response with variable slope using GraphPad Prism 4. FN3 domains were found to inhibit phosphorylated c-Met with IC50 values ranging from 4.6 nM to 1415 nM as shown in Table 8.

Inhibition of Human Tumor Cell Growth

Inhibition of c-Met-dependent cell growth was assessed by measuring viability of U87-MG cells (American Type Culture Collection, cat # HTB-14), following exposure to c-Met-binding FN3 domains. Cells were plated at 8000 cells per well in opaque white 96-well tissue culture-treated plates (Nunc) in 100 µL/well of RPMI medium, supplemented with 10% FBS and allowed to attach overnight at 37°C, 5% CO_2. Twenty-four hours after plating, medium was aspirated and cells were replenished with serum-free RPMI medium.

Table 8.

Clone		Affinity (Kd, nM)	HGF competition IC50 (nM)	H441 Cell binding (EC50, nM)	pMet inhibition in H441 cells (IC50, nM)	Inhbibition of Proliferation of U87-MG cells (IC50, nM)
Name	SEQ ID NO:					
P114AR5P74-A5	32	10.1	5.2	18.7	1078	464.4
P114AR5P75-E9	33	45.8	51.9	ND	1415	1193.9
P114AR7P92-F3	34	0.4	0.2	1.5	8.3	2.7
P114AR7P92-F6	35	3.1	2.2	4.9	165.3	350.5
P114AR7P92-G8	36	1.0	1.6	5.9	155.3	123.9
P114AR7P92-H5	37	11.6	ND	22.0	766.4	672.3
P114AR7P93-D11	38	ND	ND	2.3	16	14.4
P114AR7P93-G8	39	6.9	1	3.8	459.5	103.5
P114AR7P93-H9	40	3.3	2.9	12.9	288.2	269.9
P114AR7P94-A3	41	0.4	0.2	1.4	5	9.3
P114AR7P94-E5	42	4.2	0.7	3.4	124.3	195.6
P114AR7P95-B9	43	0.5	0.3	ND	9.8	17.4
P114AR7P95-D3	44	0.3	0.2	1.5	4.6	1.7
P114AR7P95-D4	45	0.4	ND	1.4	19.5	19.4
P114AR7P95-E3	46	1.5	ND	3.2	204.6	209.2
P114AR7P95-F10	47	4.2	1.4	4.4	187.6	129.7
P114AR7P95-G7	48	20.0	ND	11.3	659.3	692
P114AR7P95-H8	49	3.7	ND	4.1	209.8	280.7

Twenty-four hours after serum starvation, cells were treated by addition of serum-free medium containing c-Met-binding FN3 domains (30 µL/well). Cells were incubated at 37°C, 5% CO_2 for 72 hours. Viable cells were detected by addition of 100 µL/well of CellTiter-Glo® reagent (Promega), followed by mixing on a plate shaker for 10 minutes. Plates were read on a SpectraMax M5 plate reader (Molecular Devices) set to luminescence mode, with a read time of 0.5 seconds/well. Data were plotted as raw luminescence units (RLU) against the logarithm of FN3 domain molar concentration. IC_{50} values were determined by fitting data to an equation for a sigmoidal dose response with variable slope using GraphPad Prism 4. Table 8 reports IC_{50} values ranging from 1 nM to >1000 nM.

Characteristics of the c-Met binding FN3 domains are summarized in Table 8.

Thermal stability of c-Met –binding FN3 domains

Differential scanning calorimetry in PBS was used to assess the stability of each FN3 domain. Results of the experiment are shown in Table 9.

Table 9.

Clone		Thermal Stability (Tm, C)
Name	SEQ ID NO:	
P114AR5P74-A5	32	74.1
P114AR5P75-E9	33	ND
P114AR7P92-F3	34	81.5
P114AR7P92-F6	35	76.8
P114AR7P92-G8	36	90.9
P114AR7P92-H5	37	87
P114AR7P93-D11	38	ND
P114AR7P93-G8	39	76.8
P114AR7P93-H9	40	88.2
P114AR7P94-A3	41	86.2
P114AR7P94-E5	42	80
P114AR7P95-B9	43	86.3
P114AR7P95-D3	44	82
P114AR7P95-D4	45	85.3
P114AR7P95-E3	46	94.2
P114AR7P95-F10	47	85.2
P114AR7P95-G7	48	87.2
P114AR7P95-H8	49	83

EXAMPLE 7. Generation and Characterization of Bispecific anti-EGFR/c-Met molecules

Generation of bispecific EGFR/c-Met molecules

Numerous combinations of the EGFR and c-Met-binding FN3 domains described in Examples 1-6 were joined into bispecific molecules capable of binding to both EGFR and c-Met. Additionally, EGFR-binding FN3 domains having amino acid sequences shown in SEQ ID NOs: 107-110 and c-Met binding FN3 domains having amino acid sequences shown in SEQ ID NOs: 111-114 were made and joined into bispecific molecules. Synthetic genes were created to encode for the amino acid sequences described in SEQID NOs: 50-72, 106, 118-121 or 190-193 (Table 10) such that the following format was maintained: EGFR-binding FN3 domain followed by a peptide linker followed by a c-Met-binding FN3 domain. A poly-histidine tag was incorporated at the C-terminus to aid purification. In addition to those molecules described in Table 10, the linker between the two FN3 domains was varied according to length, sequence

composition and structure according to those listed in Table 11. It is envisioned that a number of other linkers could be used to link such FN3 domains Bispecific EGFR/c-Met molecules were expressed and purified from *E. coli* as described for monospecific EGFR or c-Met FN3 domains using IMAC and gel filtration chromatography steps. It is evident to the skilled in art that the bispecific EGFR/c-Met molecules may or may not contain an initiator methionine. Exemplary molecules with the initiator methionine are molecules having the amino acid sequence shown in SEQ ID NOs: 106, 118-121, 138-165, 190 and 192, and exemplary molecules without the initiator methionine are shown in SEQ ID NOs: 50-72, 191 and 193. The presence of the initiator methionine for the EGFR binding FN3 domains ensures proper activity; the initiator methionine has less impact on the c-Met FN3 domains.

Table 10.

Bispecifcic EGFR/ c-Met molecule		EGFR-binding FN3 comain		cMET-binding FN3 domain		Linker	
Clone ID	SEQ ID NO:	Clone ID	SEQ ID NO:	Clone ID	SEQ ID NO:	Sequence	SEQ ID NO:
ECB1	50	P54AR4-83v2	27	P114AR5P74-A5	32	$(GGGGS)_4$	79
ECB2	51	P54AR4-83v2	27	P114AR7P94-A3	41	$(GGGGS)_4$	79
ECB3	52	P54AR4-83v2	27	P114AR7P93-H9	40	$(GGGGS)_4$	79
ECB4	53	P54AR4-83v2	27	P114AR5P75-E9	33	$(GGGGS)_4$	79
ECB5	54	P53A1R5-17v2	107	P114AR7P94-A3	41	$(GGGGS)_4$	79
ECB6	55	P53A1R5-17v2	107	P114AR7P93-H9	40	$(GGGGS)_4$	79
ECB7	56	P53A1R5-17v2	107	P114AR5P75-E9	33	$(GGGGS)_4$	79
ECB15	57	P54AR4-83v2	27	P114AR7P94-A3	41	$(AP)_5$	81
ECB27	58	P54AR4-83v2	27	P114AR5P74-A5	32	$(AP)_5$	81
ECB60	59	P53A1R5-17v2	107	P114AR7P94-A3	41	$(AP)_5$	81
ECB37	60	P53A1R5-17v2	107	P114AR5P74-A5	32	$(AP)_5$	81
ECB94	61	P54AR4-83v22	108	P114AR7P94-A3v22	111	$(AP)_5$	81
ECB95	62	P54AR4-83v22	108	P114AR9P121-A6v2	112	$(AP)_5$	81
ECB96	63	P54AR4-83v22	108	P114AR9P122-A7v2	113	$(AP)_5$	81
ECB97	64	P54AR4-83v22	108	P114AR7P95-C5v2	114	$(AP)_5$	81
ECB106	65	P54AR4-83v23	109	P114AR7P94-A3v22	111	$(AP)_5$	81
ECB107	66	P54AR4-83v23	109	P114AR9P121-A6v2	112	$(AP)_5$	81
ECB108	67	P54AR4-83v23	109	P114AR9P122-A7v2	113	$(AP)_5$	81
ECB109	68	P54AR4-83v23	109	P114AR7P95-C5v2	114	$(AP)_5$	81
ECB118	69	P53A1R5-17v22	110	P114AR7P94-A3v22	111	$(AP)_5$	81
ECB119	70	P53A1R5-17v22	110	P114AR9P121-A6v2	112	$(AP)_5$	81
ECB120	71	P53A1R5-17v22	110	P114AR9P122-A7v2	113	$(AP)_5$	81
ECB121	72	P53A1R5-17v22	110	P114AR7P95-C5v2	114	$(AP)_5$	81
ECB91	106	P54AR4-83v22	108	P114AR7P95-C5v2	114	$(AP)_5$	81
ECB18	118	P54AR4-83v2	27	P114AR5P74-A5	32	$(AP)_5$	81
ECB28	119	P53A1R5-17v2	107	P114AR5P74-A5	32	$(AP)_5$	81
ECB38	120	P54AR4-83v2	27	P114AR7P94-A3	41	$(AP)_5$	81
ECB39	121	P53A1R5-17v2	107	P114AR7P94-A3	41	$(AP)_5$	81
ECB168	190	P54AR4-83v22	108	P114AR7P95-C5v2	114	$(AP)_5$	81
ECB176	192	P53A1R5-17v2	107	P114AR7P95-C5v2	114	$(AP)_5$	81

Table 11.

Linker	SEQ ID NO:	Linker ength in amino acids	Structure
GS	78	2	Disordered

GGGGS	105	5	Disordered
(GGGGS)2	224	10	Disordered
$(GGGGS)_4$	79	20	Disordered
$(AP)_2$	80	4	Rigid
$(AP)_5$	81	5	Rigid
$(AP)_{10}$	82	20	Rigid
$(AP)_{20}$	83	40	Rigid
$A(EAAAK)_5AAA$	84	29	α-helical

Bispecific EGFR/c-Met molecules enhance potency compared to monospecific molecules alone, suggesting avidity

NCI-H292 cells were plated in 96 well plates in RPMI medium containing 10% FBS. 24 hours later, medium was replaced with serum free RPMI. 24 hours after serum starvation, cells were treated with varying concentrations of FN3 domains: either a high affinity monospecific EGFR FN3 domain (P54AR4-83v2), a weak affinity monospecific c-Met FN3 domain (P114AR5P74-A5), the mixture of the two monospecific EGFR and c-Met FN3 domains, or a bispecific EGFR/c-Met molecules comprised of the low affinity c-Met FN3 domain linked to the high affinity EGFR FN3 domain (ECB1). Cells were treated for 1h with the monosopecific or bispecific molecules and then stimulated with EGF, HGF, or a combination of EGF and HGF for 15 minutes at 37°C, 5% CO_2. Cells were lysed with MSD Lysis Buffer and cell signaling was assessed using appropriate MSD Assay plates, according to manufacturer's instructions, as described above.

The low affinity c-Met FN3 domain inhibited phosphorylation of c-Met with an IC_{50} of 610 nM (Figure 4). As expected the EGFR FN3 domain was not able to inhibit c-Met phosphorylation and the mixture of the mono-specific molecules looked identical to the c-Met FN3 domain alone. However, the bi-specific EGFR/c-Met molecule inhibited phosphorylation of c-Met with an IC_{50} of 1 nM (Figure 4), providing more than a 2-log shift in improving potency relative to the c-Met monospecific alone.

The potential for the bispecific EGFR/c-Met molecule to enhance the inhibition of c-Met and/or EGFR phosphorylation through an avidity effect was evaluated in multiple cell types with variable c-Met and EGFR densities and ratios (Figure 5). NCI-H292, NCI-H441, or NCI-H596 cells were plated in 96 well plates in RPMI medium containing 10%

FBS. 24 hours later, medium was replaced with serum free RPMI. 24 hours after serum starvation, cells were treated with varying concentrations of either monospecific EGFR-binding FN3 domain, monospecific c-Met FN3 domain, or a bispecific EGFR/c-Met molecule (ECB5, comprised of P53A1R5-17v2 and P114AR7P94-A3). Cells were treated for 1h with the monospecific or bispecific molecules and then stimulated with EGF, HGF, or a combination of EGF and HGF for 15 minutes at 37°C, 5% CO_2. Cells were lysed with MSD Lysis Buffer and cell signaling was assessed using appropriate MSD Assay plates, according to manufacturer's instructions, as described above.

Figure 5 (A-C) shows the inhibition of EGFR using a monospecific EGFR-binding FN3 domain compared to a bispecific EGFR/cMet molecule in three different cell lines. To assess avidity in an EGFR phosphorylation assay, a medium affinity EGFR-binding FN3 domain (1.9 nM) (P53A1R5-17v2) was compared to a bispecific EGFR/c-Met molecule containing the same EGFR-binding FN3 domain linked to a high-affinity c-Met-binding FN3 domain (0.4 nM) (P114AR7P94-A3). In H292 and H596 cells, inhibition of phosphorylation of EGFR was comparable for the monospecific and bispecific molecules (Figures 5A and 5B), likely because these cell lines have a high ratio of EGFR to c-Met receptors. To test this theory, inhibition of EGFR phosphorylation was evaluated in NCI-H441 cells which exhibit more c-Met receptors than EGFR. Treatment of NCI-H441 cells with the bispecific EGFR/c-Met molecule decreased the IC_{50} for inhibition of EGFR phosphorylation compared to the monospecific EGFR-binding FN3 domain by 30-fold (Figure 5C).

The potential for enhanced potency with a bi-specific EGFR/c-Met molecule was evaluated in a c-Met phosphorylation assay using a molecule with a high affinity to EGFR (0.26 nM) and medium affinity to c-Met (10.1 nM). In both NCI-H292 and NCI-H596 cells, the inhibition of phosphorylation of c-Met was enhanced with the bispecific molecule compared to the monospecific c-Met-binding FN3 domain, by 134 and 1012 fold, respectively (Figure 3D and 3E).

It was verified that the enhanced potency for inhibition of EGFR and c-Met phosphorylation with the bispecific EGFR/c-Met molecules translated into an enhanced inhibition of signaling and proliferation. For these experiments, the mixture of FN3 EGFR-binding and c-Met-binding FN3 domains was compared to a bispecific EGFR/c-Met molecule. As described in Tables 12 and 13, the IC_{50} values for ERK phosphorylation (Table 12) and proliferation of H292 cells (Table 13) were decreased when cells were treated with the bispecific EGFR/c-Met molecule compared to the mixture of the monospecific binders. The IC_{50} for inhibition of ERK phosphorylation for the bi-specific

EGFR/c-Met molecule was 143-fold lower relative to the mixture of the two monospecific EGFR and c-Met FN3 domains, showing the effect of avidity to the potency of the molecules in this assay. In Table 12, the monospecific EGFR- and c-Met binding FN3 domains do not fully inhibit activity and therefore the IC_{50} values shown should be considered lower limits. The proliferation assay was completed using different combinations EGFR and c-Met binding FN3 domains either as a mixture or linked in a bispecific format. The IC_{50} for inhibition of proliferation for the bispecific EGFR/c-Met molecule was 34-236-fold lower relative to the mixture of the monospecific parent EGFR or c-Met binding FN3 domains. This confirmed that the avidity effect observed at the level of the receptors (Figure 4 and Figure 5) translates into an improvement in inhibiting cell signaling (Table 12) and cell proliferation (Table 13).

Table 12.

Specificity of the FN3-domain molecule	Clone #	Type	IC50 (nM) (ERK phosphorylation)
EGFR	P54AR4-83v2	monospecific	>10,000
c-Met	P114AR5P74-A5	monospecific	2366
EGFR or c-Met	P54AR4-83v2 + P114AR5P74-A5	mixture of monospecific molecules	798.4
EGFR and c-Met	ECB1	bispecific	5.6

Table 13.

EGFR-binding FN3 domain (affinity)	c-Met binding FN3 domain (affinity)	IC50 for mixture of monospecifics (nM)	IC50 for bispecific (nM)	Fold increase in IC50 for bispecific/ mixture of monospecifics
P54AR4-83v2 (0.26 nM)	P114ARP94-A3 (0.4 nM)	36.5	1.04	35
P54AR4-83v2 (0.26 nM)	P114AR7P93-H9 (3.3 nM)	274.5	8.05	34
P54AR4-83v2 (0.26 nM)	P114AR5P74-A5 (10.1 nM)	1719	7.29	236

***In vivo* tumor xenografts: PK/PD**

In order to determine efficacy of the monospecific and bispecific FN3 domain molecules *in vivo*, tumor cells were engineered to secrete human HGF (murine HGF does not bind to humanc-Met). Human HGF was stably expressed in NCI-H292 cells using lentiviral infection (Lentiviral DNA vector expressing human HGF (Accession #X16322) and lentiviral packaging kit from Genecopoeia). After infection, HGF-expressing cells were selected with 4 μg/mL puromycin (Invitrogen). Human HGF protein was detected in the conditioned medium of pooled cells using assay plates from MesoScale Discovery.

SCID Beige mice were subcutaneously inoculated with NCI-H292 cells expressing human HGF ($2.0x10^6$ cells in Cultrex (Trevigen) in a volume of 200 μL) on the dorsal flank of each animal. Tumor measurements were taken twice weekly until tumor volumes ranged between 150-250 mm^3. Mice were then given a single i.p. dose of bispecific EGFR/c-Met molecules (linked to an albumin binding domain to increase half-life) or PBS vehicle. At 6h or 72h after dosing, tumors were extracted and immediately frozen in liquid nitrogen. Blood samples were collected via cardiac puncture into 3.8% citrate containing protease inhibitors. Immediately after collection, the blood samples were centrifuged and the resulting plasma was transferred to sample tubes and stored at -80°C. Tumors were weighed, cut into small pieces, and lysed in Lysing Matrix A tubes (LMA) containing RIPA buffer with HALT protease/phosphatase inhibitors (Pierce), 50 mM sodium fluoride (Sigma), 2 mM activated sodium orthovanadate (Sigma), and 1 mM PMSF (MesoScale Discovery). Lysates were removed from LMA matrix and centrifuged to remove insoluble protein. The soluble tumor protein was quantified with a BCA protein assay and diluted to equivalent protein levels in tumor lysis buffer. Phosphorylated c-

Met, EGFR and ERK were measured using assay plates from MesoScale Discovery (according to Manufacturer's protocol and as described above).

Figure 6 shows the results of the experiments. Each bispecific EGFR/c-Met molecule significantly reduced the levels of phosphorylated c-Met, EGFR, and ERK at both 6h and 72h. The data presented in Figure 6 show the importance of inhibiting both c-Met and EGFR simultaneously and how the affinity of the bispecific EGFR/c-Met molecule for each receptor plays a role in inhibition of downstream ERK. The molecules containing the high affinity EGFR-binding FN3 domains (P54AR4-83v2; shown as "8" in the Figure, K_D=0.26 nM) inhibited phosphorylation of EGFR to a larger extent compared to those containing the medium affinity EGFR-binding FN3 domains (P53A1R5-17v2; shown as "17" in the figure K_D =1.9 nM) at both 6h and 72h. All four bispecific molecules tested completely inhibited phosphorylation of ERK at the 6 hour time point, regardless of affinity. At the 72 hour time point, the molecules containing the tight affinity c-Met-binding domain (P114AR7P94-A3; shown as "A3" in the figure K_D =0.4 nM) significantly inhibited phosphorylation of ERK compared to the medium affinity c-Met-binding FN3 domain (P114AR5P74-A5; shown as "A5" in the Figure; K_D =10.1 nM; Figure 6).

The concentration of each bispecific EGFR/c-Met molecule was measured at 6 and 72 hours after dosing in the blood and in the tumor (Figure 7). Interestingly, the bispecific molecule with the medium affinity EGFR-binding domain (P53A1R5-17v2 ; K_D =1.9 nM) but high affinity c-Met-binding FN3 domain (P114AR7P94-A3; K_D =0.4 nM) had significantly more tumor accumulation at 6 hours relative to the other molecules, while the difference is diminished by 72 hours. It can be hypothesized that cells outside the tumor have lower levels of both EGFR and c-Met surface expression and therefore the medium affinity EGFR molecule doesn't bind to normal tissue as tightly compared to the higher affinity EGFR-binding FN3 domain. Therefore there is more free medium affinity EGFR-binding FN3 domain available to bind in the tumor. Therefore, identifying the appropriate affinities to each receptor may allow for identification of a therapeutic with decreased systemic toxicities and increased tumor accumulation.

Tumor efficacy studies with bispecific EGFR/c-Met molecules

SCID Beige mice were subcutaneously inoculated with NCI-H292 cells expressing human HGF ($2.0x10^6$ cells in Cultrex (Trevigen) in 200 μL) in the dorsal flank of each animal. One week after implantation, mice were stratified into groups with equivalent tumor volumes (mean tumor volume=77.9+/-1.7mm^3). Mice were dosed three

times per week with the bispecific molecules and tumor volumes were recorded twice weekly. Tumor growth inhibition (TGI) was observed with four different bispecific molecules, with variable affinities for c-Met and EGFR. Figure 8 shows the benefit of inhibiting both c-Met and EGFR as a delay in tumor growth was observed in the mice treated with molecules containing the high affinity EGFR-binding FN3 domain compared to the medium affinity EGFR-binding FN3 domain when the c-Met-binding FN3 domain was medium affinity (open vs. closed triangles, P54AR4-83v2- P114AR5P74-A5 compared to P53A1R5-17- P114AR5P74-A5). In addition, the data shows the importance of having a high affinity c-Met-binding FN3 domain as bispecific molecules containing either the high or medium affinity EGFR-binding FN3 domain but high affinity c-Met-binding FN3 domain showed the most efficacy (dotted gray and black lines, P54AR4-83v2- P114AR7P94-A3 and P53A1R5-17v2- P114AR7P94-A3).

Efficacy of bispecfic molecule and other inhibitors of EGFR and c-Met

The *in vivo* therapeutic efficacies of a bispecific EGFR/c-Met molecule (ECB38) and the small molecule inhibitors crizotinib (c-Met inhibitor) and erlotinib (EGFR inhibitor), cetuximab (anti-EGFR antibody), each as a single agent, and the combination of crizotnib and erlontinib, were evaluated in the treatment of subcutaneous H292-HGF human lung cancer xenograft model in SCID/Beige mice.

The H292-HGF cells were maintained *in vitro* in RPMI1640 medium supplemented with fetal bovine serum (10% v/v), and L-glutamine (2 mM) at 37°C in an atmosphere of 5% CO2 in air. The cells were routinely subcultured twice weekly by trypsin-EDTA treatment. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

Table 14.

Group	**N**	**Treatment**	**Dose (mg/kg)**	**Dosing Route**	**Planned Schedule**	**Actual Schedule**
1	10	Vehicle Control	0	*i.p.*	QD×3 weeks	QD×3 weeks
2	10	bispecific EGFR/c-Met molecule	25	*i.p.*	3 times/week ×3 weeks	3 times/week ×3 weeks
3	10	Crizotinib	50	*p.o.*	QD×3 weeks	QD×17 days
4	10	Erlotinib	50	*p.o.*	QD×2 weeks	QD×3 weeks

5	10	Crizotinib	50	*p.o.*	QD×3 weeks	QD×3 weeks
6	10	Cetuximab	1 mg/mouse	*i.p.*	Q4d*6	Q4d*6

N: animal number; *p.o.:* oral administration; *i.p.*: intraperitoneal injection 3 times/week: doses were given on days 1, 3 and 5 of the week.
QD: once daily Q4d: once every four days; the interval of the combination of crizotinib and erlotinib was 0.5hrs; dosing volume was adjusted based on body weight (10 l/g); a: dosing was not given on day 14 post grouping.

Each mouse was inoculated subcutaneously at the right flank region with H292-HGF tumor cells (2×10^6) in 0.1 ml of PBS with cultrex (1:1) for tumor development. The treatments were started when the mean tumor size reached 139 mm^3. The test article administration and the animal numbers in each study group were shown in the following experimental design table. The date of tumor cell inoculation was denoted as day 0. Table 14 shows the treatment groups.

Before commencement of treatment, all animals were weighed and the tumor volumes were measured. Since the tumor volume can affect the effectiveness of any given treatment, mice were assigned into groups using randomized block design based upon their tumor volumes. This ensures that all the groups are comparable at the baseline. The randomized block design was used to assign experimental animals to groups. First, the experimental animals were divided into homogeneous blocks according to their initial tumor volume. Secondly, within each block, randomization of experimental animals to treatments was conducted. Using randomized block design to assign experimental animals ensured that each animal had the same probability of being assigned to a given treatment and therefore systematic error was reduced.

At the time of routine monitoring, the animals were checked for any effects of tumor growth and treatments on normal behavior, such as mobility, visual estimation of food and water consumption, body weight gain/loss (body weights were measured twice weekly), eye/hair matting and any other abnormal effect.

The endpoint was whether tumor growth can be delayed or tumor bearing mice can be cured. Tumor size was measured twice weekly in two dimensions using a caliper, and the volume was expressed in mm^3 using the formula: $V = 0.5\ a \times b^2$ where a and b are the long and short diameters of the tumor, respectively. The tumor size was then used for calculations of both T-C and T/C values. T-C was calculated with T as the time (in days) required for the mean tumor size of the treatment group to reach 1000 mm^3, and C was the time (in days) for the mean tumor size of the control group to reach the same size. The

T/C value (in percent) was an indication of antitumor efficacy; T and C were the mean tumor volume of the treated and control groups, respectively, on a given day. Complete tumor regression (CR) is defined as tumors that are reduced to below the limit of palpation (62.5 mm^3). Partial tumor regression (PR) is defined as tumors that are reduced from initial tumor volume. A minimum duration of CR or PR in 3 or more successive tumor measurements is required for a CP or PR to be considered durable.

Animals for which the body weight loss exceeded 20%, or for which the mean tumor size of the group exceeds 2000 mm^3 were euthanized. The study was terminated after two weeks of observation after the final dose.

Summary statistics, including mean and the standard error of the mean (SEM), are provided for the tumor volume of each group at each time point are shown in Table 15. Statistical analyses of difference in tumor volume among the groups were evaluated using a one-way ANOVA followed by individual comparisons using Games-Howell (equal variance not assumed). All data were analyzed using SPSS 18.0. $p < 0.05$ was considered to be statistically significant**.**

Table 15.

Days	Tumor volume (mm^3)a					
	Vehicle	bispecific EGFR/c-Met molecule at 25mg/kg	Crizotinib at 50mg/kg	Erlotinib at 50mg/kg	Crizotinib; Erlotinib at 50mg/kg; 50mg/kg	Cetuximab at 1 mg/mouse
7	139±7	137±7	140±9	141±8	139±8	139±10
9	230±20	142±7	217±20	201±19	134±9	168±13
13	516±45	83±6	547±43	392±46	109±10	212±20
16	808±104	44±7	914±92	560±70	127±15	252±28
20	1280±209	30±6	1438±239	872±136	214±30	371±48
23	1758±259	23±7	2102±298	1122±202	265±40	485±61
27	2264±318	21±5	--	1419±577	266±42	640±82
30	--	23±6	--	1516±623	482±61	869±100

The mean tumor size of the vehicle treated group (Group 1) reached 1,758 mm^3 at day 23 after tumor inoculation. Treatment with the bispecific EGFR/c-Met molecule at 25 mg/kg dose level (Group 2) led to complete tumor regression (CR) in all mice which were durable in >3 successive tumor measurements (average TV=23 mm^3, T/C value = 1%, p= 0.004 compared with the vehicle group at day 23).

Treatment with crizotinib as a single agent at 50 mg/kg dose level (Group 3) showed no antitumor activity; the mean tumor size was 2,102 mm^3 at day 23 (T/C value =120%, p= 0.944 compared with the vehicle group).

Treatment with erlotinib as a single agent at 50 mg/kg dosing level (Group 4) showed minor antitumor activity, but no significant difference was found compared with the vehicle group; the mean tumor size was 1,122 mm^3 at day 23 (T/C value =64%, p= 0.429 compared with the vehicle group), with 4 days of tumor growth delay at tumor size of 1,000 mm^3 compared with the vehicle group.

The combination of crizotinib (50 mg/kg, Group 5) and erlotinib (50 mg/kg, Group 5) showed significant antitumor activity; the mean tumor size was 265 mm^3 at day 23 (T/C=15%; p= 0.008), with 17 days of tumor growth delay at tumor size of 1,000 mm^3 compared with the vehicle group.

Cetuximab at 1 mg/mouse dosing level as a single agent (Group 6) showed significant antitumor activities; the mean tumor size was 485 mm^3 at day 23 (T/C=28%; p=0.018), with 17 days of tumor growth delay at tumor size of 1,000 mm^3 compared with the vehicle group. Figure 9 and Table 16 show the anti-tumor activities of the various therapies.

Table 16.

Treatment	Tumor Size (mm^3) at day 23	T/C (%)	T-C (days) at 1000 mm^3	*P value*
Vehicle	1758±259	--	--	--
bispecific EGFR/c-Met molecule (25mg/kg)	23±7	1	--	0.004
Crizotinib (50mg/kg)	2102±298	120	-1	0.944
Erlotinib (50mg/kg)	1122±202	64	4	0.429
Crizotinib+ Erlotinib (50mg/kg+50mg/kg)	265±40	15	17	0.008
Cetuximab (1 mg/mouse)	485±61	28	17	0.018

Medium to severe body weight loss was observed in the vehicle group which might be due to the increasing tumor burden; 3 mice died and 1 mouse were euthanized when BWL>20% by day 23. Slight toxicity of the bispecific EGFR/c-Met molecule was

observed in Group 2; 3 mice were euthanized when BWL>20% during the treatment period; the body weight was gradually recovered when the treatment was withdrawn during the 2 weeks of observation period. More severe body weight loss was observed in the crizotinib or erlotinib monotherapy group compared to the vehicle group, suggesting the treatment related toxicity. The combination of crizotinib and erlotinib was generally tolerated during the dosing phase, but severe body weight loss was observed at the end of the study, which might be due to the resumption of the fast tumor growth during the non-treatment period. The monotherapy of cetuximab was well tolerated in the study; body weight loss was only observed at the end of the study due to the resume of the tumor growth.

In summary, the bispecific EGFR/c-Met molecule at 25 mg/kg (3 times/week x 3 weeks) produced a complete response in H292-HGF human lung cancer xenograft model in SCID/Beige mice. The treatment was tolerated in 7 out of 10 mice, and resulted in severe body weight loss in 3 out of 10 mice. Figure 9 shows the impact of the various therapies on tumor size during the time points after treatment.

Example 8: Half-life extension of the bispecific EGFR/c-Met molecules

Numerous methods have been described to reduce kidney filtration and thus extend the serum half-life of proteins including modification with polyethylene glycol (PEG) or other polymers, binding to albumin, fusion to protein domains which bind to albumin or other serum proteins, genetic fusion to albumin, fusion to IgG Fc domains, and fusion to long, unstructured amino acid sequences.

Bispecific EGFR/c-Met molecules were modified with PEG in order to increase the hydrodynamic radius by incorporating a free cysteine at the C-terminus of the molecule. Most commonly, the free thiol group of the cysteine residue is used to attach PEG molecules that are functionalized with maleimide or iodoacetemide groups using standard methods. Various forms of PEG can be used to modify the protein including linear PEG of 1000, 2000, 5000, 10,000, 20,000, or 40,000 kDa. Branched PEG molecules of these molecular weights can also be used for modification. PEG groups may also be attached through primary amines in the bispecific EGFR/c-Met molecules in some instances.

In addition to PEGylation, the half-life of bispecific EGFR/c-Met molecules was extended by producing these proteins as fusion molecules with a naturally occurring 3-helix bundle serum albumin binding domain (ABD) or a consensus albumin binding domain (ABDCon). These protein domains were linked to the C-terminus of the c-Met-

binding FN3 domain via any of the linkers described in Table 12. The ABD or ABDCon domain may also be placed between the EGFR-binding FN3 domain and the c-Met binding FN3 domain in the primary sequence. In some cases, albumin or albumin variant (SEQ ID NO: 189) was linked to the bispecific EGFR/c-Met molecules to the C-terminus of the c-Met binding FN3 domain.

Example 9: Characterization of select bispecific EGFR/c-Met molecules

Select bispecific EGFR/c-Met molecules were characterized for their affinity to both EGFR and c-Met, their ability to inhibit EGFR and c-Met autophosphorylation, and their effect on proliferation of HGF cells. Binding affinity of the bispecific EGFR/c-Met molecules to recombinant EGFR and/or c-Met extracellular domain was further analyzed by surface Plasmon resonance methods using a Proteon Instrument (BioRad) according to protocol described in Example 3. Results of the characterization are shown in Table 17.

Table 17.

Molecule	K_D (EGFR, nM)	K_D (c-Met, nM)	pMet inhibition in H441 cells (IC_{50}, nM)	pEGFR inhibition in H292 cells (IC_{50}, nM)	H292-HGF Proliferation inhibition in HGF-induced H292 cells (IC_{50}, nM)
ECB15	0.2	2.6	n/a	4.2	23
ECB94	1	4.3	53.8	5.1	29.6
ECB95	1.1	6.2	178.8	13.6	383.4
ECB96	1.6	22.1	835.4	24.7	9480
ECB97	1.3	1.7	24.2	16.6	31.0
ECB106	16.7	5.1	53.3	367.4	484.5
ECB107	16.9	9	29.9	812.3	2637
ECB108	15.3	25.5	126.2	814.4	11372
ECB109	17.3	2.1	26	432	573.6
ECB168	0.4	0.32			3.1
ECB158*	0.9	0.58			10.8

*ECB158 is ECB168 conjugated to human serum albumin variant C34S via a $(GGGGS)_2$ linker of SEQ ID NO: 224

Example 10. Paratopes of EGFR and c-Met binding FN3 domains

A series of mutations were made to molecule P54AR4-83v2 (SEQ Id NO: 27) in order to define residues critical for binding to the EGFR extracellular domain. For this analysis, every amino acid position in the BC and FG loops were mutated to alanine one at a time to produce 18 new molecules. The affinity that these mutants bind to EGFR was determined by SPR analysis using a Proteon instrument. The results are shown in Table 18. 10 positions resulted in a loss of binding affinity greater than 10-fold indicating that these positions contribute to binding to EGFR. Fold change indicates fold change of the K_D value of a variant when compared to the parent P54AR4-83v2. A combination of residues from the BC and FG loops makes up the binding surface. 10 positions were shown to weaken binding to EGFR by greater than 10-fold, and 5 positions were shown to weaken binding to EGFR by greater than 100-fold (D23, F27, Y28, V77, G85). In addition to P54AR4-83v2, EGFR-binding molecules P54AR4-48, P54AR4-81, P53A1R5-17v2, P54AR4-83v22 and P54AR4-83v23 (SEQ ID NOs: 21, 25, 107, 108 and 109, respectively) have identical residues at paratope positions that weaken EGFR binding by greater than 100-fold when mutated. Several bispecific EGFR/c-Met molecules generated comprise the P54AR4-83v2, P54AR4-48, P54AR4-81, P53A1R5-17v2, P54AR4-83v22 or P54AR4-83v2 as their EGFR-binding FN3 domain as shown in Table 10.

Table 18.

Molecule	SEQ ID NO:	k_a (1/Ms)	k_d (1/s)	K_D (nM)	Fold Change
P54AR4-83v2	27	3.54E+05	4.98E-05	0.14	1
83v2 D22A	194	2.15E+05	3.01E-05	0.14	1
83v2 D23A	195	1.32E+05	4.20E-03	31.8	227
83v2 P24A	196	7.81E+04	2.19E-04	2.8	20
83v2 W25A	197	1.10E+05	1.69E-04	1.5	11
83v2 F27A	198	2.32E+04	5.56E-04	24	171
83v2 Y28A	199	4.36E+04	3.86E-03	88.5	632
83v2 H75A	200	1.67E+05	6.55E-04	3.9	28
83v2 N76A	201	2.08E+05	7.43E-05	0.36	3
83v2 V77A	202	7.88E+04	8.55E-03	108	771

83v2 Y78A	203	1.82E+05	5.14E-04	2.8	20
83v2 K79A	204	6.81E+05	2.83E-05	0.04	0
83v2 D80A	205	1.23E+05	5.46E-05	0.45	3
83v2 M83A	206	1.77E+05	2.74E-04	1.5	11
83v2 R84A	207	2.34E+05	1.37E-04	0.59	4
83v2 G85A	208	7.30E+04	2.20E-03	30.1	215
83v2 L86A	209	3.09E+05	1.17E-04	0.38	3
83v2 T81A	210	2.28E+05	8.38E-05	0.37	3
83v2 N82A	211	1.94E+05	9.67E-05	0.5	4

Likewise, a series of mutations were made to the presumed c-Met interaction surface of molecule P114AR7P95-A3 (SEQ ID NO: 41) in order to define positions critical for target binding. This analysis was done in the context of bispecific molecule ECB15 (SEQ ID NO: 145) and serine was used as a replacement instead of alanine as described above. Serine was chosen to decrease the hydrophobicity of the resulting mutants. Table 19 describes the SPR results with the numbering of each mutation position relative to that of molecule A3 (SEQ ID NO: 41). 7 positions were shown to weaken binding to c-Met by greater than 10-fold. No binding was measurable for mutants M72S, R34S, and I79S. F38S mutation reduced binding to c-Met by greater than 100-fold. This data demonstrates that the positions contributing for c-Met binding are distributed among the C-strand, F-strand, CD loop, and FG loop. Fold change indicates fold change of the K_D value of a variant when compared to the parent P114AR7P95-A3. In addition to P114AR7P94-A3, c-Met -binding molecules P114AR7P92-F3, P114AR7P95-D3, P114AR7P95-F10 and P114AR7P95-H8 (SEQ ID NOs: 34, 44, 47 and 49, respectively) have identical residues at paratope positions that weaken c-Met binding by greater than 100-fold when mutated.

Table 19.

Sample	SEQ ID NO:	ka (1/Ms)	kd (1/s)	KD (nM)	Fold Change
ECB15	145	3.51E+05	1.33E-04	0.4	1
A3 K78S	212	4.40E+05	1.50E-04	0.3	0.75

A3 G40S	213	1.85E+05	3.20E-04	1.7	4.25
A3 L39S	214	4.75E+05	1.27E-03	2.7	6.75
A3 V68S	215	3.29E+05	1.20E-03	3.6	9
A3 N70S	216	4.25E+05	2.49E-03	5.9	14.75
A3 P81S	217	3.21E+05	5.36E-04	1.7	4.25
A3 F36S	218	1.88E+05	5.12E-03	27.2	68
A3 W32S	219	2.89E+05	8.60E-03	29.8	74.5
A3 M72S	220	-	-	-	
A3 R34S	221	-	-	-	
A3 F38S	222	4.51E+04	3.23E-02	717	1792.5
A3 I79S	223	-	-	-	

Example 11. Inhibition of human tumor cell growth by bispecific EGFR/c-Met molecules

Inhibition of human tumor cell growth was assessed in standard attachment culture as described in Examples 3 or 6, or in low attachment conditions. To assess survival in low attachment conditions, cells were plated in Ultra Low Attachment 96-well plates (Corning Costar) in 50 µL/well of RPMI medium (Invitrogen) containing GlutaMAX and 25mM Hepes, supplemented with 1 mM sodium pyruvate (Gibco), 0.1 mM NEAA (Gibco), and 10% heat inactivated fetal bovine serum (Gibco), and allowed to attach overnight at 37°C, 5% CO_2. Cells were treated with varying concentrations of antibodies (0.035 – 700 nM final), along with HGF (7.5 ng/mL, R&D Systems cat# 294-HGN), then incubated at 37°C, 5% CO_2 for 72 hours. Some wells were left untreated with either HGF or antibodies as controls. Viable cells were detected using CellTiter-Glo® reagent (Promega), and data were analyzed as described above in "Inhibition of Human Tumor Cell Growth (NCI-H292 growth and NCI-H322 growth assay)" in Example 3, except that lysates were transferred to opaque white 96-well tissue culture-treated plates (PerkinElmer) prior to reading luminescence.

Cell line was classified as a strong responder to EGFR/c-Met bispecific molecule in those instances when maximum inhibition of cell growth was > 40% and relative IC_{50} < 5 mM.

Inhibitory activity of ECB15 was assessed in multiple cell lines having wild type, amplified or mutant EGFR and wild type or amplified c-Met. ECB15 inhibited tumor cell growth of cell lines shown in Table 20. ECB15 also inhibited growth of NCI-H1975 cell

line having mutation T790M which has been show to result in resistance to TKIs such as erlotinib.

Table 20.

Cell line	Histology	EGFR	c-Met
NCI-H1650	Broncho-alveolar-adenocarcinoma	Del(E746, A750)	WT
SKMES-1	Squamous	WT	WT
NCI-H1563	Adenocarcinoma		
GLC-82	Adenocarcinoma		
Calu-3	Adenocarcinoma		
NCI-H1573	Adenocarcinoma	AMP	AMP
NCI-H1435	NSCLC		
NCI-H1975	NSCLC	L858R; T790M	WT
NCI-H1666	Broncho-alveolar-adenocarcinoma		
HCC2935	NSCLC	del (E746 - T751), S752I	
HCC4006	Adenocarcinoma	del(L747 - E749), A750P	
H292	Mucoepidermoid	WT	WT
H322	Adenocarcinoma	WT	WT
HCC827	Adenocarcinoma	del (E746, A750); AMP	WT
H596	Adeno-squamous mixed	WT	Exon 14 deletion
H1869	Squamous	WT	WT

WT: wild type
AMP: amplified
Del: deletion

SEQUENCE LISTING

SEQ ID NO:	Type	Species	Description	Sequence
1	PRT	Artificial	Tencon	LPAPKNLVVSEVTEDSLRLSWTAPDAAFDSFLIQYQESEKVGEAINLT VPGSERSYDLTGLKPGTEYTVSIYGVKGGHRSNPLSAEFTT
2	DNA	Artificial	POP2220	GGAAACAGGATCTACCATGCTGCCGGCGCCGAAAAACCTGGTTGT TTCTGAAGTTACC
3	DNA	Artificial	TC5'toFG	AACACCGTAGATAGAAACGGT
4	DNA	Artificial	130mer	CGGCGGTTAGAACGCGGCTACAATTAATACATAACCCCATCCCCC TGTTGACAATTAATCATCGGCTCGTATAATGTGTGGAATTGTGAGC GGATAACAATTTCACACAGGAAACAGGATCTACCATGCTG
5	DNA	Artificial	POP2222	CGGCGGTTAGAACGCGGCTAC
6	DNA	Artificial	TCF7	GGTGGTGAATTCCGCAGACAGCGGSNNSNNSNNSNNSNNSNNSNN AACACCGTAGATAGAAACGGT
7	DNA	Artificial	TCF8	GGTGGTGAATTCCGCAGACAGCGGSNNSNNSNNSNNSNNSNNSNN SNNAACACCGTAGATAGAAACGGT
8	DNA	Artificial	TCF9	GGTGGTGAATTCCGCAGACAGCGGSNNSNNSNNSNNSNNSNNSNN SNNSNNAACACCGTAGATAGAAACGGT
9	DNA	Artificial	TCF10	GGTGGTGAATTCCGCAGACAGCGGSNNSNNSNNSNNSNNSNNSNN SNNSNNSNNAACACCGTAGATAGAAACGGT
10	DNA	Artificial	TCF11	GGTGGTGAATTCCGCAGACAGCGGSNNSNNSNNSNNSNNSNNSNN SNNSNNSNNSNNAACACCGTAGATAGAAACGGT
11	DNA	Artificial	TCF12	GGTGGTGAATTCCGCAGACAGCGGSNNSNNSNNSNNSNNSNNSNN SNNSNNSNNSNNSNNAACACCGTAGATAGAAACGGT
12	DNA	Artificial	POP2234	AAGATCAGTTGCGGCCGCTAGACTAGAACCGCTGCCATGGTGATG GTGATGGTGACCGCCGGTGGTGAATTCCGCAGACAG
13	DNA	Artificial	POP2250	CGGCGGTTAGAACGCGGCTACAATTAATAC
14	DNA	Artificial	DidLigRev	CATGATTACGCCAAGCTCAGAA
15	DNA	Artificial	Tcon5new 2	GAGCCGCCGCCACCGGTTTAATGGTGATGGTGATGGT GACCACCGGTGGTGAATTCCGCAGACAG
16	DNA	Artificial	Tcon6	AAGAAGGAGAACCGGTATGCTGCCGGCGCCGAAAAAC
17	DNA	Artificial	LS1008	TTTGGGAAGCTTCTAGGTCTCGGCGGTCACCATCACC ATCACCATGGCAGCGGTTCTAGTCTAGCGGCCCCAAC TGATCTTCACCAAAC
18	PRT	Artificial	P53A1R5-17 without met	LPAPKNLVVSEVTEDSLRLSWADPHGFYDSFLIQYQES EKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIYGVHNV YKDTNMRGLPLSAEFTT

19	PRT	Artificial	P54AR4-17 without met	LPAPKNLVVSEVTEDSLRLSWTYDRDGYDSFLIQYQES EKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIYGVHNV YKDTNMRGLPLSAEFTT
20	PRT	Artificial	P54AR4-47 without met	LPAPKNLVVSEVTEDSLRLSWGYNGDHFDSFLIQYQES EKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIYGVHNV YKDTNMRGLPLSAEFTT
21	PRT	Artificial	P54AR4-48 without met	LPAPKNLVVSEVTEDSLRLSWDDPRGFYESFLIQYQES EKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIYGVHNV YKDTNMRGLPLSAEFTT
22	PRT	Artificial	P54AR4-37 without met	LPAPKNLVVSEVTEDSLRLSWTWPYADLDSFLIQYQES EKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIYGVHNV YKDTNMRGLPLSAEFTT
23	PRT	Artificial	54AR4-74 without met	LPAPKNLVVSEVTEDSLRLSWGYNGDHFDSFLIQYQES EKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIYGVHNV YKDTNMRGLPLSAEFTT
24	PRT	Artificial	P54AR4-81 without met	LPAPKNLVVSEVTEDSLRLSWDYDLGVYFDSFLIQYQE SEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIYGVHN VYKDTNMRGLPLSAEFTT
25	PRT	Artificial	P54AR4-83 without met	LPAPKNLVVSEVTEDSLRLSWDDPWAFYESFLIQYQES EKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIYGVHNV YKDTNMRGLPLSAEFTT
26	PRT	Artificial	P54CR4-31 without Met	LPAPKNLVVSEVTEDSLRLSWTAPDAAFDSFLIQYQESE KVGEAINLTVPGSERSYDLTGLKPGTEYTVSIYGVLGSY VFEHDVMLPLSAEFTT
27	PRT	Artificial	P54AR4-83v2 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNV YKDTNMRGLPLSAIFTT
28	PRT	Artificial	P54CR4-31v2 without Met	LPAPKNLVVSEVTEDSARLSWTAPDAAFDSFLIQYQESE KVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVLGSY VFEHDVMLPLSAIFTT
29	PRT	Artificial	P54AR4-73v2 wihtout Met	LPAPKNLVVSEVTEDSLRLSWTWPYADLDSFLIQYQES EKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIYGVHNV YKDTNMRGLPLSAEFTT
30	DNA	Artificial	TCON6	AAG AAG GAG AAC CGG TAT GCT GCC GGC GCC GAA AAA C
31	DNA	Artificial	TCON5 E86Ishort	GAG CCG CCG CCA CCG GTT TAA TGG TGA TGG TGA TGG TGA CCA CCG GTG GTG AAG ATC GCA GAC AG
32	PRT	Artificial	P114AR5P74-A5	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYDEV VVGGEAIVLTVPGSERSYDLTGLKPGTEYYVNILGVKGG SISVPLSAIFTT
33	PRT	Artificial	P114AR5P75-E9	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFFIRYDEFL RSGEAIVLTVPGSERSYDLTGLKPGTEYWVTILGVKGGL VSTPLSAIFTT
34	PRT	Artificial	P114AR7P92-F3	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFL GSGEAIVLTVPGSERSYDLTGLKPGTEYIVNIMGVKGGSI SHPLSAIFTT

35	PRT	Artificial	P114AR7P92-F6	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGGLSVPLSAIFTT
36	PRT	Artificial	P114AR7P92-G8	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFVIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYVVQILGVKGGYISIPLSAIFTT
37	PRT	Artificial	P114AR7P92-H5	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYLEFLLGGEAIVLTVPGSERSYDLTGLKPGTEYVVQIMGVKGGTVSPPLSAIFTT
38	PRT	Artificial	P114AR7P93-D11	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYVVGINGVKGGYISYPLSAIFTT
39	PRT	Artificial	P114AR7P93-G8	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTDLKPGTEYGVTINGVKGGRVSTPLSAIFTT
40	PRT	Artificial	P114AR7P93-H9	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYVVQIIGVKGGHISLPLSAIFTT
41	PRT	Artificial	P114AR7P94-A3	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYVVNIMGVKGGKISPPLSAIFTT
42	PRT	Artificial	P114AR7P94-E5	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYAVNIMGVKGGRVSVPLSAIFTT
43	PRT	Artificial	P114AR7P95-B9	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYVVQILGVKGGSISVPLSAIFTT
44	PRT	Artificial	P114AR7P95-D3	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYVVNIMGVKGGSISYPLSAIFTT
45	PRT	Artificial	P114AR7P95-D4	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYVVQILGVKGGYISIPLSAIFTT
46	PRT	Artificial	P114AR7P95-E3	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYVVQIMGVKGGTVSPPLSAIFTT
47	PRT	Artificial	P114AR7P95-F10	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFTTAGEAIVLTVPGSERSYDLTGLKPGTEYVVNIMGVKGGSISPPLSAIFTT
48	PRT	Artificial	P114AR7P95-G7	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFELLSTGEAIVLTVPGSERSYDLTGLKPGTEYVVNIMGVKGGSISPPLSAIFTT

49	PRT	Artificial	P114AR7P95-H8	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFV SKGEAIVLTVPGSERSYDLTGLKPGTEYVVNIMGVKGGSI SPPLSAIFTT
50	PRT	Artificial	ECB1	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTGGGGSGGGGSGGGGSGGGGSM LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYDEVV VGGEAIVLTVPGSERSYDLTGLKPGTEYYVNILGVKGGSIS VPLSAIFTT
51	PRT	Artificial	ECB2	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTGGGGSGGGGSGGGGSGGGGSL PAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLG SGEAIVLTVPGSERSYDLTGLKPGTEYVVNIMGVKGGKIS PPLSAIFTT
52	PRT	Artificial	ECB3	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTGGGGSGGGGSGGGGSGGGGSM LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFL GSGEAIVLTVPGSERSYDLTGLKPGTEYVVQIIGVKGGHIS LPLSAIFTT
53	PRT	Artificial	ECB4	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTGGGGSGGGGSGGGGSGGGGSM LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFFIRYDEFLR SGEAIVLTVPGSERSYDLTGLKPGTEYWVTILGVKGGLVS TPLSAIFTT
54	PRT	Artificial	ECB5	MLPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTGGGGSGGGGSGGGGSGGGGSM LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFL GSGEAIVLTVPGSERSYDLTGLKPGTEYVVNIMGVKGGKI SPPLSAIFTT
55	PRT	Artificial	ECB6	MLPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTGGGGSGGGGSGGGGSGGGGSM LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFL GSGEAIVLTVPGSERSYDLTGLKPGTEYVVQIIGVKGGHIS LPLSAIFTT
56	PRT	Artificial	ECB7	MLPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTGGGGSGGGGSGGGGSGGGGSM LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFL GSGEAIVLTVPGSERSYDLTGLKPGTEYVVQIIGVKGGHIS LPLSAIFTT

57	PRT	Artificial	ECB15	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERS YDLTGLKPGTEYVVNIMGVKGGKISPPLSAIFTT
58	PRT	Artificial	ECB27	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYDEVVVGGEAIVLTVPGSER SYDLTGLKPGTEYYVNILGVKGGSISVPLSAIFTT
59	PRT	Artificial	ECB60	MLPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTAPAPAPAPAPMLPAPKNLVVSRVT EDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSE RSYDLTGLKPGTEYVVNIMGVKGGKISPPLSAIFTT
60	PRT	Artificial	ECB37	MLPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNMRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYDEVVVGGEAIVLTVPGSER SYDLTGLKPGTEYYVNILGVKGGSISVPLSAIFTT
61	PRT	Artificial	ECB94	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERS YDLTGLKPGTEYVVNILGVKGGKISPPLSAIFTT
62	PRT	Artificial	ECB95	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFVGSGEAIVLTVPGSER SYDLTGLKPGTEYVVNILGVKGGSISPPLSAIFTT
63	PRT	Artificial	ECB96	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFVSKGDAIVLTVPGSERS YDLTGLKPGTEYVVNILGVKGGSISPPLSAIFTT
64	PRT	Artificial	ECB97	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERS YDLTGLKPGTEYVVNILSVKGGSISPPLSAIFTT

65	PRT	Artificial	ECB106	MLPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERS YDLTGLKPGTEYVVNILGVKGGKISPPLSAIFTT
66	PRT	Artificial	ECB107	MLPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFVGSGEAIVLTVPGSER SYDLTGLKPGTEYVVNILGVKGGSISPPLSAIFTT
67	PRT	Artificial	ECB108	MLPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFVSKGDAIVLTVPGSERS YDLTGLKPGTEYVVNILGVKGGSISPPLSAIFTT
68	PRT	Artificial	ECB109	MLPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERS YDLTGLKPGTEYVVNILSVKGGSISPPLSAIFTT
69	PRT	Artificial	ECB118	MLPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERS YDLTGLKPGTEYVVNILGVKGGKISPPLSAIFTT
70	PRT	Artificial	ECB119	MLPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFVGSGEAIVLTVPGSER SYDLTGLKPGTEYVVNILGVKGGSISPPLSAIFTT
71	PRT	Artificial	ECB120	MLPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFVSKGDAIVLTVPGSERS YDLTGLKPGTEYVVNILGVKGGSISPPLSAIFTT
72	PRT	Artificial	ECB121	MLPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQES EKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYGVHNVY KDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNLVVSRVTED SARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERS YDLTGLKPGTEYVVNILSVKGGSISPPLSAIFTT

SEQ ID NO: 73, PRT, Homo Sapiens, EGFR

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  1 mrpsgtagaa llallaalcp asraleekkv cqgtsnkltq lgtfedhfls lqrmfnncev
 61 vlgnleityv qrnydlsflk tiqevagyvl ialntverip lenlqiirgn myyensyala
121 vlsnydankt glkelpmrnl qeilhgavrf snnpalcnve siqwrdivss dflsnmsmdf
181 qnhlgscqkc dpscpngscw gageencqkl tkiicaqqcs grcrgkspsd cchnqcaagc
241 tgpresdclv crkfrdeatc kdtcpplmly npttyqmdvn pegkysfgat cvkkcprnyv
301 vtdhgscvra cgadsyemee dgvrkckkce gpcrkvcngi gigefkdsls inatnikhfk
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 361 nctsisgdlh ilpvafrgds fthtppldpq eldilktvke itgflliqaw penrtdlhaf
 421 enleiirgrt kqhgqfslav vslnitslgl rslkeisdgd viisgnknlc yantinwkkl
 481 fgtsgqktki isnrgensck atgqvchalc spegcwgpep rdcvscrnvs rgrecvdkcn
 541 llegeprefv enseciqchp eclpqamnit ctgrgpdnci qcahyidgph cvktcpagvm
 601 genntlvwky adaghvchlc hpnctygctg pglegcptng pkipsiatgm vgallllvv
 661 algiglfmrr rhivrkrtlr rllqerelve pltpsgeapn qallrilket efkkikvlgs
 721 gafgtvykgl wipegekvki pvaikelrea tspkankeil deayvmasvd nphvcrllgi
 781 cltstvqlit qlmpfgclld yvrehkdnig sqyllnwcvq iakgmnyled rrlvhrdlaa
 841 rnvlvktpqh vkitdfglak llgaeekeyh aeggkvpikw malesilhri ythqsdvwsy
 901 gvtvwelmtf gskpydgipa seissilekg erlpqppict idvymimvkc wmidadsrpk
 961 freliiefsk mardpqrylv iqgdermhlp sptdsnfyra lmdeedmddv vdadeylipq
1021 qgffsspsts rtpllsslsa tsnnstvaci drnglqscpi kedsflqrys sdptgalted
1081 siddtflpvp eyinqsvpkr pagsvqnpvy hnqplnpaps rdphyqdphs tavgnpeyln
1141 tvqptcvnst fdspahwaqk gshqisldnp dyqqdffpke akpngifkgs taenaeylrv
1201 apqssefiga
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74	PRT	Homo sapiens	EGF	NSDSECPLSHDGYCLHDGVCMYIEALDKYACNCVVGYIG ERCQYRDLKWWELR

SEQ ID NO: 75, PRT, Homo Sapiens, Tenascin-C

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   1 mgamtqllag vflaflalat eggvlkkvir hkrqsgvnat lpeenqpvvf nhvyniklpv
  61 gsqcsvdles asgekdlapp sepsesfqeh tvdgenqivf thriniprra cgcaaapdvk
 121 ellsrleele nlvsslreqc tagagcclqp atgrldtrpf csgrgnfste gcgcvcepgw
 181 kgpncsepec pgnchlrgrc idgqcicddg ftgedcsqla cpsdcndqgk cvngvcicfe
 241 gyagadcsre icpvpcseeh gtcvdglcvc hdgfagddcn kplclnncyn rgrcvenecv
 301 cdegftgedc selicpndcf drgrcingtc yceegftged cgkptcphac htqgrceegq
 361 cvcdegfagv dcsekrcpad chnrgrcvdg rcecddgftg adcgelkcpn gcsghgrcvn
 421 gqcvcdegyt gedcsqlrcp ndchsrgrcv egkcvceqgf kgydcsdmsc pndchqhgrc
 481 vngmcvcddg ytgedcrdrq cprdcsnrgl cvdgqcvced gftgpdcael scpndchgqg
 541 rcvngqcvch egfmgkdcke qrcpsdchgq grcvdgqcic hegftgldcg qhscpsdcnn
 601 lgqcvsgrci cnegysgedc sevsppkdlv vtevteetvn lawdnemrvt eylvvytpth
 661 egglemqfrv pgdqtstiiq elepgveyfi rvfailenkk sipvsarvat ylpapeglkf
 721 ksiketsvev ewdpldiafe tweiifrnmn kedegeitks lrrpetsyrq tglapgqeye
 781 islhivknnt rgpglkrvtt trldapsqie vkdvtdttal itwfkplaei dgieltygik
 841 dvpgdrttid ltedenqysi gnlkpdteye vslisrrgdm ssnpaketft tgldaprnlr
 901 rvsqtdnsit lewrngkaai dsyrikyapi sggdhaevdv pksqqattkt tltglrpgte
 961 ygigvsavke dkesnpatin aateldtpkd lqvsetaets ltllwktpla kfdryrlnys
1021 lptgqwvgvq lprnttsyvl rglepgqeyn vlltaekgrh kskparvkas teqapelenl
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1081 tvtevgwdgl rlnwtaadqa yehfiiqvqe ankveaarnl tvpgslravd ipglkaatpy
1141 tvsiygviqg yrtpvlsaea stgetpnlge vvvaevgwda lklnwtapeg ayeyffiqvq
1201 eadtveaaqn ltvpgglrst dlpglkaath ytitirgvtq dfsttplsve vlteevpdmg
1261 nltvtevswd alrlnwttpd gtydqftiqv qeadqveeah nltvpgslrs meipglragt
1321 pytvtlhgev rghstrplav evvtedlpql gdlavsevgw dglrlnwtaa dnayehfviq
1381 vqevnkveaa qnltlpgslr avdipgleaa tpyrvsiygv irgyrtpvls aeastakepe
1441 ignlnvsdit pesfnlswma tdgifetfti eiidsnrlle tveynisgae rtahisglpp
1501 stdfivylsg lapsirtkti satattealp llenltisdi npygftvswm asenafdsfl
1561 vtvvdsgkll dpqeftlsgt qrklelrgli tgigyevmvs gftqghqtkp lraeivteae
1621 pevdnllvsd atpdgfrlsw tadegvfdnf vlkirdtkkq sepleitlla pertrditgl
1681 reateyeiel ygiskgrrsq tvsaiattam gspkevifsd itensatvsw raptaqvesf
1741 rityvpitgg tpsmvtvdgt ktqtrlvkli pgveylvsii amkgfeesep vsgsfttald
1801 gpsglvtani tdsealarwq paiatvdsyv isytgekvpe itrtvsgntv eyaltdlepa
1861 teytlrifae kgpqksstit akfttdldsp rdltatevqs etalltwrpp rasvtgyllv
1921 yesvdgtvke vivgpdttsy sladlspsth ytakiqalng plrsnmiqti fttigllypf
1981 pkdcsqamln gdttsglyti ylngdkaeal evfcdmtsdg ggwivflrrk ngrenfyqnw
2041 kayaagfgdr reefwlgldn lnkitaqgqy elrvdlrdhg etafavydkf svgdaktryk
2101 lkvegysgta gdsmayhngr sfstfdkdtd saitncalsy kgafwyrnch rvnlmgrygd
2161 nnhsqgvnwf hwkghehsiq faemklrpsn frnlegrrkr a
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76	PRT	Artificial	Fibcon	Ldaptdlqvtnvtdtsitvswtppsatitgyritytpsngpgepkeltvppsstsv titgltpgveyvvslyalkdnqespplvgtqtt
77	PRT	Artificial	10th FN3 domain of fibronectin (FN10)	VSDVPRDLEVVAATPTSLLISWDAPAVTVRYYRITYGETGGNSPV QEFTVPGSKSTATISGLKPGVDYTITVYAVTGRGDSPASSKPISINY RT
78	PRT	Artificial	Linker	GSGS
79	PRT	Artificial	Linker	GGGGSGGGGSGGGGSGGGGSGGGGS
80	PRT	Artificial	Linker	APAP
81	PRT	Artificial	Linker	APAPAPAPAP
82	PRT	Artificial	Linker	APAPAPAPAPAPAPAPAPAP
83	PRT	Artificial	Linker	APAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAPAP

84	PRT	Artificial	Linker	AEAAAKEAAAKEAAAKEAAAKEAAAKAAA
85	PRT	Artificial	Tencon BC loop	TAPDAAFD
86	PRT	Artificial	Tencon GF loop	KGGHRSN
87	PRT	Artificial	P53A1R5-17 BC loop	ADPHGFYD
88	PRT	Artificial	P54AR4-17 BC loop	TYDRDGYD
89	PRT	Artificial	P54AR4-47 BC loop	WDPFSFYD
90	PRT	Artificial	P54AR4-48 BC loop	DDPRGFYE
91	PRT	Artificial	P54AR4-73 BC loop	TWPYADLD
92	PRT	Artificial	P54AR4-74 BC loop	GYNGDHFD

93	PRT	Artificial	P54AR4-81 BC loop	DYDLGVYD
94	PRT	Artificial	P54AR4-83 BC loop	DDPWDFYE
95	PRT	Artificial	FG loops of EGFR	HNVYKDTNMRGL
96	PRT	Artificial	FG loops of EGFR	LGSYVFEHDVM
97	DNA	Artificial	>EGFR part ECB97; P54AR4-83v22	Atgttgccagcgccgaagaacctggtagttagcgaggttactgaggac agcgcgcgtctgagctgggacgatccgtgggcgttctacgagagctttct gatccagtatcaagagagcgagaaagtcggtgaagcgattgtgctgac cgtcccgggctccgagcgttcctacgacctgaccggtttgaagccgggt accgagtatacggtgagcatctacggtgttcacaatgtctataaggaca ctaatatccgcggtctgcctctgagcgccattttcaccacc
98	DNA	Artificial	>EGFR part ECB15; P54AR4-83v2	Atgctgccagcccctaagaatctggtcgtgagcgaagtaaccgagga cagcgcccgcctgagctgggacgacccgtgggcgttctatgagtctttcc tgattcagtatcaagaaagcgaaaaagttggcgaagcgatcgtcctga ccgtcccgggtagcgagcgctcctacgatctgaccggcctgaaaccgg gtacggagtacacggtgtccatttacggtgttcacaatgtgtataaagac accaacatgcgtggcctgccgctgtcggcgattttcaccacc
99	PRT	Artificial	tencon 27	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VKGGHRSNPLSAIFTT
100	PRT	Artificial	TCL14 library	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFXIXYX EXXXXGEAIVLTVPGSERSYDLTGLKPGTEYXVXIXG VKGGXXSXPLSAIFTT

>SEQ ID NO: 101
PRT
Homo sapiens
cMet

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       1 mkapavlapg ilvllftlvq rsngeckeal aksemnvnmk yqlpnftaet piqnvilheh
      61 hiflgatnyi yvlneedlqk vaeyktgpvl ehpdcfpcqd csskanlsgg vwkdninmal
     121 vvdtyyddql iscgsvnrgt cqrhvfphnh tadiqsevhc ifspqieeps qcpdcvvsal
     181 gakvlssvkd rfinffvgnt inssyfpdhp lhsisvrrlk etkdgfmflt dqsyidvlpe
     241 frdsypikyv hafesnnfiy fltvqretld aqtfhtriir fcsinsglhs ymemplecil
     301 tekrkkrstk kevfnilqaa yvskpgaqla rqigaslndd ilfgvfaqsk pdsaepmdrs
     361 amcafpikyv ndffnkivnk nnvrclqhfy gpnhehcfnr tllrnssgce arrdeyrtef
     421 ttalqrvdlf mgqfsevllt sistfikgdl tianlgtseg rfmqvvvsrs gpstphvnfl
     481 ldshpvspev ivehtlnqng ytlvitgkki tkiplnglgc rhfqscsqcl sappfvqcgw
     541 chdkcvrsee clsgtwtqqi clpaiykvfp nsapleggtr lticgwdfgf rrnnkfdlkk
     601 trvllgnesc tltlsestmn tlkctvgpam nkhfnmsiii snghgttqys tfsyvdpvit
     661 sispkygpma ggtlltltgn ylnsgnsrhi siggktctlk svsnsilecy tpaqtistef
     721 avklkidlan retsifsyre dpivyeihpt ksfistwwke plnivsflfc fasggstitg
     781 vgknlnsvsv prmvinvhea grnftvacqh rsnseiicct tpslqqlnlq lplktkaffm
     841 ldgilskyfd liyvhnpvfk pfekpvmism gnenvleikg ndidpeavkg evlkvgnksc
     901 enihlhseav lctvpndllk lnselniewk qaisstvlgk vivqpdqnft gliagvvsis
     961 tallllgff lwlkkrkqik dlgselvryd arvhtphldr lvsarsvspt temvsnesvd
    1021 yratfpedqf pnssqngscr qvqypltdms piltsgdsdi ssplqntvh idlsalnpel
    1081 vqavqhvvig psslivhfne vigrghfgcv yhgtlldndg kkihcavksl nritdigevs
    1141 qfltegiimk dfshpnvlsl lgiclrsegs plvvlpymkh gdlrnfirne thnptvkdli
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1201 gfglqvakgm kylaskkfvh rdlaarncml dekftvkvad fglardmydk eyysvhnktg

1261 aklpvkwmal eslqtqkftt ksdvwsfgvl lwelmtrgap pypdvntfdi tvyllqgrrl

1321 lqpeycpdpl yevmlkcwhp kaemrpsfse lvsrisaifs tfigehyvhv natyvnvkcv

1381 apypsllsse dnaddevdtr pasfwets

102	PRT	Homo sapiens	HGF	QRKRRNTIHEFKKSAKTTLIKIDPALKIK TKKVNTADQCANRCTRNKGLPFTCKAFVFDKARKQCLWFPFNSMS SGVKKEFGHEFDLYE NKDYIRNCIIGKGRSYKGTVSITKSGIKCQPWSSMIPHEHSFLPSSYRG KDLQENYCRNP RGEEGGPWCFTSNPEVRYEVCDIPQCSEVECMTCNGESYRGLMDH TESGKICQRWDHQTP HRHKFLPERYPDKGFDDNYCRNPDGQPRPWCYTLDPHTRWEYCAIK TCADNTMNDTDVPL ETTECIQGQGEGYRGTVNTIWNGIPCQRWDSQYPHEHDMTPENFKC KDLRENYCRNPDGS ESPWCFTTDPNIRVGYCSQIPNCDMSHGQDCYRGNGKNYMGNLSQT RSGLTCSMWDKNME DLHRHIFWEPDASKLNENYCRNPDDDAHGPWCYTGNPLIPWDYCPIS RCEGDTTPTIVNL DHPVISCAKTKQLRVVNGIPTRTNIGWMVSLRYRNKHICGGSLIKESW VLTARQCFPSRD LKDYEAWLGIHDVHGRGDEKCKQVLNVSQLVYGPEGSDLVLMKLAR PAVLDDFVSTIDLP NYGCTIPEKTSCSVYGWGYTGLINYDGLLRVAHLYIMGNEKCSQHHRG KVTLNESEICAG AEKIGSGPCEGDYGGPLVCEQHKMRMVLGVIVPGRGCAIPNRPGIFV RVAYYAKWIHKII LTYKVPQS
103	DNA	Artificial	>cMET part ECB97 P114AR7P95-C5v2	Ctgccggctccgaagaacttggtggtgagccgtgttaccgaagatagc gcacgcctgagctggacggcaccggatgcggcgttcgatagcttctgg attcgctattttgagtttctgggtagcggtgaggcaattgttctgacggtgcc gggctctgaacgctcctacgatttgaccggtctgaaaccgggcaccga gtatgtggtgaacattctgagcgttaagggcggtagcatcagcccaccg ctgagcgcgatcttcacgactggtggttgc
104	DNA	Artificial	>cMET part ECB15 P114AR7P94-A3	Ctgccggcaccgaagaacctggttgtcagccgtgtgaccgaggatag cgcacgtttgagctggaccgctccggatgcagcctttgacagcttctgga ttcgttactttgaatttctgggtagcggtgaggcgatcgttctgacggtgccg ggctctgaacgcagctatgatttgacgggcctgaagccgggtactgagt acgtggttaacatcatgggcgttaagggtggtaaaatcagcccgccatt gtccgcgatctttaccacg
105	PRT	Artificial	linker	GGGGS
106	PRT	Artificial	ECB91	mlpapknlvvsevtedsarlswddpwafyesfliqyqesekvgeaivltvpgse rsydltglkpgteytvsiygvhnvykdtnirglplsaifttapapapapapLPAP KNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTV PGSERSYDLTGLKPGTEYVVNILSVKGGSISPPLSAIFTT
107	PRT	Artificial	P53A1R5-17v2	lpapknlvvsevtedsarlswadphgfydsfliqyqesekvgeaivltvpgsersy dltglkpgteytvsiygvhnvykdtnmrglplsaiftt

108	PRT	Artificial	P54AR4-83v22	lpapknlvvsevtedsarlswddpwafyesfliqyqesekvgeaivltvpgsersydltglkpgteytvsiygvhnvykdtnirglplsaiftt
109	PRT	Artificial	P54AR4-83v23	lpapknlvvsevtedsarlswddphafyesfliqyqesekvgeaivltvpgsersydltglkpgteytvsiygvhnvykdtnirglplsaiftt
110	PRT	Artificial	P53A1R5-17v22	lpapknlvvsevtedsarlswadphgfydsfliqyqesekvgeaivltvpgsersydltglkpgteytvsiygvhnvykdtnirglplsaiftt
111	PRT	Artificial	P114AR7P94-A3v22	lpapknlvvsrvtedsarlswtapdaafdsfwiryfeflgsgeaivltvpgsersydltglkpgteyvvnilgvkggkispplsaiftt
112	PRT	Artificial	P114AR9P121-A6v2	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVGSGEAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSISPPLSAIFTT
113	PRT	Artificial	P114AR9P122-A7v2	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVSKGDAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSISPPLSAIFTT
114	PRT	Artificial	P114AR7P95-C5v2	LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGTEYVVNILSVKGGSISPPLSAIFTT
115	DNA	Artificial	ECB97	atgttgccagcgccgaagaacctggtagttagcgaggttactgaggacagcgcgcgtctgagctgggacgatccgtgggcgttctacgagagctttctgatccagtatcaagagagcgagaaagtcggtgaagcgattgtgctgaccgtcccgggctccgagcgttcctacgacctgaccggtttgaagccgggtaccgagtatacggtgagcatctacggtgttcacaatgtctataaggacactaatatccgcggtctgcctctgagcgccattttcaccaccgcaccggcaccggctccggctcctgccccgctgccggctccgaagaacttggtggtgagccgtgttaccgaagatagcgcacgcctgagctggacggcaccggatgcggcgttcgatagcttctggattcgctattttgagtttctgggtagcggtgaggcaattgttctgacggtgccgggctctgaacgctcctacgatttgaccggtctgaaaccgggcaccgagtatgtggtgaacattctgagcgttaagggcggtagcatcagcccaccgctgagcgcgatcttcacgactggtggttgc
116	DNA	Artificial	ECB15	atgctgccagcccctaagaatctggtcgtgagcgaagtaaccgaggacagcgcccgcctgagctgggacgacccgtgggcgttctatgagtctttcctgattcagtatcaagaaagcgaaaaagttggcgaagcgatcgtcctgaccgtcccgggtagcgagcgctcctacgatctgaccggcctgaaaccgggtacggagtacacggtgtccatttacggtgttcacaatgtgtataaagacaccaacatgcgtggcctgccgctgtcggcgattttcaccaccgcgcctgccagcgcctgcaccggctccgctgccggcaccgaagaacctggttgtcagccgtgtgaccgaggatagcgcacgtttgagctggaccgctccggatgcagcctttgacagcttctggattcgttactttgaatttctgggtagcggtgaggcgatcgttctgacggtgccgggctctgaacgcagctatgatttgacggcctgaagccgggtactgagtacgtggttaacatcatgggcgttaaggtggtaaaatcagcccgccattgtccgcgatctttaccacg
117	PRT	Artificial	albumin binding domain	tidewllkeakekaieelkkagitsdyyfdlinkaktvegvnalkdeilka

118	PRT	Artificial	ECB18	mlpapknlvvsevtedsarlswddpwafyesfliqyqesekvgeaivltv pgsersydltglkpgteytvsiygvhnvykdtnmrglplsaifttapapapa paplpapknlvvsrvtedsarlswtapdaafdsfwirydevvvggeaivlt vpgsersydltglkpgteyyvnilgvkggsisvplsaifttapapapapapl aeakvlanreldkygvsdyyknlinnaktvegvkalldeilaalp
119	PRT	Artificial	ECB28	mlpapknlvvsevtedsarlswadphgfydsfliqyqesekvgeaivltv pgsersydltglkpgteytvsiygvhnvykdtnmrglplsaifttapapapa paplpapknlvvsrvtedsarlswtapdaafdsfwirydevvvggeaivlt vpgsersydltglkpgteyyvnilgvkggsisvplsaifttapapapapapl aeakvlanreldkygvsdyyknlinnaktvegvkalldeilaalp
120	PRT	Artificial	ECB38	mlpapknlvvsevtedsarlswddpwafyesfliqyqesekvgeaivltv pgsersydltglkpgteytvsiygvhnvykdtnmrglplsaifttapapapa paplpapknlvvsrvtedsarlswtapdaafdsfwiryfeflgsgeaivltv pgsersydltglkpgteyvvnimgvkggkispplsaifttapapapapapl aeakvlanreldkygvsdyyknlinnaktvegvkalldeilaalp
121	PRT	Artificial	ECB39	mlpapknlvvsevtedsarlswadphgfydsfliqyqesekvgeaivltv pgsersydltglkpgteytvsiygvhnvykdtnmrglplsaifttapapapa paplpapknlvvsrvtedsarlswtapdaafdsfwiryfeflgsgeaivltv pgsersydltglkpgteyvvnimgvkggkispplsaifttapapapapapl aeakvlanreldkygvsdyyknlinnaktvegvkalldeilaalp
122	PRT	Artificial	P53A1R5-17 wthMet	MLPAPKNLVVSEVTEDSLRLSWADPHGFYDSFLIQY QESEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNMRGLPLSAEFTT
123	PRT	Artificial	P54AR4-17 with Met	MLPAPKNLVVSEVTEDSLRLSWTYDRDGYDSFLIQY QESEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNMRGLPLSAEFTT
124	PRT	Artificial	P54AR4-47 with Met	MLPAPKNLVVSEVTEDSLRLSWGYNGDHFDSFLIQY QESEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNMRGLPLSAEFTT
125	PRT	Artificial	P54AR4-48 with Met	MLPAPKNLVVSEVTEDSLRLSWDDPRGFYESFLIQY QESEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNMRGLPLSAEFTT
126	PRT	Artificial	P54AR4-73 with Met	MLPAPKNLVVSEVTEDSLRLSWTWPYADLDSFLIQY QESEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNMRGLPLSAEFTT
127	PRT	Artificial	54AR4-74 with Met	MLPAPKNLVVSEVTEDSLRLSWGYNGDHFDSFLIQY QESEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNMRGLPLSAEFTT
128	PRT	Artificial	P54AR4-81 with Met	MLPAPKNLVVSEVTEDSLRLSWDYDLGVYFDSFLIQ YQESEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSI YGVHNVYKDTNMRGLPLSAEFTT
129	PRT	Artificial	P54AR4-83 with Met	MLPAPKNLVVSEVTEDSLRLSWDDPWAFYESFLIQY QESEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNMRGLPLSAEFTT

130	PRT	Artificial	P54CR4-31 with Met	MLPAPKNLVVSEVTEDSLRLSWTAPDAAFDSFLIQY QESEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIY GVLGSYVFEHDVMLPLSAEFTT
131	PRT	Artificial	P54AR4-83v2 with Met	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQY QESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNMRGLPLSAIFTT
132	PRT	Artificial	P54CR4-31v2 with Met	MLPAPKNLVVSEVTEDSARLSWTAPDAAFDSFLIQY QESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIY GVLGSYVFEHDVMLPLSAIFTT
133	PRT	Artificial	P54AR4-73v2 withMet	MLPAPKNLVVSEVTEDSLRLSWTWPYADLDSFLIQY QESEKVGEAINLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNMRGLPLSAEFTT
134	PRT	Artificial	P53A1R5-17v2 with Met	mlpapknlvvsevtedsarlswadphgfydsfliqyqesekvgeaivltvpgser sydltglkpgteytvsiygvhnvykdtnmrglplsaiftt
135	PRT	Artificial	P54AR4-83v22 with Met	mlpapknlvvsevtedsarlswddpwafyesfliqyqesekvgeaivltvpgse rsydltglkpgteytvsiygvhnvykdtnirglplsaiftt
136	PRT	Artificial	P54AR4-83v23 with Met	mlpapknlvvsevtedsarlswddphafyesfliqyqesekvgeaivltvpgser sydltglkpgteytvsiygvhnvykdtnirglplsaiftt
137	PRT	Artificial	P53A1R5-17v22 with Met	mlpapknlvvsevtedsarlswadphgfydsfliqyqesekvgeaivltvpgser sydltglkpgteytvsiygvhnvykdtnirglplsaiftt
138	PRT	Artificial	ECB1 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTGGGGSGGGGSGGGG SGGGGSMLPAPKNLVVSRVTEDSARLSWTAPDAAF DSFWIRYDEVVVGGEAIVLTVPGSERSYDLTGLKPG TEYYVNILGVKGGSISVPLSAIFTT
139	PRT	Artificial	ECB2 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTGGGGSGGGGSGGGG SGGGGSLPAPKNLVVSRVTEDSARLSWTAPDAAFD SFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPGT EYVVNIMGVKGGKISPPLSAIFTT
140	PRT	Artificial	ECB3 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTGGGGSGGGGSGGGG SGGGGSMLPAPKNLVVSRVTEDSARLSWTAPDAAF DSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPG TEYVVQIIGVKGGHISLPLSAIFTT

141	PRT	Artificial	ECB4 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTGGGGSGGGGSGGGG SGGGGSMLPAPKNLVVSRVTEDSARLSWTAPDAAF DSFFIRYDEFLRSGEAIVLTVPGSERSYDLTGLKPGT EYWVTILGVKGGLVSTPLSAIFTT
142	PRT	Artificial	ECB5 without Met	LPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTGGGGSGGGGSGGGG SGGGGSMLPAPKNLVVSRVTEDSARLSWTAPDAAF DSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPG TEYVVNIMGVKGGKISPPLSAIFTT
143	PRT	Artificial	ECB6 without Met	LPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTGGGGSGGGGSGGGG SGGGGSMLPAPKNLVVSRVTEDSARLSWTAPDAAF DSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPG TEYVVQIIGVKGGHISLPLSAIFTT
144	PRT	Artificial	ECB7 without Met	LPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTGGGGSGGGGSGGGG SGGGGSMLPAPKNLVVSRVTEDSARLSWTAPDAAF DSFWIRYFEFLGSGEAIVLTVPGSERSYDLTGLKPG TEYVVQIIGVKGGHISLPLSAIFTT
145	PRT	Artificial	ECB15 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSG EAIVLTVPGSERSYDLTGLKPGTEYVVNIMGVKGGKI SPPLSAIFTT
146	PRT	Artificial	ECB27 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYDEVVVGG EAIVLTVPGSERSYDLTGLKPGTEYYVNILGVKGGSI SVPLSAIFTT
147	PRT	Artificial	ECB60 without Met	LPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTAPAPAPAPAPMLPAPK NLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGS GEAIVLTVPGSERSYDLTGLKPGTEYVVNIMGVKGG KISPPLSAIFTT
148	PRT	Artificial	ECB37 without Met	LPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNMRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYDEVVVGG EAIVLTVPGSERSYDLTGLKPGTEYYVNILGVKGGSI SVPLSAIFTT

149	PRT	Artificial	ECB94 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGE AIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGKIS PPLSAIFTT
150	PRT	Artificial	ECB95 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVGSG EAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSI SPPLSAIFTT
151	PRT	Artificial	ECB96 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVSKGD AIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSIS PPLSAIFTT
152	PRT	Artificial	ECB97 without Met	LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGE AIVLTVPGSERSYDLTGLKPGTEYVVNILSVKGGSISP PLSAIFTT
153	PRT	Artificial	ECB106 without Met	LPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGE AIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGKIS PPLSAIFTT
154	PRT	Artificial	ECB107 without Met	LPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVGSG EAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSI SPPLSAIFTT
155	PRT	Artificial	ECB108 without Met	LPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVSKGD AIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSIS PPLSAIFTT
156	PRT	Artificial	ECB109 without Met	LPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGE AIVLTVPGSERSYDLTGLKPGTEYVVNILSVKGGSISP PLSAIFTT

157	PRT	Artificial	ECB118 without Met	LPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGE AIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGKIS PPLSAIFTT
158	PRT	Artificial	ECB119 without Met	LPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVGSG EAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSI SPPLSAIFTT
159	PRT	Artificial	ECB120 without Met	LPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVSKGD AIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSIS PPLSAIFTT
160	PRT	Artificial	ECB121 without Met	LPAPKNLVVSEVTEDSARLSWADPHGFYDSFLIQYQ ESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIYG VHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKNL VVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGE AIVLTVPGSERSYDLTGLKPGTEYVVNILSVKGGSISP PLSAIFTT
161	PRT	Artificial	ECB91 without Met	lpapknlvvsevtedsarlswddpwafyesfliqyqesekvgeaivltvpgsers ydltglkpgteytvsiygvhnvykdtnirglplsaifttapapapapapLPAPK NLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVP GSERSYDLTGLKPGTEYVVNILSVKGGSISPPLSAIFTT
162	PRT	Artificial	ECB18 without Met	lpapknlvvsevtedsarlswddpwafyesfliqyqesekvgeaivltvp gsersydltglkpgteytvsiygvhnvykdtnmrglplsaifttapapapap aplpapknlvvsrvtedsarlswtapdaafdsfwirydevvvggeaivltv pgsersydltglkpgteyyvnilgvkggsisvplsaifttapapapapapla eakvlanreldkygvsdyyknlinnaktvegvkalldeilaalp
163	PRT	Artificial	ECB28 without Met	lpapknlvvsevtedsarlswadphgfydsfliqyqesekvgeaivltvpg sersydltglkpgteytvsiygvhnvykdtnmrglplsaifttapapapapa plpapknlvvsrvtedsarlswtapdaafdsfwirydevvvggeaivltvp gsersydltglkpgteyyvnilgvkggsisvplsaifttapapapapaplae akvlanreldkygvsdyyknlinnaktvegvkalldeilaalp
164	PRT	Artificial	ECB38 without Met	lpapknlvvsevtedsarlswddpwafyesfliqyqesekvgeaivltvp gsersydltglkpgteytvsiygvhnvykdtnmrglplsaifttapapapap aplpapknlvvsrvtedsarlswtapdaafdsfwiryfeflgsgeaivltvp gsersydltglkpgteyvvnimgvkggkispplsaifttapapapapapla eakvlanreldkygvsdyyknlinnaktvegvkalldeilaalp

165	PRT	Artificial	ECB39 without Met	lpapknlvvsevtedsarlswadphgfydsfliqyqesekvgeaivltvpg sersydltglkpgteytvsiygvhnvykdtnmrglplsaifttapapapapa plpapknlvvsrvtedsarlswtapdaafdsfwiryfeflgsgeaivltvpg sersydltglkpgteyvvnimgvkggkispplsaifttapapapapaplae akvlanreldkygvsdyyknlinnaktvegvkalldeilaalp
166	DNA	Artificial	ECB97 without Met	ttgccagcgccgaagaacctggtagttagcgaggttactgaggacagc gcgcgtctgagctgggacgatccgtgggcgttctacgagagctttctgat ccagtatcaagagagcgagaaagtcggtgaagcgattgtgctgaccgt cccgggctccgagcgttcctacgacctgaccggtttgaagccgggtacc gagtatacggtgagcatctacggtgttcacaatgtctataaggacactaa tatccgcggtctgcctctgagcgccattttcaccaccgcaccggcaccg gctccggctcctgccccgctgccggctccgaagaacttggtggtgagcc gtgttaccgaagatagcgcacgcctgagctggacggcaccggatgcg gcgttcgatagcttctggattcgctattttgagtttctgggtagcggtgaggc aattgttctgacggtgccgggctctgaacgctcctacgatttgaccggtct gaaaccgggcaccgagtatgtggtgaacattctgagcgttaagggcggt agcatcagcccaccgctgagcgcgatcttcacgactggtggttgc
167	DNA	Artificial	ECB15 without Met	ctgccagcccctaagaatctggtcgtgagcgaagtaaccgaggacag cgcccgcctgagctgggacgacccgtgggcgttctatgagtctttcctga ttcagtatcaagaaagcgaaaaagttggcgaagcgatcgtcctgaccg tcccgggtagcgagcgctcctacgatctgaccggcctgaaaccgggta cggagtacacggtgtccatttacggtgttcacaatgtgtataaagacacc aacatgcgtggcctgccgctgtcggcgattttcaccaccgcgcctgcgc cagcgcctgcaccggctccgctgccggcaccgaagaacctggttgtca gccgtgtgaccgaggatagcgcacgtttgagctggaccgctccggatg cagcctttgacagcttctggattcgttactttgaatttctgggtagcggtgag gcgatcgttctgacggtgccgggctctgaacgcagctatgatttgacggg cctgaagccgggtactgagtacgtggttaacatcatgggcgttaagggtg gtaaaatcagcccgccattgtccgcgatctttaccacg
168	DNA	Artificial	>EGFR part ECB97; P54AR4-83v22 without met	ttgccagcgccgaagaacctggtagttagcgaggttactgaggacagc gcgcgtctgagctgggacgatccgtgggcgttctacgagagctttctgat ccagtatcaagagagcgagaaagtcggtgaagcgattgtgctgaccgt cccgggctccgagcgttcctacgacctgaccggtttgaagccgggtacc gagtatacggtgagcatctacggtgttcacaatgtctataaggacactaa tatccgcggtctgcctctgagcgccattttcaccacc
169	DNA	Artificial	>EGFR part ECB15; P54AR4-83v2 without Met	ctgccagcccctaagaatctggtcgtgagcgaagtaaccgaggacag cgcccgcctgagctgggacgacccgtgggcgttctatgagtctttcctga ttcagtatcaagaaagcgaaaaagttggcgaagcgatcgtcctgaccg tcccgggtagcgagcgctcctacgatctgaccggcctgaaaccgggta cggagtacacggtgtccatttacggtgttcacaatgtgtataaagacacc aacatgcgtggcctgccgctgtcggcgattttcaccacc
170	PRT	Artificial	ECB94 with C-ter cysteine	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQY QESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSG EAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGKI SPPLSAIFTTC
171	PRT	Artificial	ECB95 with C-ter cysteine	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQY QESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVGSG EAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSI SPPLSAIFTTC

172	PRT	Artificial	ECB96 with C-ter cysteine	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQY QESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVSKG DAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSI SPPLSAIFTTC
173	PRT	Artificial	ECB97 with C-ter cysteine	MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQY QESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSG EAIVLTVPGSERSYDLTGLKPGTEYVVNILSVKGGSIS PPLSAIFTTC
174	PRT	Artificial	ECB106 with C-ter cysteine	MLPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQY QESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSG EAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGKI SPPLSAIFTTC
175	PRT	Artificial	ECB107 with C-ter cysteine	MLPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQY QESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVGSG EAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSI SPPLSAIFTTC
176	PRT	Artificial	ECB108 with C-ter cysteine	MLPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQY QESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFVSKG DAIVLTVPGSERSYDLTGLKPGTEYVVNILGVKGGSI SPPLSAIFTTC
177	PRT	Artificial	ECB109 with C-ter cysteine	MLPAPKNLVVSEVTEDSARLSWDDPHAFYESFLIQY QESEKVGEAIVLTVPGSERSYDLTGLKPGTEYTVSIY GVHNVYKDTNIRGLPLSAIFTTAPAPAPAPAPLPAPKN LVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSG EAIVLTVPGSERSYDLTGLKPGTEYVVNILSVKGGSIS PPLSAIFTTC
178	PRT	Artificial	ECB91 with C-ter cysteine	mlpapknlvvsevtedsarlswddpwafyesfliqyqesekvgeaivltvpgse rsydltglkpgteytvsiygvhnvykdtnirglplsaifttapapapapapLPAP KNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTV PGSERSYDLTGLKPGTEYVVNILSVKGGSISPPLSAIFTTC

>SEQ ID NO: 179

PRT

Artificial

An FG loop of EGFR binding FN3 domain

HNVYKDTNX$_9$RGL;
wherein X$_9$ is M or I

>SEQ ID NO: 180
PRT
Artificial
A FG loop of EGFR binding FN3 domain
LGSYVFEHDVML (SEQ ID NO: 180),

>SEQ ID NO: 181
PRT
Artificial
a BC loop of EGFR binding FN3 domain
X$_1$X$_2$X$_3$X$_4$X$_5$X$_6$X$_7$X$_8$ (SEQ ID NO: 181), wherein
X$_1$ is A, T, G or D;
X$_2$ is A, D, Y or W;
X$_3$ is P, D or N;
X$_4$ is L or absent;
X$_5$ is D, H, R, G, Y or W;
X$_6$ is G, D or A;
X$_7$ is A, F, G, H or D; and
X$_8$ is Y, F or L.

>SEQ ID NO: 182
PRT
Artificial
EGFR binding FN3 domain
LPAPKNLVVSEVTEDSLRLSWX$_1$X$_2$X$_3$X$_4$X$_5$X$_6$X$_7$X$_8$DSFLIQYQESEKVGEAINLTVP
GSERSYDLTGLKPGTEYTVSIYGVHNVYKDTNX$_9$RGLPLSAEFTT (SEQ ID NO:
182),
X$_1$ is A, T, G or D;
X$_2$ is A, D, Y or W;
X$_3$ is P, D or N;
X$_4$ is L or absent;

X_5 is D, H, R, G, Y or W;

X_6 is G, D or A;

X_7 is A, F, G, H or D;

X_8 is Y, F or L; and

X_9 is M or I

>SEQ ID NO: 183

PRT

Artificial

EGFR binding FN3 domain

LPAPKNLVVSEVTEDSLRLSW$X_1X_2X_3X_4X_5X_6X_7X_8$DSFLIQYQESEKVGEAINLTVP GSERSYDLTGLKPGTEYTVSIYGVLGSYVFEHDVMLPLSAEFTT (SEQ ID NO: 183),

wherein

X_1 is A, T, G or D;

X_2 is A, D, Y or W;

X_3 is P, D or N;

X_4 is L or absent;

X_5 is D, H, R, G, Y or W;

X_6 is G, D or A;

X_7 is A, F, G, H or D; and

X_8 is Y, F or L.

>SEQ ID NO: 184

PRT

Artificial

A C-met binding FN3 domain C strand and a CD loop sequence

DSFX_{10}IRYX_{11}E $X_{12}X_{13}X_{14}X_{15}$GX_{16} (SEQ ID NO: 184), wherein

X_{10} is W, F or V;

X_{11} is D, F or L;

X_{12} is V, F or L;

X_{13} is V, L or T;

X_{14} is V, R, G, L, T or S;

X_{15} is G, S, A, T or K; and

X_{16} is E or D; and

>SEQ ID NO: 185

PRT

Artificial

A c-Met binding FN3 domain F strand and a FG loop

TEYX_{17}VX_{18}I$X_{19}X_{20}$V KGG$X_{21}X_{22}$SX_{23} (SEQ ID NO: 185), wherein

X_{17} is Y, W, I, V, G or A;

X_{18} is N, T, Q or G;

X_{19} is L, M, N or I;

X_{20} is G or S;

X_{21} is S, L, G, Y, T, R, H or K;

X_{22} is I, V or L; and

X_{23} is V, T, H, I, P, Y or L.

>SEQ ID NO: 186

PRT

Artificial

a c-Met binding FN3 domain

LPAPKNLVVSRVTEDSARLSWTAPDAAF DSFX_{10}IRYX_{11}E $X_{12}X_{13}X_{14}X_{15}$GX_{16} AIVLTVPGSERSYDLTGLKPGTEYX_{17}VX_{18}I$X_{19}X_{20}$VKGG$X_{21}X_{22}$SX_{23}PLSAEFTT (SEQ ID NO: 186),

wherein

X_{10} is W, F or V; and

X_{11} is D, F or L;

X_{12} is V, F or L;

X_{13} is V, L or T;

X_{14} is V, R, G, L, T or S;

X_{15} is G, S, A, T or K;

X_{16} is E or D;

X_{17} is Y, W, I, V, G or A;

X_{18} is N, T, Q or G;

X_{19} is L, M, N or I;

X_{20} is G or S;

X_{21} is S, L, G, Y, T, R, H or K;

X_{22} is I, V or L; and

X_{23} is V, T, H, I, P, Y or L.

>SEQ ID NO: 187

PRT

Artificial

EGFR FN3 domain of a bispecific EGFR/c-Met FN3 domain containing molecule

LPAPKNLVVSX$_{24}$VTX$_{25}$DSX$_{26}$RLSWDDPX$_{27}$AFYX$_{28}$SFLIQYQX$_{29}$SEKVGEAIX$_{30}$LT VPGSERSYDLTGLKPGTEYTVSIYX$_{31}$VHNVYKDTNX$_{32}$RGLPLSAX$_{33}$FTT (SEQ ID NO: 187), wherein

X_{24} is E, N or R;

X_{25} is E or P;

X_{26} is L or A;

X_{27} is H or W;

X_{28} is E or D;

X_{29} is E or P;

X_{30} is N or V;

X_{31} is G or Y;

X_{32} is M or I; and

X_{33} is E or I;

>SEQ ID NO: 188

c-Met FN3 domain of a bispecific EGFR/c-Met FN3 domain containing molecule

LPAPKNLVVSX$_{34}$VTX$_{35}$DSX$_{36}$RLSWTAPDAAFDSFWIRYFX$_{37}$FX$_{38}$X$_{39}$X$_{40}$GX$_{41}$AIX$_{42}$ LTVPGSERSYDLTGLKPGTEYVVNIX$_{43}$X$_{44}$VKGGX$_{45}$ISPPLSAX$_{46}$FTT (SEQ ID NO: 188); wherein

X_{34} is E, N or R;

X_{35} is E or P;

X_{36} is L or A;

X_{37} is E or P;

X_{38} is V or L;

X_{39} is G or S;

X_{40} is S or K;

X_{41} is E or D;

X_{42} is N or V;

X_{43} is L or M;

X_{44} is G or S;

X_{45} is S or K; and

X_{46} is E or I.

>SEQ ID NO: 189

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ECFLQHKDDNPNLPRLVRPEVDVMCTAFHDNEETFLKKYLYEIARRHPYF
YAPELLFFAKRYKAAFTECCQAADKAACLLPKLDELRDEGKASSAKQRLK
CASLQKFGERAFKAWAVARLSQRFPKAEFAEVSKLVTDLTKVHTECCHG
DLLECADDRADLAKYICENQDSISSKLKECCEKPLLEKSHCIAEVENDEMP
ADLPSLAADFVESKDVCKNYAEAKDVFLGMFLYEYARRHPDYSVVLLLR
LAKTYETTLEKCCAAADPHECYAKVFDEFKPLVEEPQNLIKQNCELFEQLG
EYKFQNALLVRYTKKVPQVSTPTLVEVSRNLGKVGSKCCKHPEAKRMPC
AEDYLSVVLNQLCVLHEKTPVSDRVTKCCTESLVNRRPCFSALEVDETYV
PKEFNAETFTFHADICTLSEKERQIKKQTALVELVKHKPKATKEQLKAVM
DDFAAFVEKCCKADDKETCFAEEGKKLVAASQAALGL

>SEQ ID NO: 190

ECB168

MLPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQESEKVGEAIVLTVP
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APLPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTV
PGSERSYDLTGLKPGTEYVVNILSVKGGSISPPLSAIFTT

>SEQ ID NO: 191

ECB168 without Met

LPAPKNLVVSEVTEDSARLSWDDPWAFYESFLIQYQESEKVGEAIVLTVPG
SERSYDLTGLKPGTEYTVSIYGVHNVYKDTNIRGLPLSAIFTTAPAPAPAPA
PLPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVP
GSERSYDLTGLKPGTEYVVNILSVKGGSISPPLSAIFTT

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ECB no name last in the list 17v2-C5v2

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nvykdtnmrglplsaifttapapapapap
LPAPKNLVVSRVTEDSARLSWTAPDAAFDSFWIRYFEFLGSGEAIVLTVPG
SERSYDLTGLKPGTEYVVNILSVKGGSISPPLSAIFTT

>193

ECB no name without met last in the list 17v2-C5v2

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vykdtnmrglplsaifttapapapapap
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SEQ ID NO: 213
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SEQ ID NO: 214
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PRT

Artificial

Linker

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SEQUENCE LISTING

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Diem, Michael
Hyun, Linus
Jacobs, Steven
King, Alastair
Klein, Donna
Moores, Sheri
O'Neil, Karyn
Picha, Kristen

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35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
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<210> 16
<211> 37
<212> DNA
<213> Artificial Sequence

<220>
<223> primer

<400> 16
aagaaggaga accggtatgc tgccggcgcc gaaaaac 37

<210> 17
<211> 89
<212> DNA
<213> Artificial Sequence

<220>
<223> primer

<400> 17
tttgggaagc ttctaggtct cggcggtcac catcaccatc accatggcag cggttctagt 60

ctagcggccc caactgatct tcaccaaac 89

<210> 18
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 18

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90

<210> 19
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 19

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Thr Tyr Asp Arg Asp Gly Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90

<210> 20
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 20

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Gly Tyr Asn Gly Asp His Phe Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90

<210> 21
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 21

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Asp Asp Pro Arg Gly Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90

<210> 22
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 22

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Thr Trp Pro Tyr Ala Asp Leu Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90

<210> 23
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 23

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Gly Tyr Asn Gly Asp His Phe Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90

<210> 24
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 24

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Asp Tyr Asp Leu Gly Val Tyr Phe Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 25
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 25

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90

<210> 26
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 26

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

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

Glu His Asp Val Met Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90

<210> 27
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 27

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 28
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 28

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

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

Glu His Asp Val Met Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 29
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 29

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Thr Trp Pro Tyr Ala Asp Leu Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90

<210> 30
<211> 37
<212> PRT
<213> Artificial Sequence

<220>
<223> primer

<400> 30

Ala Ala Gly Ala Ala Gly Gly Ala Gly Ala Ala Cys Cys Gly Gly Thr
1 5 10 15

Ala Thr Gly Cys Thr Gly Cys Cys Gly Gly Cys Gly Cys Cys Gly Ala
20 25 30

Ala Ala Ala Ala Cys
35

<210> 31
<211> 65
<212> PRT
<213> Artificial Sequence

<220>
<223> primer

<400> 31

Gly Ala Gly Cys Cys Gly Cys Cys Gly Cys Cys Ala Cys Cys Gly Gly
1 5 10 15

Thr Thr Thr Ala Ala Thr Gly Gly Thr Gly Ala Thr Gly Gly Thr Gly
20 25 30

Ala Thr Gly Gly Thr Gly Ala Cys Cys Ala Cys Cys Gly Gly Thr Gly
35 40 45

Gly Thr Gly Ala Ala Gly Ala Thr Cys Gly Cys Ala Gly Ala Cys Ala
50 55 60

Gly
65

<210> 32
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 32

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Asp Glu Val Val Val Gly Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Tyr Val Asn Ile Leu Gly Val Lys Gly Gly Ser Ile Ser
65 70 75 80

Val Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 33
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 33

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Phe
20 25 30

Ile Arg Tyr Asp Glu Phe Leu Arg Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Trp Val Thr Ile Leu Gly Val Lys Gly Gly Leu Val Ser
65   70   75   80

Thr Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 34
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 34

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Ile Val Asn Ile Met Gly Val Lys Gly Gly Ser Ile Ser
65   70   75   80

His Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 35
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 35

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Asn Ile Leu Gly Val Lys Gly Gly Gly Leu Ser
65   70   75   80

Val Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 36
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 36

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Val
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Gln Ile Leu Gly Val Lys Gly Gly Tyr Ile Ser
65   70   75   80

Ile Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 37
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 37

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Leu Glu Phe Leu Leu Gly Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Gln Ile Met Gly Val Lys Gly Gly Thr Val Ser
65   70   75   80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 38
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 38

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Gly Ile Asn Gly Val Lys Gly Gly Tyr Ile Ser
65   70   75   80

Tyr Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 39
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 39

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Asp Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Gly Val Thr Ile Asn Gly Val Lys Gly Gly Arg Val Ser
65   70   75   80

Thr Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 40
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 40

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Gln Ile Ile Gly Val Lys Gly Gly His Ile Ser
65   70   75   80

Leu Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 41
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 41

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Lys Ile Ser
65   70   75   80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 42
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 42

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Ala Val Asn Ile Met Gly Val Lys Gly Gly Arg Val Ser
65   70   75   80

Val Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 43
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 43

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Gln Ile Leu Gly Val Lys Gly Gly Ser Ile Ser
65   70   75   80

Val Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 44
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 44

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Ser Ile Ser
65   70   75   80

Tyr Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 45
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 45

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Gln Ile Leu Gly Val Lys Gly Gly Tyr Ile Ser
65   70   75   80

Ile Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 46
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 46

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Gln Ile Met Gly Val Lys Gly Gly Thr Val Ser
65   70   75   80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 47
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 47

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Thr Thr Ala Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Ser Ile Ser
65   70   75   80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 48
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 48

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Leu Leu Ser Thr Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Ser Ile Ser
65   70   75   80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 49
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 49

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1   5   10   15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20   25   30

Ile Arg Tyr Phe Glu Phe Val Ser Lys Gly Glu Ala Ile Val Leu Thr
        35   40   45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50   55   60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Ser Ile Ser
65   70   75   80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
                85

<210> 50
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 50

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1   5   10   15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
            20   25   30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
        35   40   45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
    50   55   60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65   70   75   80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly
                85   90   95

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
            100   105   110

Gly Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val
        115   120   125

Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe
    130   135   140

Asp Ser Phe Trp Ile Arg Tyr Asp Glu Val Val Val Gly Gly Glu Ala
145   150   155   160

Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly
165 170 175

Leu Lys Pro Gly Thr Glu Tyr Tyr Val Asn Ile Leu Gly Val Lys Gly
180 185 190

Gly Ser Ile Ser Val Pro Leu Ser Ala Ile Phe Thr Thr
195 200 205

<210> 51
<211> 204
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 51

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly
85 90 95

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
100 105 110

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

Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp
130 135 140

Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile
145 150 155 160

Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu
165 170 175

Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly
180 185 190

Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr Thr
195 200

<210> 52
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 52

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly
85 90 95

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val
115 120 125

Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe
130 135 140

Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala
145 150 155 160

Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly
165 170 175

Leu Lys Pro Gly Thr Glu Tyr Val Val Gln Ile Ile Gly Val Lys Gly
180 185 190

Gly His Ile Ser Leu Pro Leu Ser Ala Ile Phe Thr Thr
195 200 205

<210> 53
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 53

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly
85 90 95

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val
115 120 125

Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe
130 135 140

Asp Ser Phe Phe Ile Arg Tyr Asp Glu Phe Leu Arg Ser Gly Glu Ala
145 150 155 160

Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly
165 170 175

Leu Lys Pro Gly Thr Glu Tyr Trp Val Thr Ile Leu Gly Val Lys Gly
180 185 190

Gly Leu Val Ser Thr Pro Leu Ser Ala Ile Phe Thr Thr
195 200 205

<210> 54
<211> 205
<212> PRT
<213> Artificial Sequence

<220>

<223> bispecific EGFR/cMet binding molecule

<400> 54

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly
85 90 95

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val
115 120 125

Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe
130 135 140

Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala
145 150 155 160

Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly
165 170 175

Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly
180 185 190

Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr Thr
195 200 205

<210> 55
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 55

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly
85 90 95

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val
115 120 125

Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe
130 135 140

Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala
145 150 155 160

Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly
165 170 175

Leu Lys Pro Gly Thr Glu Tyr Val Val Gln Ile Ile Gly Val Lys Gly
180 185 190

Gly His Ile Ser Leu Pro Leu Ser Ala Ile Phe Thr Thr
195 200 205

<210> 56
<211> 205
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 56

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly
85 90 95

Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly
100 105 110

Gly Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val
115 120 125

Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe
130 135 140

Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala
145 150 155 160

Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly
165 170 175

Leu Lys Pro Gly Thr Glu Tyr Val Val Gln Ile Ile Gly Val Lys Gly
180 185 190

Gly His Ile Ser Leu Pro Leu Ser Ala Ile Phe Thr Thr
195 200 205

<210> 57
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 57

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Met Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 58
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 58

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Asp Glu Val Val
130 135 140

Val Gly Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Tyr Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Val Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 59
<211> 195
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 59

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Met Leu Pro Ala Pro Lys Asn
100 105 110

Leu Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr
115 120 125

Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe
130 135 140

Leu Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg
145 150 155 160

Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn
165 170 175

Ile Met Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile
180 185 190

Phe Thr Thr
195

<210> 60
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 60

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Asp Glu Val Val
130 135 140

Val Gly Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Tyr Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Val Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 61
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 61

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 62
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 62

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 63
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 63

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val
130 135 140

Ser Lys Gly Asp Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 64
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 64

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 65
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 65

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 66
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 66

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 67
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 67

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val
130 135 140

Ser Lys Gly Asp Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 68
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 68

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 69
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 69

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 70
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 70

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 71
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 71

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val
130 135 140

Ser Lys Gly Asp Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 72
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> bispecific EGFR/cMet binding molecule

<400> 72

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 73
<211> 1210
<212> PRT
<213> HOMO SAPIENS

<400> 73

Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala
1 5 10 15

Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val Cys Gln
20 25 30

Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp His Phe
35 40 45

Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn
50 55 60

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

Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val
85 90 95

Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr
100 105 110

Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn
115 120 125

Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu
130 135 140

His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu
145 150 155 160

Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met
165 170 175

Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro

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            180                 185                 190

Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn Cys Gln
        195                 200                 205

Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg
    210                 215                 220

Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys
225                 230                 235                 240

Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp
                245                 250                 255

Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro
            260                 265                 270

Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser Phe Gly
        275                 280                 285

Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr Asp His
    290                 295                 300

Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met Glu Glu
305                 310                 315                 320

Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg Lys Val
                325                 330                 335

Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn
            340                 345                 350

Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp
        355                 360                 365

Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr
    370                 375                 380

Pro Pro Leu Asp Pro Gln Glu Leu Asp Ile Leu Lys Thr Val Lys Glu
385                 390                 395                 400

Ile Thr Gly Phe Leu Leu Ile Gln Ala Trp Pro Glu Asn Arg Thr Asp
                405                 410                 415

Leu His Ala Phe Glu Asn Leu Glu Ile Ile Arg Gly Arg Thr Lys Gln
            420                 425                 430

His Gly Gln Phe Ser Leu Ala Val Val Ser Leu Asn Ile Thr Ser Leu
        435                 440                 445

Gly Leu Arg Ser Leu Lys Glu Ile Ser Asp Gly Asp Val Ile Ile Ser
```

```
    450                 455                 460

Gly Asn Lys Asn Leu Cys Tyr Ala Asn Thr Ile Asn Trp Lys Lys Leu
465                 470                 475                 480

Phe Gly Thr Ser Gly Gln Lys Thr Lys Ile Ile Ser Asn Arg Gly Glu
                485                 490                 495

Asn Ser Cys Lys Ala Thr Gly Gln Val Cys His Ala Leu Cys Ser Pro
            500                 505                 510

Glu Gly Cys Trp Gly Pro Glu Pro Arg Asp Cys Val Ser Cys Arg Asn
        515                 520                 525

Val Ser Arg Gly Arg Glu Cys Val Asp Lys Cys Asn Leu Leu Glu Gly
    530                 535                 540

Glu Pro Arg Glu Phe Val Glu Asn Ser Glu Cys Ile Gln Cys His Pro
545                 550                 555                 560

Glu Cys Leu Pro Gln Ala Met Asn Ile Thr Cys Thr Gly Arg Gly Pro
                565                 570                 575

Asp Asn Cys Ile Gln Cys Ala His Tyr Ile Asp Gly Pro His Cys Val
            580                 585                 590

Lys Thr Cys Pro Ala Gly Val Met Gly Glu Asn Asn Thr Leu Val Trp
        595                 600                 605

Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys
    610                 615                 620

Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly
625                 630                 635                 640

Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu
                645                 650                 655

Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His
            660                 665                 670

Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu
        675                 680                 685

Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu
    690                 695                 700

Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser
705                 710                 715                 720

Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu
```

725 730 735

Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser
740 745 750

Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser
755 760 765

Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser
770 775 780

Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp
785 790 795 800

Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn
805 810 815

Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg
820 825 830

Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro
835 840 845

Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala
850 855 860

Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp
865 870 875 880

Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp
885 890 895

Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser
900 905 910

Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu
915 920 925

Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr
930 935 940

Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys
945 950 955 960

Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln
965 970 975

Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro
980 985 990

Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp

995 1000 1005

Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe
1010 1015 1020

Phe Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu
1025 1030 1035

Ser Ala Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn
1040 1045 1050

Gly Leu Gln Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg
1055 1060 1065

Tyr Ser Ser Asp Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp
1070 1075 1080

Asp Thr Phe Leu Pro Val Pro Glu Tyr Ile Asn Gln Ser Val Pro
1085 1090 1095

Lys Arg Pro Ala Gly Ser Val Gln Asn Pro Val Tyr His Asn Gln
1100 1105 1110

Pro Leu Asn Pro Ala Pro Ser Arg Asp Pro His Tyr Gln Asp Pro
1115 1120 1125

His Ser Thr Ala Val Gly Asn Pro Glu Tyr Leu Asn Thr Val Gln
1130 1135 1140

Pro Thr Cys Val Asn Ser Thr Phe Asp Ser Pro Ala His Trp Ala
1145 1150 1155

Gln Lys Gly Ser His Gln Ile Ser Leu Asp Asn Pro Asp Tyr Gln
1160 1165 1170

Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn Gly Ile Phe Lys
1175 1180 1185

Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val Ala Pro Gln
1190 1195 1200

Ser Ser Glu Phe Ile Gly Ala
1205 1210

<210> 74
<211> 53
<212> PRT
<213> HOMO SAPIENS

<400> 74

Asn Ser Asp Ser Glu Cys Pro Leu Ser His Asp Gly Tyr Cys Leu His
1 5 10 15

Asp Gly Val Cys Met Tyr Ile Glu Ala Leu Asp Lys Tyr Ala Cys Asn
20 25 30

Cys Val Val Gly Tyr Ile Gly Glu Arg Cys Gln Tyr Arg Asp Leu Lys
35 40 45

Trp Trp Glu Leu Arg
50

<210> 75
<211> 2201
<212> PRT
<213> Homo sapiens

<400> 75

Met Gly Ala Met Thr Gln Leu Leu Ala Gly Val Phe Leu Ala Phe Leu
1 5 10 15

Ala Leu Ala Thr Glu Gly Gly Val Leu Lys Lys Val Ile Arg His Lys
20 25 30

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

Val Phe Asn His Val Tyr Asn Ile Lys Leu Pro Val Gly Ser Gln Cys
50 55 60

Ser Val Asp Leu Glu Ser Ala Ser Gly Glu Lys Asp Leu Ala Pro Pro
65 70 75 80

Ser Glu Pro Ser Glu Ser Phe Gln Glu His Thr Val Asp Gly Glu Asn
85 90 95

Gln Ile Val Phe Thr His Arg Ile Asn Ile Pro Arg Arg Ala Cys Gly
100 105 110

Cys Ala Ala Ala Pro Asp Val Lys Glu Leu Leu Ser Arg Leu Glu Glu
115 120 125

Leu Glu Asn Leu Val Ser Ser Leu Arg Glu Gln Cys Thr Ala Gly Ala
130 135 140

Gly Cys Cys Leu Gln Pro Ala Thr Gly Arg Leu Asp Thr Arg Pro Phe
145 150 155 160

Cys Ser Gly Arg Gly Asn Phe Ser Thr Glu Gly Cys Gly Cys Val Cys
165 170 175

Glu Pro Gly Trp Lys Gly Pro Asn Cys Ser Glu Pro Glu Cys Pro Gly
180 185 190

```
Asn Cys His Leu Arg Gly Arg Cys Ile Asp Gly Gln Cys Ile Cys Asp
        195                 200                 205

Asp Gly Phe Thr Gly Glu Asp Cys Ser Gln Leu Ala Cys Pro Ser Asp
    210                 215                 220

Cys Asn Asp Gln Gly Lys Cys Val Asn Gly Val Cys Ile Cys Phe Glu
225                 230                 235                 240

Gly Tyr Ala Gly Ala Asp Cys Ser Arg Glu Ile Cys Pro Val Pro Cys
                245                 250                 255

Ser Glu Glu His Gly Thr Cys Val Asp Gly Leu Cys Val Cys His Asp
            260                 265                 270

Gly Phe Ala Gly Asp Asp Cys Asn Lys Pro Leu Cys Leu Asn Asn Cys
        275                 280                 285

Tyr Asn Arg Gly Arg Cys Val Glu Asn Glu Cys Val Cys Asp Glu Gly
    290                 295                 300

Phe Thr Gly Glu Asp Cys Ser Glu Leu Ile Cys Pro Asn Asp Cys Phe
305                 310                 315                 320

Asp Arg Gly Arg Cys Ile Asn Gly Thr Cys Tyr Cys Glu Glu Gly Phe
                325                 330                 335

Thr Gly Glu Asp Cys Gly Lys Pro Thr Cys Pro His Ala Cys His Thr
            340                 345                 350

Gln Gly Arg Cys Glu Glu Gly Gln Cys Val Cys Asp Glu Gly Phe Ala
        355                 360                 365

Gly Val Asp Cys Ser Glu Lys Arg Cys Pro Ala Asp Cys His Asn Arg
    370                 375                 380

Gly Arg Cys Val Asp Gly Arg Cys Glu Cys Asp Asp Gly Phe Thr Gly
385                 390                 395                 400

Ala Asp Cys Gly Glu Leu Lys Cys Pro Asn Gly Cys Ser Gly His Gly
                405                 410                 415

Arg Cys Val Asn Gly Gln Cys Val Cys Asp Glu Gly Tyr Thr Gly Glu
            420                 425                 430

Asp Cys Ser Gln Leu Arg Cys Pro Asn Asp Cys His Ser Arg Gly Arg
        435                 440                 445

Cys Val Glu Gly Lys Cys Val Cys Glu Gln Gly Phe Lys Gly Tyr Asp
    450                 455                 460
```

```
Cys Ser Asp Met Ser Cys Pro Asn Asp Cys His Gln His Gly Arg Cys
465                 470                 475                 480

Val Asn Gly Met Cys Val Cys Asp Asp Gly Tyr Thr Gly Glu Asp Cys
                485                 490                 495

Arg Asp Arg Gln Cys Pro Arg Asp Cys Ser Asn Arg Gly Leu Cys Val
            500                 505                 510

Asp Gly Gln Cys Val Cys Glu Asp Gly Phe Thr Gly Pro Asp Cys Ala
        515                 520                 525

Glu Leu Ser Cys Pro Asn Asp Cys His Gly Gln Gly Arg Cys Val Asn
    530                 535                 540

Gly Gln Cys Val Cys His Glu Gly Phe Met Gly Lys Asp Cys Lys Glu
545                 550                 555                 560

Gln Arg Cys Pro Ser Asp Cys His Gly Gln Gly Arg Cys Val Asp Gly
                565                 570                 575

Gln Cys Ile Cys His Glu Gly Phe Thr Gly Leu Asp Cys Gly Gln His
            580                 585                 590

Ser Cys Pro Ser Asp Cys Asn Asn Leu Gly Gln Cys Val Ser Gly Arg
        595                 600                 605

Cys Ile Cys Asn Glu Gly Tyr Ser Gly Glu Asp Cys Ser Glu Val Ser
    610                 615                 620

Pro Pro Lys Asp Leu Val Val Thr Glu Val Thr Glu Glu Thr Val Asn
625                 630                 635                 640

Leu Ala Trp Asp Asn Glu Met Arg Val Thr Glu Tyr Leu Val Val Tyr
                645                 650                 655

Thr Pro Thr His Glu Gly Gly Leu Glu Met Gln Phe Arg Val Pro Gly
            660                 665                 670

Asp Gln Thr Ser Thr Ile Ile Gln Glu Leu Glu Pro Gly Val Glu Tyr
        675                 680                 685

Phe Ile Arg Val Phe Ala Ile Leu Glu Asn Lys Lys Ser Ile Pro Val
    690                 695                 700

Ser Ala Arg Val Ala Thr Tyr Leu Pro Ala Pro Glu Gly Leu Lys Phe
705                 710                 715                 720

Lys Ser Ile Lys Glu Thr Ser Val Glu Val Glu Trp Asp Pro Leu Asp
                725                 730                 735
```

```
Ile Ala Phe Glu Thr Trp Glu Ile Ile Phe Arg Asn Met Asn Lys Glu
            740                 745                 750

Asp Glu Gly Glu Ile Thr Lys Ser Leu Arg Arg Pro Glu Thr Ser Tyr
        755                 760                 765

Arg Gln Thr Gly Leu Ala Pro Gly Gln Glu Tyr Glu Ile Ser Leu His
    770                 775                 780

Ile Val Lys Asn Asn Thr Arg Gly Pro Gly Leu Lys Arg Val Thr Thr
785                 790                 795                 800

Thr Arg Leu Asp Ala Pro Ser Gln Ile Glu Val Lys Asp Val Thr Asp
                805                 810                 815

Thr Thr Ala Leu Ile Thr Trp Phe Lys Pro Leu Ala Glu Ile Asp Gly
            820                 825                 830

Ile Glu Leu Thr Tyr Gly Ile Lys Asp Val Pro Gly Asp Arg Thr Thr
        835                 840                 845

Ile Asp Leu Thr Glu Asp Glu Asn Gln Tyr Ser Ile Gly Asn Leu Lys
    850                 855                 860

Pro Asp Thr Glu Tyr Glu Val Ser Leu Ile Ser Arg Arg Gly Asp Met
865                 870                 875                 880

Ser Ser Asn Pro Ala Lys Glu Thr Phe Thr Thr Gly Leu Asp Ala Pro
                885                 890                 895

Arg Asn Leu Arg Arg Val Ser Gln Thr Asp Asn Ser Ile Thr Leu Glu
            900                 905                 910

Trp Arg Asn Gly Lys Ala Ala Ile Asp Ser Tyr Arg Ile Lys Tyr Ala
        915                 920                 925

Pro Ile Ser Gly Gly Asp His Ala Glu Val Asp Val Pro Lys Ser Gln
    930                 935                 940

Gln Ala Thr Thr Lys Thr Thr Leu Thr Gly Leu Arg Pro Gly Thr Glu
945                 950                 955                 960

Tyr Gly Ile Gly Val Ser Ala Val Lys Glu Asp Lys Glu Ser Asn Pro
                965                 970                 975

Ala Thr Ile Asn Ala Ala Thr Glu Leu Asp Thr Pro Lys Asp Leu Gln
            980                 985                 990

Val Ser Glu Thr Ala Glu Thr Ser  Leu Thr Leu Leu Trp  Lys Thr Pro
        995                 1000                1005
```

```
Leu Ala  Lys Phe Asp Arg Tyr  Arg Leu Asn Tyr Ser  Leu Pro Thr
    1010                 1015                 1020

Gly Gln  Trp Val Gly Val Gln  Leu Pro Arg Asn Thr  Thr Ser Tyr
    1025                 1030                 1035

Val Leu  Arg Gly Leu Glu Pro  Gly Gln Glu Tyr Asn  Val Leu Leu
    1040                 1045                 1050

Thr Ala  Glu Lys Gly Arg His  Lys Ser Lys Pro Ala  Arg Val Lys
    1055                 1060                 1065

Ala Ser  Thr Glu Gln Ala Pro  Glu Leu Glu Asn Leu  Thr Val Thr
    1070                 1075                 1080

Glu Val  Gly Trp Asp Gly Leu  Arg Leu Asn Trp Thr  Ala Ala Asp
    1085                 1090                 1095

Gln Ala  Tyr Glu His Phe Ile  Ile Gln Val Gln Glu  Ala Asn Lys
    1100                 1105                 1110

Val Glu  Ala Ala Arg Asn Leu  Thr Val Pro Gly Ser  Leu Arg Ala
    1115                 1120                 1125

Val Asp  Ile Pro Gly Leu Lys  Ala Ala Thr Pro Tyr  Thr Val Ser
    1130                 1135                 1140

Ile Tyr  Gly Val Ile Gln Gly  Tyr Arg Thr Pro Val  Leu Ser Ala
    1145                 1150                 1155

Glu Ala  Ser Thr Gly Glu Thr  Pro Asn Leu Gly Glu  Val Val Val
    1160                 1165                 1170

Ala Glu  Val Gly Trp Asp Ala  Leu Lys Leu Asn Trp  Thr Ala Pro
    1175                 1180                 1185

Glu Gly  Ala Tyr Glu Tyr Phe  Phe Ile Gln Val Gln  Glu Ala Asp
    1190                 1195                 1200

Thr Val  Glu Ala Ala Gln Asn  Leu Thr Val Pro Gly  Gly Leu Arg
    1205                 1210                 1215

Ser Thr  Asp Leu Pro Gly Leu  Lys Ala Ala Thr His  Tyr Thr Ile
    1220                 1225                 1230

Thr Ile  Arg Gly Val Thr Gln  Asp Phe Ser Thr Thr  Pro Leu Ser
    1235                 1240                 1245

Val Glu  Val Leu Thr Glu Glu  Val Pro Asp Met Gly  Asn Leu Thr
    1250                 1255                 1260
```

```
Val Thr  Glu Val Ser Trp Asp  Ala Leu Arg Leu Asn  Trp Thr Thr
    1265                 1270                 1275

Pro Asp  Gly Thr Tyr Asp Gln  Phe Thr Ile Gln Val  Gln Glu Ala
    1280                 1285                 1290

Asp Gln  Val Glu Glu Ala His  Asn Leu Thr Val Pro  Gly Ser Leu
    1295                 1300                 1305

Arg Ser  Met Glu Ile Pro Gly  Leu Arg Ala Gly Thr  Pro Tyr Thr
    1310                 1315                 1320

Val Thr  Leu His Gly Glu Val  Arg Gly His Ser Thr  Arg Pro Leu
    1325                 1330                 1335

Ala Val  Glu Val Val Thr Glu  Asp Leu Pro Gln Leu  Gly Asp Leu
    1340                 1345                 1350

Ala Val  Ser Glu Val Gly Trp  Asp Gly Leu Arg Leu  Asn Trp Thr
    1355                 1360                 1365

Ala Ala  Asp Asn Ala Tyr Glu  His Phe Val Ile Gln  Val Gln Glu
    1370                 1375                 1380

Val Asn  Lys Val Glu Ala Ala  Gln Asn Leu Thr Leu  Pro Gly Ser
    1385                 1390                 1395

Leu Arg  Ala Val Asp Ile Pro  Gly Leu Glu Ala Ala  Thr Pro Tyr
    1400                 1405                 1410

Arg Val  Ser Ile Tyr Gly Val  Ile Arg Gly Tyr Arg  Thr Pro Val
    1415                 1420                 1425

Leu Ser  Ala Glu Ala Ser Thr  Ala Lys Glu Pro Glu  Ile Gly Asn
    1430                 1435                 1440

Leu Asn  Val Ser Asp Ile Thr  Pro Glu Ser Phe Asn  Leu Ser Trp
    1445                 1450                 1455

Met Ala  Thr Asp Gly Ile Phe  Glu Thr Phe Thr Ile  Glu Ile Ile
    1460                 1465                 1470

Asp Ser  Asn Arg Leu Leu Glu  Thr Val Glu Tyr Asn  Ile Ser Gly
    1475                 1480                 1485

Ala Glu  Arg Thr Ala His Ile  Ser Gly Leu Pro Pro  Ser Thr Asp
    1490                 1495                 1500

Phe Ile  Val Tyr Leu Ser Gly  Leu Ala Pro Ser Ile  Arg Thr Lys
    1505                 1510                 1515
```

```
Thr Ile  Ser Ala Thr Ala Thr  Thr Glu Ala Leu Pro  Leu Leu Glu
    1520                1525                1530

Asn Leu  Thr Ile Ser Asp Ile  Asn Pro Tyr Gly Phe  Thr Val Ser
    1535                1540                1545

Trp Met  Ala Ser Glu Asn Ala  Phe Asp Ser Phe Leu  Val Thr Val
    1550                1555                1560

Val Asp  Ser Gly Lys Leu Leu  Asp Pro Gln Glu Phe  Thr Leu Ser
    1565                1570                1575

Gly Thr  Gln Arg Lys Leu Glu  Leu Arg Gly Leu Ile  Thr Gly Ile
    1580                1585                1590

Gly Tyr  Glu Val Met Val Ser  Gly Phe Thr Gln Gly  His Gln Thr
    1595                1600                1605

Lys Pro  Leu Arg Ala Glu Ile  Val Thr Glu Ala Glu  Pro Glu Val
    1610                1615                1620

Asp Asn  Leu Leu Val Ser Asp  Ala Thr Pro Asp Gly  Phe Arg Leu
    1625                1630                1635

Ser Trp  Thr Ala Asp Glu Gly  Val Phe Asp Asn Phe  Val Leu Lys
    1640                1645                1650

Ile Arg  Asp Thr Lys Lys Gln  Ser Glu Pro Leu Glu  Ile Thr Leu
    1655                1660                1665

Leu Ala  Pro Glu Arg Thr Arg  Asp Ile Thr Gly Leu  Arg Glu Ala
    1670                1675                1680

Thr Glu  Tyr Glu Ile Glu Leu  Tyr Gly Ile Ser Lys  Gly Arg Arg
    1685                1690                1695

Ser Gln  Thr Val Ser Ala Ile  Ala Thr Thr Ala Met  Gly Ser Pro
    1700                1705                1710

Lys Glu  Val Ile Phe Ser Asp  Ile Thr Glu Asn Ser  Ala Thr Val
    1715                1720                1725

Ser Trp  Arg Ala Pro Thr Ala  Gln Val Glu Ser Phe  Arg Ile Thr
    1730                1735                1740

Tyr Val  Pro Ile Thr Gly Gly  Thr Pro Ser Met Val  Thr Val Asp
    1745                1750                1755

Gly Thr  Lys Thr Gln Thr Arg  Leu Val Lys Leu Ile  Pro Gly Val
    1760                1765                1770
```

```
Glu Tyr  Leu Val Ser Ile Ile  Ala Met Lys Gly Phe  Glu Glu Ser
    1775                 1780                 1785

Glu Pro  Val Ser Gly Ser Phe  Thr Thr Ala Leu Asp  Gly Pro Ser
    1790                 1795                 1800

Gly Leu  Val Thr Ala Asn Ile  Thr Asp Ser Glu Ala  Leu Ala Arg
    1805                 1810                 1815

Trp Gln  Pro Ala Ile Ala Thr  Val Asp Ser Tyr Val  Ile Ser Tyr
    1820                 1825                 1830

Thr Gly  Glu Lys Val Pro Glu  Ile Thr Arg Thr Val  Ser Gly Asn
    1835                 1840                 1845

Thr Val  Glu Tyr Ala Leu Thr  Asp Leu Glu Pro Ala  Thr Glu Tyr
    1850                 1855                 1860

Thr Leu  Arg Ile Phe Ala Glu  Lys Gly Pro Gln Lys  Ser Ser Thr
    1865                 1870                 1875

Ile Thr  Ala Lys Phe Thr Thr  Asp Leu Asp Ser Pro  Arg Asp Leu
    1880                 1885                 1890

Thr Ala  Thr Glu Val Gln Ser  Glu Thr Ala Leu Leu  Thr Trp Arg
    1895                 1900                 1905

Pro Pro  Arg Ala Ser Val Thr  Gly Tyr Leu Leu Val  Tyr Glu Ser
    1910                 1915                 1920

Val Asp  Gly Thr Val Lys Glu  Val Ile Val Gly Pro  Asp Thr Thr
    1925                 1930                 1935

Ser Tyr  Ser Leu Ala Asp Leu  Ser Pro Ser Thr His  Tyr Thr Ala
    1940                 1945                 1950

Lys Ile  Gln Ala Leu Asn Gly  Pro Leu Arg Ser Asn  Met Ile Gln
    1955                 1960                 1965

Thr Ile  Phe Thr Thr Ile Gly  Leu Leu Tyr Pro Phe  Pro Lys Asp
    1970                 1975                 1980

Cys Ser  Gln Ala Met Leu Asn  Gly Asp Thr Thr Ser  Gly Leu Tyr
    1985                 1990                 1995

Thr Ile  Tyr Leu Asn Gly Asp  Lys Ala Glu Ala Leu  Glu Val Phe
    2000                 2005                 2010

Cys Asp  Met Thr Ser Asp Gly  Gly Gly Trp Ile Val  Phe Leu Arg
    2015                 2020                 2025
```

Arg Lys Asn Gly Arg Glu Asn Phe Tyr Gln Asn Trp Lys Ala Tyr
2030 2035 2040

Ala Ala Gly Phe Gly Asp Arg Arg Glu Glu Phe Trp Leu Gly Leu
2045 2050 2055

Asp Asn Leu Asn Lys Ile Thr Ala Gln Gly Gln Tyr Glu Leu Arg
2060 2065 2070

Val Asp Leu Arg Asp His Gly Glu Thr Ala Phe Ala Val Tyr Asp
2075 2080 2085

Lys Phe Ser Val Gly Asp Ala Lys Thr Arg Tyr Lys Leu Lys Val
2090 2095 2100

Glu Gly Tyr Ser Gly Thr Ala Gly Asp Ser Met Ala Tyr His Asn
2105 2110 2115

Gly Arg Ser Phe Ser Thr Phe Asp Lys Asp Thr Asp Ser Ala Ile
2120 2125 2130

Thr Asn Cys Ala Leu Ser Tyr Lys Gly Ala Phe Trp Tyr Arg Asn
2135 2140 2145

Cys His Arg Val Asn Leu Met Gly Arg Tyr Gly Asp Asn Asn His
2150 2155 2160

Ser Gln Gly Val Asn Trp Phe His Trp Lys Gly His Glu His Ser
2165 2170 2175

Ile Gln Phe Ala Glu Met Lys Leu Arg Pro Ser Asn Phe Arg Asn
2180 2185 2190

Leu Glu Gly Arg Arg Lys Arg Ala
2195 2200

<210> 76
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> Fibcon FN3 domain

<400> 76

Leu Asp Ala Pro Thr Asp Leu Gln Val Thr Asn Val Thr Asp Thr Ser
1 5 10 15

Ile Thr Val Ser Trp Thr Pro Pro Ser Ala Thr Ile Thr Gly Tyr Arg
20 25 30

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

35 40 45

Val Pro Pro Ser Ser Thr Ser Val Thr Ile Thr Gly Leu Thr Pro Gly
50 55 60

Val Glu Tyr Val Val Ser Leu Tyr Ala Leu Lys Asp Asn Gln Glu Ser
65 70 75 80

Pro Pro Leu Val Gly Thr Gln Thr Thr
85

<210> 77
<211> 94
<212> PRT
<213> Homo sapiens

<400> 77

Val Ser Asp Val Pro Arg Asp Leu Glu Val Val Ala Ala Thr Pro Thr
1 5 10 15

Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala Val Thr Val Arg Tyr Tyr
20 25 30

Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn Ser Pro Val Gln Glu Phe
35 40 45

Thr Val Pro Gly Ser Lys Ser Thr Ala Thr Ile Ser Gly Leu Lys Pro
50 55 60

Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala Val Thr Gly Arg Gly Asp
65 70 75 80

Ser Pro Ala Ser Ser Lys Pro Ile Ser Ile Asn Tyr Arg Thr
85 90

<210> 78
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 78

Gly Ser Gly Ser
1

<210> 79
<211> 25
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 79

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly
1 5 10 15

Gly Gly Gly Ser Gly Gly Gly Gly Ser
20 25

<210> 80
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 80

Ala Pro Ala Pro
1

<210> 81
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 81

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
1 5 10

<210> 82
<211> 20
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 82

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
1 5 10 15

Ala Pro Ala Pro
20

<210> 83
<211> 40
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 83

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
1 5 10 15

Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro
20 25 30

Ala Pro Ala Pro Ala Pro Ala Pro
35 40

<210> 84
<211> 29
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 84

Ala Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys
1 5 10 15

Glu Ala Ala Ala Lys Glu Ala Ala Ala Lys Ala Ala Ala
20 25

<210> 85
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> tencon BC loop

<400> 85

Thr Ala Pro Asp Ala Ala Phe Asp
1 5

<210> 86
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> tencon FG loop

<400> 86

Lys Gly Gly His Arg Ser Asn
1 5

<210> 87
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain BC loop

<400> 87

Ala Asp Pro His Gly Phe Tyr Asp
1 5

<210> 88
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain BC loop

<400> 88

Thr Tyr Asp Arg Asp Gly Tyr Asp
1 5

<210> 89
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain BC loop

<400> 89

Trp Asp Pro Phe Ser Phe Tyr Asp
1 5

<210> 90
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain BC loop

<400> 90

Asp Asp Pro Arg Gly Phe Tyr Glu
1 5

<210> 91
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain BC loop

<400> 91

Thr Trp Pro Tyr Ala Asp Leu Asp
1 5

<210> 92
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain BC loop

<400> 92

Gly Tyr Asn Gly Asp His Phe Asp
1 5

<210> 93
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain BC loop

<400> 93

Asp Tyr Asp Leu Gly Val Tyr Asp
1 5

<210> 94
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain BC loop

<400> 94

Asp Asp Pro Trp Asp Phe Tyr Glu
1 5

<210> 95
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain FG loop

<400> 95

His Asn Val Tyr Lys Asp Thr Asn Met Arg Gly Leu
1 5 10

<210> 96
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain FG loop

<400> 96

Leu Gly Ser Tyr Val Phe Glu His Asp Val Met
1 5 10

<210> 97
<211> 285
<212> DNA
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain from ECB97; P54AR4-83V22

<400> 97
atgttgccag cgccgaagaa cctggtagtt agcgaggtta ctgaggacag cgcgcgtctg 60

agctgggacg atccgtgggc gttctacgag agctttctga tccagtatca agagagcgag 120

aaagtcggtg aagcgattgt gctgaccgtc ccgggctccg agcgttccta cgacctgacc 180

ggtttgaagc cgggtaccga gtatacggtg agcatctacg gtgttcacaa tgtctataag 240

gacactaata tccgcggtct gcctctgagc gccattttca ccacc 285

<210> 98
<211> 285
<212> DNA
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain from ECB15; P54AR4-83V2

<400> 98
atgctgccag cccctaagaa tctggtcgtg agcgaagtaa ccgaggacag cgcccgcctg 60

agctgggacg acccgtgggc gttctatgag tctttcctga ttcagtatca agaaagcgaa 120

aaagttggcg aagcgatcgt cctgaccgtc ccgggtagcg agcgctccta cgatctgacc 180

ggcctgaaac cgggtacgga gtacacggtg tccatttacg gtgttcacaa tgtgtataaa 240

gacaccaaca tgcgtggcct gccgctgtcg gcgattttca ccacc 285

<210> 99
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> tencon27 FN3 domain

<400> 99

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val Lys Gly Gly His Arg Ser
65 70 75 80

Asn Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 100
<211> 89

<212> PRT
<213> Artificial Sequence

<220>
<223> TCL14 library

<220>
<221> MISC_FEATURE
<222> (32)..(32)
<223> Xaa is any amino acid

<220>
<221> MISC_FEATURE
<222> (34)..(34)
<223> Xaa is any amino acid

<220>
<221> MISC_FEATURE
<222> (36)..(36)
<223> Xaa is any amino acid

<220>
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<222> (38)..(38)
<223> Xaa is any amino acid

<220>
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<222> (39)..(39)
<223> Xaa is any amino acid

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<221> MISC_FEATURE
<222> (40)..(40)
<223> Xaa is any amino acid

<220>
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<223> Xaa is any amino acid

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<223> Xaa is any amino acid

<220>
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<222> (70)..(70)
<223> Xaa is any amino acid

<220>
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<223> Xaa is any amino acid

<220>
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<222> (78)..(78)
<223> Xaa is any amino acid

<220>
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<222> (79)..(79)
<223> Xaa is any amino acid

<220>

<221> MISC_FEATURE
<222> (81)..(81)
<223> Xaa is any amino acid

<400> 100

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Xaa
20 25 30

Ile Xaa Tyr Xaa Glu Xaa Xaa Xaa Xaa Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Xaa Val Xaa Ile Xaa Gly Val Lys Gly Gly Xaa Xaa Ser
65 70 75 80

Xaa Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 101
<211> 1408
<212> PRT
<213> HOMO SAPIENS

<400> 101

Met Lys Ala Pro Ala Val Leu Ala Pro Gly Ile Leu Val Leu Leu Phe
1 5 10 15

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

Ser Glu Met Asn Val Asn Met Lys Tyr Gln Leu Pro Asn Phe Thr Ala
35 40 45

Glu Thr Pro Ile Gln Asn Val Ile Leu His Glu His His Ile Phe Leu
50 55 60

Gly Ala Thr Asn Tyr Ile Tyr Val Leu Asn Glu Glu Asp Leu Gln Lys
65 70 75 80

Val Ala Glu Tyr Lys Thr Gly Pro Val Leu Glu His Pro Asp Cys Phe
85 90 95

Pro Cys Gln Asp Cys Ser Ser Lys Ala Asn Leu Ser Gly Gly Val Trp
100 105 110

Lys Asp Asn Ile Asn Met Ala Leu Val Val Asp Thr Tyr Tyr Asp Asp
115 120 125

```
Gln Leu Ile Ser Cys Gly Ser Val Asn Arg Gly Thr Cys Gln Arg His
    130                 135                 140

Val Phe Pro His Asn His Thr Ala Asp Ile Gln Ser Glu Val His Cys
145                 150                 155                 160

Ile Phe Ser Pro Gln Ile Glu Glu Pro Ser Gln Cys Pro Asp Cys Val
                165                 170                 175

Val Ser Ala Leu Gly Ala Lys Val Leu Ser Ser Val Lys Asp Arg Phe
            180                 185                 190

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

His Pro Leu His Ser Ile Ser Val Arg Arg Leu Lys Glu Thr Lys Asp
    210                 215                 220

Gly Phe Met Phe Leu Thr Asp Gln Ser Tyr Ile Asp Val Leu Pro Glu
225                 230                 235                 240

Phe Arg Asp Ser Tyr Pro Ile Lys Tyr Val His Ala Phe Glu Ser Asn
                245                 250                 255

Asn Phe Ile Tyr Phe Leu Thr Val Gln Arg Glu Thr Leu Asp Ala Gln
            260                 265                 270

Thr Phe His Thr Arg Ile Ile Arg Phe Cys Ser Ile Asn Ser Gly Leu
        275                 280                 285

His Ser Tyr Met Glu Met Pro Leu Glu Cys Ile Leu Thr Glu Lys Arg
    290                 295                 300

Lys Lys Arg Ser Thr Lys Lys Glu Val Phe Asn Ile Leu Gln Ala Ala
305                 310                 315                 320

Tyr Val Ser Lys Pro Gly Ala Gln Leu Ala Arg Gln Ile Gly Ala Ser
                325                 330                 335

Leu Asn Asp Asp Ile Leu Phe Gly Val Phe Ala Gln Ser Lys Pro Asp
            340                 345                 350

Ser Ala Glu Pro Met Asp Arg Ser Ala Met Cys Ala Phe Pro Ile Lys
        355                 360                 365

Tyr Val Asn Asp Phe Phe Asn Lys Ile Val Asn Lys Asn Asn Val Arg
    370                 375                 380

Cys Leu Gln His Phe Tyr Gly Pro Asn His Glu His Cys Phe Asn Arg
385                 390                 395                 400
```

```
Thr Leu Leu Arg Asn Ser Ser Gly Cys Glu Ala Arg Arg Asp Glu Tyr
                405                 410                 415

Arg Thr Glu Phe Thr Thr Ala Leu Gln Arg Val Asp Leu Phe Met Gly
            420                 425                 430

Gln Phe Ser Glu Val Leu Leu Thr Ser Ile Ser Thr Phe Ile Lys Gly
        435                 440                 445

Asp Leu Thr Ile Ala Asn Leu Gly Thr Ser Glu Gly Arg Phe Met Gln
    450                 455                 460

Val Val Val Ser Arg Ser Gly Pro Ser Thr Pro His Val Asn Phe Leu
465                 470                 475                 480

Leu Asp Ser His Pro Val Ser Pro Glu Val Ile Val Glu His Thr Leu
                485                 490                 495

Asn Gln Asn Gly Tyr Thr Leu Val Ile Thr Gly Lys Lys Ile Thr Lys
            500                 505                 510

Ile Pro Leu Asn Gly Leu Gly Cys Arg His Phe Gln Ser Cys Ser Gln
        515                 520                 525

Cys Leu Ser Ala Pro Pro Phe Val Gln Cys Gly Trp Cys His Asp Lys
    530                 535                 540

Cys Val Arg Ser Glu Glu Cys Leu Ser Gly Thr Trp Thr Gln Gln Ile
545                 550                 555                 560

Cys Leu Pro Ala Ile Tyr Lys Val Phe Pro Asn Ser Ala Pro Leu Glu
                565                 570                 575

Gly Gly Thr Arg Leu Thr Ile Cys Gly Trp Asp Phe Gly Phe Arg Arg
            580                 585                 590

Asn Asn Lys Phe Asp Leu Lys Lys Thr Arg Val Leu Leu Gly Asn Glu
        595                 600                 605

Ser Cys Thr Leu Thr Leu Ser Glu Ser Thr Met Asn Thr Leu Lys Cys
    610                 615                 620

Thr Val Gly Pro Ala Met Asn Lys His Phe Asn Met Ser Ile Ile Ile
625                 630                 635                 640

Ser Asn Gly His Gly Thr Thr Gln Tyr Ser Thr Phe Ser Tyr Val Asp
                645                 650                 655

Pro Val Ile Thr Ser Ile Ser Pro Lys Tyr Gly Pro Met Ala Gly Gly
            660                 665                 670
```

```
Thr Leu Leu Thr Leu Thr Gly Asn Tyr Leu Asn Ser Gly Asn Ser Arg
        675                 680                 685

His Ile Ser Ile Gly Gly Lys Thr Cys Thr Leu Lys Ser Val Ser Asn
    690                 695                 700

Ser Ile Leu Glu Cys Tyr Thr Pro Ala Gln Thr Ile Ser Thr Glu Phe
705                 710                 715                 720

Ala Val Lys Leu Lys Ile Asp Leu Ala Asn Arg Glu Thr Ser Ile Phe
                725                 730                 735

Ser Tyr Arg Glu Asp Pro Ile Val Tyr Glu Ile His Pro Thr Lys Ser
            740                 745                 750

Phe Ile Ser Thr Trp Trp Lys Glu Pro Leu Asn Ile Val Ser Phe Leu
        755                 760                 765

Phe Cys Phe Ala Ser Gly Gly Ser Thr Ile Thr Gly Val Gly Lys Asn
    770                 775                 780

Leu Asn Ser Val Ser Val Pro Arg Met Val Ile Asn Val His Glu Ala
785                 790                 795                 800

Gly Arg Asn Phe Thr Val Ala Cys Gln His Arg Ser Asn Ser Glu Ile
                805                 810                 815

Ile Cys Cys Thr Thr Pro Ser Leu Gln Gln Leu Asn Leu Gln Leu Pro
            820                 825                 830

Leu Lys Thr Lys Ala Phe Phe Met Leu Asp Gly Ile Leu Ser Lys Tyr
        835                 840                 845

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

Pro Val Met Ile Ser Met Gly Asn Glu Asn Val Leu Glu Ile Lys Gly
865                 870                 875                 880

Asn Asp Ile Asp Pro Glu Ala Val Lys Gly Glu Val Leu Lys Val Gly
                885                 890                 895

Asn Lys Ser Cys Glu Asn Ile His Leu His Ser Glu Ala Val Leu Cys
            900                 905                 910

Thr Val Pro Asn Asp Leu Leu Lys Leu Asn Ser Glu Leu Asn Ile Glu
        915                 920                 925

Trp Lys Gln Ala Ile Ser Ser Thr Val Leu Gly Lys Val Ile Val Gln
    930                 935                 940
```

```
Pro Asp Gln Asn Phe Thr Gly Leu Ile Ala Gly Val Val Ser Ile Ser
945                 950                 955                 960

Thr Ala Leu Leu Leu Leu Leu Gly Phe Phe Leu Trp Leu Lys Lys Arg
                965                 970                 975

Lys Gln Ile Lys Asp Leu Gly Ser Glu Leu Val Arg Tyr Asp Ala Arg
            980                 985                 990

Val His Thr Pro His Leu Asp Arg  Leu Val Ser Ala Arg  Ser Val Ser
        995                 1000                1005

Pro Thr  Thr Glu Met Val Ser  Asn Glu Ser Val Asp  Tyr Arg Ala
    1010                1015                1020

Thr Phe  Pro Glu Asp Gln Phe  Pro Asn Ser Ser Gln  Asn Gly Ser
    1025                1030                1035

Cys Arg  Gln Val Gln Tyr Pro  Leu Thr Asp Met Ser  Pro Ile Leu
    1040                1045                1050

Thr Ser  Gly Asp Ser Asp Ile  Ser Ser Pro Leu Leu  Gln Asn Thr
    1055                1060                1065

Val His  Ile Asp Leu Ser Ala  Leu Asn Pro Glu Leu  Val Gln Ala
    1070                1075                1080

Val Gln  His Val Val Ile Gly  Pro Ser Ser Leu Ile  Val His Phe
    1085                1090                1095

Asn Glu  Val Ile Gly Arg Gly  His Phe Gly Cys Val  Tyr His Gly
    1100                1105                1110

Thr Leu  Leu Asp Asn Asp Gly  Lys Lys Ile His Cys  Ala Val Lys
    1115                1120                1125

Ser Leu  Asn Arg Ile Thr Asp  Ile Gly Glu Val Ser  Gln Phe Leu
    1130                1135                1140

Thr Glu  Gly Ile Ile Met Lys  Asp Phe Ser His Pro  Asn Val Leu
    1145                1150                1155

Ser Leu  Leu Gly Ile Cys Leu  Arg Ser Glu Gly Ser  Pro Leu Val
    1160                1165                1170

Val Leu  Pro Tyr Met Lys His  Gly Asp Leu Arg Asn  Phe Ile Arg
    1175                1180                1185

Asn Glu  Thr His Asn Pro Thr  Val Lys Asp Leu Ile  Gly Phe Gly
    1190                1195                1200
```

```
Leu Gln  Val Ala Lys Gly Met  Lys Tyr Leu Ala Ser  Lys Lys Phe
    1205                 1210                 1215

Val His  Arg Asp Leu Ala Ala  Arg Asn Cys Met Leu  Asp Glu Lys
    1220                 1225                 1230

Phe Thr  Val Lys Val Ala Asp  Phe Gly Leu Ala Arg  Asp Met Tyr
    1235                 1240                 1245

Asp Lys  Glu Tyr Tyr Ser Val  His Asn Lys Thr Gly  Ala Lys Leu
    1250                 1255                 1260

Pro Val  Lys Trp Met Ala Leu  Glu Ser Leu Gln Thr  Gln Lys Phe
    1265                 1270                 1275

Thr Thr  Lys Ser Asp Val Trp  Ser Phe Gly Val Leu  Leu Trp Glu
    1280                 1285                 1290

Leu Met  Thr Arg Gly Ala Pro  Pro Tyr Pro Asp Val  Asn Thr Phe
    1295                 1300                 1305

Asp Ile  Thr Val Tyr Leu Leu  Gln Gly Arg Arg Leu  Leu Gln Pro
    1310                 1315                 1320

Glu Tyr  Cys Pro Asp Pro Leu  Tyr Glu Val Met Leu  Lys Cys Trp
    1325                 1330                 1335

His Pro  Lys Ala Glu Met Arg  Pro Ser Phe Ser Glu  Leu Val Ser
    1340                 1345                 1350

Arg Ile  Ser Ala Ile Phe Ser  Thr Phe Ile Gly Glu  His Tyr Val
    1355                 1360                 1365

His Val  Asn Ala Thr Tyr Val  Asn Val Lys Cys Val  Ala Pro Tyr
    1370                 1375                 1380

Pro Ser  Leu Leu Ser Ser Glu  Asp Asn Ala Asp Asp  Glu Val Asp
    1385                 1390                 1395

Thr Arg  Pro Ala Ser Phe Trp  Glu Thr Ser
    1400                 1405
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<210> 102
<211> 697
<212> PRT
<213> HOMO SAPIENS

<400> 102

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Gln Arg Lys Arg Arg Asn Thr Ile His Glu Phe Lys Lys Ser Ala Lys
1               5                  10                  15
```

```
Thr Thr Leu Ile Lys Ile Asp Pro Ala Leu Lys Ile Lys Thr Lys Lys
            20                  25                  30

Val Asn Thr Ala Asp Gln Cys Ala Asn Arg Cys Thr Arg Asn Lys Gly
        35                  40                  45

Leu Pro Phe Thr Cys Lys Ala Phe Val Phe Asp Lys Ala Arg Lys Gln
    50                  55                  60

Cys Leu Trp Phe Pro Phe Asn Ser Met Ser Ser Gly Val Lys Lys Glu
65                  70                  75                  80

Phe Gly His Glu Phe Asp Leu Tyr Glu Asn Lys Asp Tyr Ile Arg Asn
                85                  90                  95

Cys Ile Ile Gly Lys Gly Arg Ser Tyr Lys Gly Thr Val Ser Ile Thr
            100                 105                 110

Lys Ser Gly Ile Lys Cys Gln Pro Trp Ser Ser Met Ile Pro His Glu
        115                 120                 125

His Ser Phe Leu Pro Ser Ser Tyr Arg Gly Lys Asp Leu Gln Glu Asn
    130                 135                 140

Tyr Cys Arg Asn Pro Arg Gly Glu Glu Gly Gly Pro Trp Cys Phe Thr
145                 150                 155                 160

Ser Asn Pro Glu Val Arg Tyr Glu Val Cys Asp Ile Pro Gln Cys Ser
                165                 170                 175

Glu Val Glu Cys Met Thr Cys Asn Gly Glu Ser Tyr Arg Gly Leu Met
            180                 185                 190

Asp His Thr Glu Ser Gly Lys Ile Cys Gln Arg Trp Asp His Gln Thr
        195                 200                 205

Pro His Arg His Lys Phe Leu Pro Glu Arg Tyr Pro Asp Lys Gly Phe
    210                 215                 220

Asp Asp Asn Tyr Cys Arg Asn Pro Asp Gly Gln Pro Arg Pro Trp Cys
225                 230                 235                 240

Tyr Thr Leu Asp Pro His Thr Arg Trp Glu Tyr Cys Ala Ile Lys Thr
                245                 250                 255

Cys Ala Asp Asn Thr Met Asn Asp Thr Asp Val Pro Leu Glu Thr Thr
            260                 265                 270

Glu Cys Ile Gln Gly Gln Gly Glu Gly Tyr Arg Gly Thr Val Asn Thr
        275                 280                 285
```

```
Ile Trp Asn Gly Ile Pro Cys Gln Arg Trp Asp Ser Gln Tyr Pro His
    290                 295                 300

Glu His Asp Met Thr Pro Glu Asn Phe Lys Cys Lys Asp Leu Arg Glu
305                 310                 315                 320

Asn Tyr Cys Arg Asn Pro Asp Gly Ser Glu Ser Pro Trp Cys Phe Thr
                325                 330                 335

Thr Asp Pro Asn Ile Arg Val Gly Tyr Cys Ser Gln Ile Pro Asn Cys
            340                 345                 350

Asp Met Ser His Gly Gln Asp Cys Tyr Arg Gly Asn Gly Lys Asn Tyr
        355                 360                 365

Met Gly Asn Leu Ser Gln Thr Arg Ser Gly Leu Thr Cys Ser Met Trp
    370                 375                 380

Asp Lys Asn Met Glu Asp Leu His Arg His Ile Phe Trp Glu Pro Asp
385                 390                 395                 400

Ala Ser Lys Leu Asn Glu Asn Tyr Cys Arg Asn Pro Asp Asp Asp Ala
                405                 410                 415

His Gly Pro Trp Cys Tyr Thr Gly Asn Pro Leu Ile Pro Trp Asp Tyr
            420                 425                 430

Cys Pro Ile Ser Arg Cys Glu Gly Asp Thr Thr Pro Thr Ile Val Asn
        435                 440                 445

Leu Asp His Pro Val Ile Ser Cys Ala Lys Thr Lys Gln Leu Arg Val
    450                 455                 460

Val Asn Gly Ile Pro Thr Arg Thr Asn Ile Gly Trp Met Val Ser Leu
465                 470                 475                 480

Arg Tyr Arg Asn Lys His Ile Cys Gly Gly Ser Leu Ile Lys Glu Ser
                485                 490                 495

Trp Val Leu Thr Ala Arg Gln Cys Phe Pro Ser Arg Asp Leu Lys Asp
            500                 505                 510

Tyr Glu Ala Trp Leu Gly Ile His Asp Val His Gly Arg Gly Asp Glu
        515                 520                 525

Lys Cys Lys Gln Val Leu Asn Val Ser Gln Leu Val Tyr Gly Pro Glu
    530                 535                 540

Gly Ser Asp Leu Val Leu Met Lys Leu Ala Arg Pro Ala Val Leu Asp
545                 550                 555                 560
```

Asp Phe Val Ser Thr Ile Asp Leu Pro Asn Tyr Gly Cys Thr Ile Pro
565 570 575

Glu Lys Thr Ser Cys Ser Val Tyr Gly Trp Gly Tyr Thr Gly Leu Ile
580 585 590

Asn Tyr Asp Gly Leu Leu Arg Val Ala His Leu Tyr Ile Met Gly Asn
595 600 605

Glu Lys Cys Ser Gln His His Arg Gly Lys Val Thr Leu Asn Glu Ser
610 615 620

Glu Ile Cys Ala Gly Ala Glu Lys Ile Gly Ser Gly Pro Cys Glu Gly
625 630 635 640

Asp Tyr Gly Gly Pro Leu Val Cys Glu Gln His Lys Met Arg Met Val
645 650 655

Leu Gly Val Ile Val Pro Gly Arg Gly Cys Ala Ile Pro Asn Arg Pro
660 665 670

Gly Ile Phe Val Arg Val Ala Tyr Tyr Ala Lys Trp Ile His Lys Ile
675 680 685

Ile Leu Thr Tyr Lys Val Pro Gln Ser
690 695

<210> 103
<211> 276
<212> DNA
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 103
ctgccggctc cgaagaactt ggtggtgagc cgtgttaccg aagatagcgc acgcctgagc 60

tggacggcac cggatgcggc gttcgatagc ttctggattc gctattttga gtttctgggt 120

agcggtgagg caattgttct gacggtgccg ggctctgaac gctcctacga tttgaccggt 180

ctgaaaccgg gcaccgagta tgtggtgaac attctgagcg ttaagggcgg tagcatcagc 240

ccaccgctga gcgcgatctt cacgactggt ggttgc 276

<210> 104
<211> 267
<212> DNA
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 104
ctgccggcac cgaagaacct ggttgtcagc cgtgtgaccg aggatagcgc acgtttgagc 60

tggaccgctc cggatgcagc ctttgacagc ttctggattc gttactttga atttctgggt 120

agcggtgagg cgatcgttct gacggtgccg ggctctgaac gcagctatga tttgacgggc 180

ctgaagccgg gtactgagta cgtggttaac atcatgggcg ttaagggtgg taaaatcagc 240

ccgccattgt ccgcgatctt taccacg 267

<210> 105
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 105

Gly Gly Gly Gly Ser
1 5

<210> 106
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 106

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 107
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 107

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 108
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 108

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 109
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 109

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 110
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 110

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

```
Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
        35                  40                  45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50                  55                  60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65                  70                  75                  80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
                85                  90
```

<210> 111
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 111

```
Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1               5                   10                  15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20                  25                  30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
        35                  40                  45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50                  55                  60

Thr Glu Tyr Val Val Asn Ile Leu Gly Val Lys Gly Gly Lys Ile Ser
65                  70                  75                  80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
                85
```

<210> 112
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 112

```
Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1               5                   10                  15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
            20                  25                  30
```

Ile Arg Tyr Phe Glu Phe Val Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Val Val Asn Ile Leu Gly Val Lys Gly Gly Ser Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 113
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 113

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Phe Val Ser Lys Gly Asp Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Val Val Asn Ile Leu Gly Val Lys Gly Gly Ser Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 114
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 114

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Val Val Asn Ile Leu Ser Val Lys Gly Gly Ser Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 115
<211> 591
<212> DNA
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 115
atgttgccag cgccgaagaa cctggtagtt agcgaggtta ctgaggacag cgcgcgtctg 60

agctgggacg atccgtgggc gttctacgag agctttctga tccagtatca agagagcgag 120

aaagtcggtg aagcgattgt gctgaccgtc ccgggctccg agcgttccta cgacctgacc 180

ggtttgaagc cgggtaccga gtatacggtg agcatctacg gtgttcacaa tgtctataag 240

gacactaata tccgcggtct gcctctgagc gccattttca ccaccgcacc ggcaccggct 300

ccggctcctg ccccgctgcc ggctccgaag aacttggtgg tgagccgtgt taccgaagat 360

agcgcacgcc tgagctggac ggcaccggat gcggcgttcg atagcttctg gattcgctat 420

tttgagtttc tgggtagcgg tgaggcaatt gttctgacgg tgccgggctc tgaacgctcc 480

tacgatttga ccggtctgaa accgggcacc gagtatgtgg tgaacattct gagcgttaag 540

ggcggtagca tcagcccacc gctgagcgcg atcttcacga ctggtggttg c 591

<210> 116
<211> 582
<212> DNA
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 116
atgctgccag cccctaagaa tctggtcgtg agcgaagtaa ccgaggacag cgcccgcctg 60

agctgggacg acccgtgggc gttctatgag tctttcctga ttcagtatca agaaagcgaa 120

aaagttggcg aagcgatcgt cctgaccgtc ccgggtagcg agcgctccta cgatctgacc 180

ggcctgaaac cgggtacgga gtacacggtg tccatttacg gtgttcacaa tgtgtataaa 240

gacaccaaca tgcgtggcct gccgctgtcg gcgattttca ccaccgcgcc tgcgccagcg 300

cctgcaccgg ctccgctgcc ggcaccgaag aacctggttg tcagccgtgt gaccgaggat 360

agcgcacgtt tgagctggac cgctccggat gcagcctttg acagcttctg gattcgttac 420

tttgaatttc tgggtagcgg tgaggcgatc gttctgacgg tgccgggctc tgaacgcagc 480

tatgatttga cgggcctgaa gccgggtact gagtacgtgg ttaacatcat gggcgttaag 540

ggtggtaaaa tcagcccgcc attgtccgcg atctttacca cg 582

<210> 117
<211> 51
<212> PRT
<213> Artificial Sequence

<220>
<223> albumin binding domain

<400> 117

Thr Ile Asp Glu Trp Leu Leu Lys Glu Ala Lys Glu Lys Ala Ile Glu
1 5 10 15

Glu Leu Lys Lys Ala Gly Ile Thr Ser Asp Tyr Tyr Phe Asp Leu Ile
20 25 30

Asn Lys Ala Lys Thr Val Glu Gly Val Asn Ala Leu Lys Asp Glu Ile
35 40 45

Leu Lys Ala
50

<210> 118
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 118

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Asp Glu Val Val
130 135 140

Val Gly Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Tyr Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Val Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Ala Glu Ala
195 200 205

Lys Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly Val Ser Asp Tyr
210 215 220

Tyr Lys Asn Leu Ile Asn Asn Ala Lys Thr Val Glu Gly Val Lys Ala
225 230 235 240

Leu Leu Asp Glu Ile Leu Ala Ala Leu Pro
245 250

<210> 119
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 119

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

```
Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
                85                  90                  95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
            100                 105                 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
        115                 120                 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Asp Glu Val Val
    130                 135                 140

Val Gly Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145                 150                 155                 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Tyr Val Asn Ile
                165                 170                 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Val Pro Leu Ser Ala Ile Phe
            180                 185                 190

Thr Thr Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Ala Glu Ala
        195                 200                 205

Lys Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly Val Ser Asp Tyr
    210                 215                 220

Tyr Lys Asn Leu Ile Asn Asn Ala Lys Thr Val Glu Gly Val Lys Ala
225                 230                 235                 240

Leu Leu Asp Glu Ile Leu Ala Ala Leu Pro
                245                 250


<210>  120
<211>  250
<212>  PRT
<213>  Artificial Sequence

<220>
<223>  Bispecific EGFR/c-Met binding molecule

<400>  120

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1               5                   10                  15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
            20                  25                  30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
        35                  40                  45
```

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Met Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Ala Glu Ala
195 200 205

Lys Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly Val Ser Asp Tyr
210 215 220

Tyr Lys Asn Leu Ile Asn Asn Ala Lys Thr Val Glu Gly Val Lys Ala
225 230 235 240

Leu Leu Asp Glu Ile Leu Ala Ala Leu Pro
245 250

<210> 121
<211> 250
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 121

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Met Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Ala Glu Ala
195 200 205

Lys Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly Val Ser Asp Tyr
210 215 220

Tyr Lys Asn Leu Ile Asn Asn Ala Lys Thr Val Glu Gly Val Lys Ala
225 230 235 240

Leu Leu Asp Glu Ile Leu Ala Ala Leu Pro
245 250

<210> 122
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 122

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Leu Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 123
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 123

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Leu Arg Leu Ser Trp Thr Tyr Asp Arg Asp Gly Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 124
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 124

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Leu Arg Leu Ser Trp Gly Tyr Asn Gly Asp His Phe Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 125
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 125

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Leu Arg Leu Ser Trp Asp Asp Pro Arg Gly Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 126
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 126

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Leu Arg Leu Ser Trp Thr Trp Pro Tyr Ala Asp Leu Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 127
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 127

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Leu Arg Leu Ser Trp Gly Tyr Asn Gly Asp His Phe Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 128
<211> 96
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 128

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Leu Arg Leu Ser Trp Asp Tyr Asp Leu Gly Val Tyr Phe Asp Ser
20 25 30

Phe Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn
35 40 45

Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys
50 55 60

Pro Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr
65 70 75 80

Lys Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 129
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 129

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Leu Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 130
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 130

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Leu Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

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

Phe Glu His Asp Val Met Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 131
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 131

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90 95

<210> 132
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 132

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

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

Phe Glu His Asp Val Met Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90 95

<210> 133
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 133

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Leu Arg Leu Ser Trp Thr Trp Pro Tyr Ala Asp Leu Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 134
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 134

```
Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1               5                   10                  15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
            20                  25                  30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
        35                  40                  45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
    50                  55                  60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65                  70                  75                  80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
                85                  90                  95
```

<210> 135
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 135

```
Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1               5                   10                  15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
            20                  25                  30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
        35                  40                  45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
    50                  55                  60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65                  70                  75                  80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
                85                  90                  95
```

<210> 136
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 136

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90 95

<210> 137
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 137

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90 95

<210> 138
<211> 204
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 138

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly Gly
85 90 95

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
100 105 110

Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr
115 120 125

Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp
130 135 140

Ser Phe Trp Ile Arg Tyr Asp Glu Val Val Val Gly Gly Glu Ala Ile
145 150 155 160

Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu
165 170 175

Lys Pro Gly Thr Glu Tyr Tyr Val Asn Ile Leu Gly Val Lys Gly Gly
180 185 190

Ser Ile Ser Val Pro Leu Ser Ala Ile Phe Thr Thr
195 200

<210> 139
<211> 203
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 139

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly Gly
85 90 95

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
100 105 110

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

Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser
130 135 140

Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val
145 150 155 160

Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys
165 170 175

Pro Gly Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Lys
180 185 190

Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr Thr
195 200

<210> 140
<211> 204
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 140

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly Gly
85 90 95

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
100 105 110

Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr
115 120 125

Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp
130 135 140

Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile
145 150 155 160

Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu
165 170 175

Lys Pro Gly Thr Glu Tyr Val Val Gln Ile Ile Gly Val Lys Gly Gly
180 185 190

His Ile Ser Leu Pro Leu Ser Ala Ile Phe Thr Thr
195 200

<210> 141
<211> 204
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 141

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly Gly
85 90 95

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
100 105 110

Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr
115 120 125

Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp
130 135 140

Ser Phe Phe Ile Arg Tyr Asp Glu Phe Leu Arg Ser Gly Glu Ala Ile
145 150 155 160

Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu
165 170 175

Lys Pro Gly Thr Glu Tyr Trp Val Thr Ile Leu Gly Val Lys Gly Gly
180 185 190

Leu Val Ser Thr Pro Leu Ser Ala Ile Phe Thr Thr
195 200

<210> 142
<211> 204
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 142

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly Gly
85 90 95

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
100 105 110

Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr
115 120 125

Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp
130 135 140

Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile
145 150 155 160

Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu
165 170 175

Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly
180 185 190

Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr Thr
195 200

<210> 143
<211> 204
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 143

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly Gly
85 90 95

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
100 105 110

Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr
115 120 125

Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp
130 135 140

Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile
145 150 155 160

Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu
165 170 175

Lys Pro Gly Thr Glu Tyr Val Val Gln Ile Ile Gly Val Lys Gly Gly
180 185 190

His Ile Ser Leu Pro Leu Ser Ala Ile Phe Thr Thr
195 200

<210> 144
<211> 204
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 144

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Gly Gly
85 90 95

Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly
100 105 110

Gly Ser Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr
115 120 125

Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp
130 135 140

Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile
145 150 155 160

Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu
165 170 175

Lys Pro Gly Thr Glu Tyr Val Val Gln Ile Ile Gly Val Lys Gly Gly
180 185 190

His Ile Ser Leu Pro Leu Ser Ala Ile Phe Thr Thr
195 200

<210> 145
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 145

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Met
165 170 175

Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 146
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 146

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Asp Glu Val Val Val
130 135 140

Gly Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Tyr Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Ser Ile Ser Val Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 147
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 147

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Met Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Met Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 148
<211> 193

<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 148

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Asp Glu Val Val Val
130 135 140

Gly Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Tyr Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Ser Ile Ser Val Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 149
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 149

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 150
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 150

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 151
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 151

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val Ser
130 135 140

Lys Gly Asp Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 152
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 152

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 153
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 153

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 154
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 154

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 155
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 155

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val Ser
130 135 140

Lys Gly Asp Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 156
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 156

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 157
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 157

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 158
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 158

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 159
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 159

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val Ser
130 135 140

Lys Gly Asp Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 160
<211> 193
<212> PRT
<213> Artificial Sequence

<220>

<223> Bispecific EGFR/c-Met binding domain

<400> 160

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 161
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 161

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

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Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
            20                  25                  30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
        35                  40                  45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50                  55                  60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65                  70                  75                  80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
                85                  90                  95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
            100                 105                 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
        115                 120                 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
    130                 135                 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145                 150                 155                 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
                165                 170                 175

Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
            180                 185                 190

Thr
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<210> 162
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 162

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Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1               5                   10                  15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
            20                  25                  30
```

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Asp Glu Val Val Val
130 135 140

Gly Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Tyr Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Ser Ile Ser Val Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Ala Glu Ala Lys
195 200 205

Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly Val Ser Asp Tyr Tyr
210 215 220

Lys Asn Leu Ile Asn Asn Ala Lys Thr Val Glu Gly Val Lys Ala Leu
225 230 235 240

Leu Asp Glu Ile Leu Ala Ala Leu Pro
245

<210> 163
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 163

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Asp Glu Val Val Val
130 135 140

Gly Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Tyr Val Asn Ile Leu
165 170 175

Gly Val Lys Gly Gly Ser Ile Ser Val Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Ala Glu Ala Lys
195 200 205

Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly Val Ser Asp Tyr Tyr
210 215 220

Lys Asn Leu Ile Asn Asn Ala Lys Thr Val Glu Gly Val Lys Ala Leu
225 230 235 240

Leu Asp Glu Ile Leu Ala Ala Leu Pro
245

<210> 164
<211> 249
<212> PRT
<213> Artificial Sequence

<220>

<223> Bispecific EGFR/c-Met binding domain

<400> 164

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Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1               5                  10                  15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
            20                  25                  30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
        35                  40                  45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
    50                  55                  60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65                  70                  75                  80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
                85                  90                  95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
            100                 105                 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
        115                 120                 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
    130                 135                 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145                 150                 155                 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Met
                165                 170                 175

Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
            180                 185                 190

Thr Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Ala Glu Ala Lys
        195                 200                 205

Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly Val Ser Asp Tyr Tyr
    210                 215                 220

Lys Asn Leu Ile Asn Asn Ala Lys Thr Val Glu Gly Val Lys Ala Leu
225                 230                 235                 240

Leu Asp Glu Ile Leu Ala Ala Leu Pro
                245
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<210> 165
<211> 249
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 165

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Met
165 170 175

Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr Ala Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Ala Glu Ala Lys
195 200 205

Val Leu Ala Asn Arg Glu Leu Asp Lys Tyr Gly Val Ser Asp Tyr Tyr
210 215 220

Lys Asn Leu Ile Asn Asn Ala Lys Thr Val Glu Gly Val Lys Ala Leu
225 230 235 240

Leu Asp Glu Ile Leu Ala Ala Leu Pro
245

<210> 166
<211> 588
<212> DNA
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 166
ttgccagcgc cgaagaacct ggtagttagc gaggttactg aggacagcgc gcgtctgagc 60

tgggacgatc cgtgggcgtt ctacgagagc tttctgatcc agtatcaaga gagcgagaaa 120

gtcggtgaag cgattgtgct gaccgtcccg ggctccgagc gttcctacga cctgaccggt 180

ttgaagccgg gtaccgagta tacggtgagc atctacggtg ttcacaatgt ctataaggac 240

actaatatcc gcggtctgcc tctgagcgcc attttcacca ccgcaccggc accggctccg 300

gctcctgccc cgctgccggc tccgaagaac ttggtggtga gccgtgttac cgaagatagc 360

gcacgcctga gctggacggc accggatgcg gcgttcgata gcttctggat tcgctatttt 420

gagtttctgg gtagcggtga ggcaattgtt ctgacggtgc cgggctctga acgctcctac 480

gatttgaccg gtctgaaacc gggcaccgag tatgtggtga acattctgag cgttaagggc 540

ggtagcatca gcccaccgct gagcgcgatc ttcacgactg gtggttgc 588

<210> 167
<211> 579
<212> DNA
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding domain

<400> 167
ctgccagccc ctaagaatct ggtcgtgagc gaagtaaccg aggacagcgc ccgcctgagc 60

tgggacgacc cgtgggcgtt ctatgagtct ttcctgattc agtatcaaga aagcgaaaaa 120

gttggcgaag cgatcgtcct gaccgtcccg ggtagcgagc gctcctacga tctgaccggc 180

ctgaaaccgg gtacggagta cacggtgtcc atttacggtg ttcacaatgt gtataaagac 240

accaacatgc gtggcctgcc gctgtcggcg attttcacca ccgcgcctgc gccagcgcct 300

gcaccggctc cgctgccggc accgaagaac ctggttgtca gccgtgtgac cgaggatagc 360

gcacgtttga gctggaccgc tccggatgca gcctttgaca gcttctggat tcgttacttt 420

gaatttctgg gtagcggtga ggcgatcgtt ctgacggtgc cgggctctga acgcagctat 480

gatttgacgg gcctgaagcc gggtactgag tacgtggtta acatcatggg cgttaagggt 540

ggtaaaatca gcccgccatt gtccgcgatc tttaccacg 579

<210> 168
<211> 282

<212> DNA
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain from ECB97

<400> 168
ttgccagcgc cgaagaacct ggtagttagc gaggttactg aggacagcgc gcgtctgagc 60

tgggacgatc cgtgggcgtt ctacgagagc tttctgatcc agtatcaaga gagcgagaaa 120

gtcggtgaag cgattgtgct gaccgtcccg ggctccgagc gttcctacga cctgaccggt 180

ttgaagccgg gtaccgagta tacggtgagc atctacggtg ttcacaatgt ctataaggac 240

actaatatcc gcggtctgcc tctgagcgcc attttcacca cc 282

<210> 169
<211> 282
<212> DNA
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain from ECB15

<400> 169
ctgccagccc ctaagaatct ggtcgtgagc gaagtaaccg aggacagcgc ccgcctgagc 60

tgggacgacc cgtgggcgtt ctatgagtct ttcctgattc agtatcaaga aagcgaaaaa 120

gttggcgaag cgatcgtcct gaccgtcccg ggtagcgagc gctcctacga tctgaccggc 180

ctgaaaccgg gtacggagta cacggtgtcc atttacggtg ttcacaatgt gtataaagac 240

accaacatgc gtggcctgcc gctgtcggcg attttcacca cc 282

<210> 170
<211> 195
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 170

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Cys
195

<210> 171
<211> 195
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 171

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Cys
195

<210> 172
<211> 195
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 172

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val
130 135 140

Ser Lys Gly Asp Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Cys
195

<210> 173
<211> 195
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 173

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Cys
195

<210> 174
<211> 195
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 174

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Lys Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Cys
195

<210> 175
<211> 195
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 175

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Cys
195

<210> 176
<211> 195
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 176

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Val
130 135 140

Ser Lys Gly Asp Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Gly Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Cys
195

<210> 177
<211> 195
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 177

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro His Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Cys
195

<210> 178
<211> 195
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met binding molecule

<400> 178

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr Cys
195

<210> 179
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Consensus FG loop of EGFR bindiing FN3 domain

<220>
<221> VARIANT
<222> (9)..(9)
<223> Xaa may be Met or Ile

<400> 179

His Asn Val Tyr Lys Asp Thr Asn Xaa Arg Gly Leu
1 5 10

<210> 180
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> GF loop of EGFR binding FN3 domain

<400> 180

Leu Gly Ser Tyr Val Phe Glu His Asp Val Met Leu
1 5 10

<210> 181
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Consensus BC loop of EGFR binding FN3 domain

<220>
<221> VARIANT
<222> (1)..(1)
<223> Xaa may be Ala, Thr, Gly or Asp

<220>
<221> VARIANT
<222> (2)..(2)
<223> Xaa may be Ala, Asp, Tyr or Trp

<220>
<221> VARIANT
<222> (3)..(3)
<223> Xaa may be Pro, Asp or Asn

<220>
<221> VARIANT
<222> (4)..(4)
<223> Xaa may be Leu or absent

<220>
<221> VARIANT
<222> (5)..(5)
<223> Xaa may be Asp, His, Arg, Gly, Tyr or Trp

<220>
<221> VARIANT
<222> (6)..(6)
<223> Xaa may be Glu, Asp or Ala

<220>
<221> VARIANT
<222> (7)..(7)
<223> Xaa may be Ala, Phe, Gly, His or Asp

<220>
<221> VARIANT
<222> (8)..(8)
<223> Xaa may be Tyr, Phe or Leu

<400> 181

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 182
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain consensus sequence

<220>
<221> VARIANT
<222> (22)..(22)
<223> Xaa may be Ala, Thr, Gly or Asp

<220>
<221> VARIANT
<222> (23)..(23)
<223> Xaa may be Ala, Asp, Tyr or Trp

<220>
<221> VARIANT
<222> (24)..(24)
<223> Xaa may be Pro, Asp or Asn

<220>
<221> VARIANT
<222> (25)..(25)
<223> Xaa may be Leu or absent

<220>
<221> VARIANT
<222> (26)..(26)
<223> Xaa may be Asp, His, Arg, Gly, Tyr or Trp

<220>
<221> VARIANT
<222> (27)..(27)
<223> Xaa may be Gly, Asp or Ala

<220>
<221> VARIANT
<222> (28)..(28)
<223> Xaa may be Ala, Phe, Gly, His or Asp

<220>
<221> VARIANT
<222> (29)..(29)
<223> Xaa may be Tyr, Phe or Leu

<220>
<221> VARIANT
<222> (84)..(84)
<223> Xaa may be Met or Ile

<400> 182

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Xaa Arg Gly Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 183
<211> 95
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain consensus sequence

<220>
<221> VARIANT
<222> (22)..(22)
<223> Xaa may be Ala, Thr, Gly or Asp

<220>
<221> VARIANT
<222> (23)..(23)
<223> Xaa may be Ala, Asp, Tyr or Trp

<220>
<221> VARIANT
<222> (24)..(24)
<223> Xaa may be Pro, Asp or Asn

<220>
<221> VARIANT
<222> (25)..(25)
<223> Xaa may be Leu or absent

<220>
<221> VARIANT
<222> (26)..(26)
<223> Xaa may be Asp, His, Arg, Gly, Tyr or Trp

<220>
<221> VARIANT
<222> (27)..(27)
<223> Xaa may be Gly, Asp or Ala

<220>
<221> VARIANT
<222> (28)..(28)
<223> Xaa may be Ala, Phe, Gly, His or Asp

<220>
<221> VARIANT
<222> (29)..(29)
<223> Xaa may be Tyr, Phe or Leu

<400> 183

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Leu Arg Leu Ser Trp Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Asn Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

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

Phe Glu His Asp Val Met Leu Pro Leu Ser Ala Glu Phe Thr Thr
85 90 95

<210> 184
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain C strand and CD loop consensus sequence

<220>
<221> VARIANT
<222> (4)..(4)
<223> Xaa is Trp, Phe or Val

<220>
<221> VARIANT
<222> (8)..(8)
<223> Xaa is Asp, Phe or Leu

<220>
<221> VARIANT
<222> (10)..(10)
<223> Xaa is Val, Phe or Leu

<220>
<221> VARIANT
<222> (11)..(11)
<223> Xaa is Val, Leu or Thr

<220>
<221> VARIANT
<222> (12)..(12)
<223> Xaa is Val, Arg, Gly, Leu, Thr or Ser

<220>
<221> VARIANT
<222> (13)..(13)
<223> Xaa is Gly, Ser, Ala, Thr or Lys

<220>
<221> VARIANT
<222> (15)..(15)
<223> Xaa is Glu or Asp

<400> 184

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

<210> 185
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain F strand and FG loop consensus sequence

<220>
<221> VARIANT
<222> (4)..(4)
<223> Xaa is Tyr, Trp, Ile, Val, Gly or Ala

<220>
<221> VARIANT
<222> (6)..(6)
<223> Xaa is Asn, Thr, Qln or Gly

<220>
<221> VARIANT
<222> (8)..(8)
<223> Xaa is Leu, Met, Asn or Ile

<220>
<221> VARIANT
<222> (9)..(9)
<223> Xaa is Gly or Ser

<220>
<221> VARIANT
<222> (14)..(14)
<223> Xaa is Ser, Leu, Gly, Tyr, Thr, Arg, His or Lys

<220>
<221> VARIANT
<222> (15)..(15)
<223> Xaa is Ile, Val or Leu

<220>
<221> VARIANT
<222> (17)..(17)
<223> Xaa is Val, Thr, His, Ile, Pro, Tyr or Leu

<400> 185

Thr Glu Tyr Xaa Val Xaa Ile Xaa Xaa Val Lys Gly Gly Xaa Xaa Ser
1 5 10 15

Xaa

<210> 186
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain consensus sequence

<220>
<221> VARIANT
<222> (32)..(32)
<223> Xaa is Trp, Phe or Val

<220>
<221> VARIANT
<222> (36)..(36)
<223> Xaa is Asp, Phe or Leu

<220>
<221> VARIANT
<222> (38)..(38)
<223> Xaa is Val, Phe or Leu

<220>
<221> VARIANT
<222> (39)..(39)
<223> Xaa is Val, Leu or Thr

<220>
<221> VARIANT
<222> (40)..(40)
<223> Xaa is Val, Arg, Gly, Leu, Thr or Ser

<220>
<221> VARIANT
<222> (41)..(41)
<223> Xaa is Gly, Ser, Ala, Thr or Lys

<220>
<221> VARIANT
<222> (43)..(43)
<223> Xaa is Glu or Asp

<220>
<221> VARIANT
<222> (68)..(68)
<223> Xaa is Tyr, Trp, Ile, Val, Gly or Ala

<220>
<221> VARIANT
<222> (70)..(70)
<223> Xaa is Asn, Thr, Qln or Gly

<220>
<221> VARIANT
<222> (72)..(72)
<223> Xaa is Leu, Met, Asn or Ile

<220>
<221> VARIANT
<222> (73)..(73)
<223> Xaa is Gly or Ser

<220>
<221> VARIANT
<222> (78)..(78)
<223> Xaa is Ser, Leu, Gly, Tyr, Thr, Arg, His or Lys

<220>
<221> VARIANT
<222> (79)..(79)
<223> Xaa is Ile, Val or Leu

<220>
<221> VARIANT

<222> (81)..(81)
<223> Xaa is Val, Thr, His, Ile, Pro, Tyr or Leu

<400> 186

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Xaa
20 25 30

Ile Arg Tyr Xaa Glu Xaa Xaa Xaa Xaa Gly Xaa Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Xaa Val Xaa Ile Xaa Xaa Val Lys Gly Gly Xaa Xaa Ser
65 70 75 80

Xaa Pro Leu Ser Ala Glu Phe Thr Thr
85

<210> 187
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR consensus FN3 domain of bispecific EGFR/c-Met molecule

<220>
<221> VARIANT
<222> (11)..(11)
<223> Xaa is Glu, Asn or Arg

<220>
<221> VARIANT
<222> (14)..(14)
<223> Xaa is Glu or Pro

<220>
<221> VARIANT
<222> (17)..(17)
<223> Xaa is Leu or Ala

<220>
<221> VARIANT
<222> (25)..(25)
<223> Xaa is His or Trp

<220>
<221> VARIANT
<222> (29)..(29)
<223> Xaa is Glu or Asp

<220>
<221> VARIANT
<222> (37)..(37)
<223> Xaa is Glu or Pro

<220>
<221> VARIANT
<222> (46)..(46)
<223> Xaa is Asn or Val

<220>
<221> VARIANT
<222> (73)..(73)
<223> Xaa is Gly or Tyr

<220>
<221> VARIANT
<222> (83)..(83)
<223> Xaa is Met or Ile

<220>
<221> VARIANT
<222> (91)..(91)
<223> Xaa is Glu or Ile

<400> 187

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Xaa Val Thr Xaa Asp Ser
1 5 10 15

Xaa Arg Leu Ser Trp Asp Asp Pro Xaa Ala Phe Tyr Xaa Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Xaa Ser Glu Lys Val Gly Glu Ala Ile Xaa Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Xaa Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Xaa Arg Gly Leu Pro Leu Ser Ala Xaa Phe Thr Thr
85 90

<210> 188
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met consensus FN3 domain of bispecific EGFR/c-Met molecule

<220>
<221> VARIANT
<222> (11)..(11)
<223> Xaa is Glu, Asn or Arg

<220>
<221> VARIANT
<222> (14)..(14)
<223> Xaa is Glu or Pro

<220>
<221> VARIANT
<222> (17)..(17)

<223> Xaa is Leu or Ala

<220>
<221> VARIANT
<222> (37)..(37)
<223> Xaa is Glu or Pro

<220>
<221> VARIANT
<222> (39)..(39)
<223> Xaa is Val or Leu

<220>
<221> VARIANT
<222> (40)..(40)
<223> Xaa is Gly or Ser

<220>
<221> VARIANT
<222> (41)..(41)
<223> Xaa is Ser or Lys

<220>
<221> VARIANT
<222> (43)..(43)
<223> Xaa is Glu or Asp

<220>
<221> VARIANT
<222> (46)..(46)
<223> Xaa is Asn or Val

<220>
<221> VARIANT
<222> (72)..(72)
<223> Xaa is Leu or Met

<220>
<221> VARIANT
<222> (73)..(73)
<223> Xaa is Gly or Ser

<220>
<221> VARIANT
<222> (78)..(78)
<223> Xaa is Ser or Lys

<220>
<221> VARIANT
<222> (86)..(86)
<223> Xaa is Glu or Ile

<400> 188

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Xaa Val Thr Xaa Asp Ser
1 5 10 15

Xaa Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Xaa Phe Xaa Xaa Xaa Gly Xaa Ala Ile Xaa Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Val Val Asn Ile Xaa Xaa Val Lys Gly Gly Xaa Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Xaa Phe Thr Thr
85

<210> 189
<211> 585
<212> PRT
<213> Homo sapiens

<220>
<221> VARIANT
<222> (34)..(34)
<223> C34S

<400> 189

Asp Ala His Lys Ser Glu Val Ala His Arg Phe Lys Asp Leu Gly Glu
1 5 10 15

Glu Asn Phe Lys Ala Leu Val Leu Ile Ala Phe Ala Gln Tyr Leu Gln
20 25 30

Gln Ser Pro Phe Glu Asp His Val Lys Leu Val Asn Glu Val Thr Glu
35 40 45

Phe Ala Lys Thr Cys Val Ala Asp Glu Ser Ala Glu Asn Cys Asp Lys
50 55 60

Ser Leu His Thr Leu Phe Gly Asp Lys Leu Cys Thr Val Ala Thr Leu
65 70 75 80

Arg Glu Thr Tyr Gly Glu Met Ala Asp Cys Cys Ala Lys Gln Glu Pro
85 90 95

Glu Arg Asn Glu Cys Phe Leu Gln His Lys Asp Asp Asn Pro Asn Leu
100 105 110

Pro Arg Leu Val Arg Pro Glu Val Asp Val Met Cys Thr Ala Phe His
115 120 125

Asp Asn Glu Glu Thr Phe Leu Lys Lys Tyr Leu Tyr Glu Ile Ala Arg
130 135 140

Arg His Pro Tyr Phe Tyr Ala Pro Glu Leu Leu Phe Phe Ala Lys Arg
145 150 155 160

Tyr Lys Ala Ala Phe Thr Glu Cys Cys Gln Ala Ala Asp Lys Ala Ala
165 170 175

Cys Leu Leu Pro Lys Leu Asp Glu Leu Arg Asp Glu Gly Lys Ala Ser

180 185 190

Ser Ala Lys Gln Arg Leu Lys Cys Ala Ser Leu Gln Lys Phe Gly Glu
195 200 205

Arg Ala Phe Lys Ala Trp Ala Val Ala Arg Leu Ser Gln Arg Phe Pro
210 215 220

Lys Ala Glu Phe Ala Glu Val Ser Lys Leu Val Thr Asp Leu Thr Lys
225 230 235 240

Val His Thr Glu Cys Cys His Gly Asp Leu Leu Glu Cys Ala Asp Asp
245 250 255

Arg Ala Asp Leu Ala Lys Tyr Ile Cys Glu Asn Gln Asp Ser Ile Ser
260 265 270

Ser Lys Leu Lys Glu Cys Cys Glu Lys Pro Leu Leu Glu Lys Ser His
275 280 285

Cys Ile Ala Glu Val Glu Asn Asp Glu Met Pro Ala Asp Leu Pro Ser
290 295 300

Leu Ala Ala Asp Phe Val Glu Ser Lys Asp Val Cys Lys Asn Tyr Ala
305 310 315 320

Glu Ala Lys Asp Val Phe Leu Gly Met Phe Leu Tyr Glu Tyr Ala Arg
325 330 335

Arg His Pro Asp Tyr Ser Val Val Leu Leu Leu Arg Leu Ala Lys Thr
340 345 350

Tyr Glu Thr Thr Leu Glu Lys Cys Cys Ala Ala Ala Asp Pro His Glu
355 360 365

Cys Tyr Ala Lys Val Phe Asp Glu Phe Lys Pro Leu Val Glu Glu Pro
370 375 380

Gln Asn Leu Ile Lys Gln Asn Cys Glu Leu Phe Glu Gln Leu Gly Glu
385 390 395 400

Tyr Lys Phe Gln Asn Ala Leu Leu Val Arg Tyr Thr Lys Lys Val Pro
405 410 415

Gln Val Ser Thr Pro Thr Leu Val Glu Val Ser Arg Asn Leu Gly Lys
420 425 430

Val Gly Ser Lys Cys Cys Lys His Pro Glu Ala Lys Arg Met Pro Cys
435 440 445

Ala Glu Asp Tyr Leu Ser Val Val Leu Asn Gln Leu Cys Val Leu His

450 455 460

Glu Lys Thr Pro Val Ser Asp Arg Val Thr Lys Cys Cys Thr Glu Ser
465 470 475 480

Leu Val Asn Arg Arg Pro Cys Phe Ser Ala Leu Glu Val Asp Glu Thr
485 490 495

Tyr Val Pro Lys Glu Phe Asn Ala Glu Thr Phe Thr Phe His Ala Asp
500 505 510

Ile Cys Thr Leu Ser Glu Lys Glu Arg Gln Ile Lys Lys Gln Thr Ala
515 520 525

Leu Val Glu Leu Val Lys His Lys Pro Lys Ala Thr Lys Glu Gln Leu
530 535 540

Lys Ala Val Met Asp Asp Phe Ala Ala Phe Val Glu Lys Cys Cys Lys
545 550 555 560

Ala Asp Asp Lys Glu Thr Cys Phe Ala Glu Glu Gly Lys Lys Leu Val
565 570 575

Ala Ala Ser Gln Ala Ala Leu Gly Leu
580 585

<210> 190
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met molecule

<400> 190

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 191
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met molecule

<400> 191

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ile Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro

115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu
165 170 175

Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 192
<211> 194
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met molecule

<400> 192

Met Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp
1 5 10 15

Ser Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe
20 25 30

Leu Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu
35 40 45

Thr Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro
50 55 60

Gly Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys
65 70 75 80

Asp Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala
85 90 95

Pro Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu
100 105 110

Val Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala
115 120 125

Pro Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu
130 135 140

Gly Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser
145 150 155 160

Tyr Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile
165 170 175

Leu Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe
180 185 190

Thr Thr

<210> 193
<211> 193
<212> PRT
<213> Artificial Sequence

<220>
<223> Bispecific EGFR/c-Met molecule

<400> 193

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro His Gly Phe Tyr Asp Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr Ala Pro
85 90 95

Ala Pro Ala Pro Ala Pro Ala Pro Leu Pro Ala Pro Lys Asn Leu Val
100 105 110

Val Ser Arg Val Thr Glu Asp Ser Ala Arg Leu Ser Trp Thr Ala Pro
115 120 125

Asp Ala Ala Phe Asp Ser Phe Trp Ile Arg Tyr Phe Glu Phe Leu Gly
130 135 140

Ser Gly Glu Ala Ile Val Leu Thr Val Pro Gly Ser Glu Arg Ser Tyr
145 150 155 160

Asp Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Val Val Asn Ile Leu

165 170 175

Ser Val Lys Gly Gly Ser Ile Ser Pro Pro Leu Ser Ala Ile Phe Thr
180 185 190

Thr

<210> 194
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 194

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Ala Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 195
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 195

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Ala Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 196
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 196

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Ala Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 197
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 197

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Ala Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 198
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 198

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Ala Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 199
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 199

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Ala Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 200
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 200

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

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

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 201
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 201

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Ala Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 202
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 202

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Ala Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 203
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 203

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Ala Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 204
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 204

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Ala Asp
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 205
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 205

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Ala
65 70 75 80

Thr Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 206
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 206

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Ala Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 207
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 207

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Ala Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 208
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 208

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Ala Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 209
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 209

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Asn Met Arg Gly Ala Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 210
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 210

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Ala Asn Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 211
<211> 94
<212> PRT
<213> Artificial Sequence

<220>
<223> EGFR binding FN3 domain

<400> 211

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Glu Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Asp Asp Pro Trp Ala Phe Tyr Glu Ser Phe Leu
20 25 30

Ile Gln Tyr Gln Glu Ser Glu Lys Val Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Thr Val Ser Ile Tyr Gly Val His Asn Val Tyr Lys Asp
65 70 75 80

Thr Ala Met Arg Gly Leu Pro Leu Ser Ala Ile Phe Thr Thr
85 90

<210> 212
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 212

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Ser Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 213
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 213

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Phe Leu Ser Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Lys Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 214
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 214

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Phe Ser Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Lys Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 215
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 215

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Ser Val Asn Ile Met Gly Val Lys Gly Gly Lys Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 216
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 216

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Val Val Ser Ile Met Gly Val Lys Gly Gly Lys Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 217
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 217

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Lys Ile Ser
65 70 75 80

Ser Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 218
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 218

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Ser Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Lys Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 219
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 219

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Ser
20 25 30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Lys Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 220
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 220

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Val Val Asn Ile Ser Gly Val Lys Gly Gly Lys Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 221
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 221

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Ser Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Lys Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 222
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 222

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Ser Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly
50 55 60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Lys Ile Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 223
<211> 89
<212> PRT
<213> Artificial Sequence

<220>
<223> c-Met binding FN3 domain

<400> 223

Leu Pro Ala Pro Lys Asn Leu Val Val Ser Arg Val Thr Glu Asp Ser
1 5 10 15

Ala Arg Leu Ser Trp Thr Ala Pro Asp Ala Ala Phe Asp Ser Phe Trp
20 25 30

Ile Arg Tyr Phe Glu Phe Leu Gly Ser Gly Glu Ala Ile Val Leu Thr
35 40 45

Val Pro Gly Ser Glu Arg Ser Tyr Asp Leu Thr Gly Leu Lys Pro Gly

50 55 60

Thr Glu Tyr Val Val Asn Ile Met Gly Val Lys Gly Gly Lys Ser Ser
65 70 75 80

Pro Pro Leu Ser Ala Ile Phe Thr Thr
85

<210> 224
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> linker

<400> 224

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10

WHAT IS CLAIMED

1) An isolated bispecific FN3 domain containing molecule comprising a first fibronectin type III (FN3) domain and a second FN3 domain, wherein the first FN3 domain specifically binds epidermal growth factor receptor (EGFR) and blocks binding of epidermal growth factor (EGF) to EGFR, and the second FN3 domain specifically binds hepatocyte growth factor receptor (c-Met), and blocks binding of hepatocyte growth factor (HGF) to c-Met.
2) The bispecific molecule of claim 1, wherein
   a) the first FN3 domain inhibits EGF-induced EGFR phosphorylation at EGFR residue Tyrosine 1173 with an IC_{50} value of less than about 2.5×10^{-6} M when measured in A431 cells using 50 ng/mL human EGF, and the second FN3 domain inhibits HGF- induced c-Met phosphorylation at c-Met residue Tyrosine 1349 with an IC_{50} value of less than about 1.5×10^{-6} M when measured in NCI-H441 cells using 100 ng/mL human HGF;
   b) the first FN3 domain inhibits EGF-induced EGFR phosphorylation at EGFR residue Tyrosine 1173 with an IC_{50} value between about 1.8×10^{-8} M and about 2.5×10^{-6} M when measured in A431 cells using 50 ng/mL human EGF, and the second FN3 domain inhibits HGF- induced c-Met phosphorylation at c-Met residue Tyrosine 1349 with an IC_{50} value between about 4×10^{-9} M and about 1.5×10^{-6} M when measured in NCI-H441 cells using 100 ng/mL human HGF;
   c) the first FN3 domain binds human EGFR with a dissociation constant (K_D) of less than about 1×10^{-8} M, and the second FN3 domain binds human c-Met with a K_D of less than about 5×10^{-8} M, wherein the K_D is measured using surface plasmon resonance as described in Example 3; or
   d) the first FN3 domain binds human EGFR with a K_D of between about 2×10^{-10} to about 1×10^{-8} M, and the second FN3 domain binds human c-Met with a K_D of between about 3×10^{-10} to about 5×10^{-8} M, wherein the K_D is measured using surface plasmon resonance as described in Example 5.
3) The bispecific molecule of claim 1 or 2, wherein the bispecific molecule inhibits NCI-H292 cell proliferation with an IC_{50} value that is at least 30-fold less when compared to the IC_{50} value of inhibition of NCI-H292 cell growth with a mixture of the first FN3 domain and the second FN3 domain, wherein the cell proliferation is induced with 10% FBS containing 7.5 ng/mL HGF.
4) The bispecific molecule of any of the claims 1-3, wherein the bispecific molecule

a) inhibits EGF-induced EGFR phosphorylation at EGFR residue Tyrosine 1173 with an IC_{50} value of less than about $8x10^{-7}$ M when measured in NCI-H292 cells using 50 ng/mL human EGF;

b) inhibits HGF-induced c-Met phosphorylation at c-Met residue Tyrosine 1349 with an IC_{50} value of less than about $8.4x10^{-7}$ M when measured in NCI-H441 cells using 100 ng/mL human HGF;

c) inhibits HGF-induced NCI-H292 cell proliferation with an IC_{50} value of less than about $9.5x10^{-6}$ M, wherein the cell proliferation is induced with 10% FBS containing 7.5 ng HGF;

d) binds EGFR with a K_D of less than about $2.0x10^{-8}$ M; or

e) binds c-Met with a K_D of less than about $2.0x10^{-8}$ M, wherein the K_D is measured using surface plasmon resonance as described in Example 3 and Example 5.

5) The bispecific molecule of any of the claims 1-4, wherein the first FN3 domain comprises an amino acid sequence at least 87% identical to the amino acid sequence of SEQ ID NO: 27, and the second FN3 domain comprises an amino acid sequence at least 83% identical to the amino acid sequence of SEQ ID NO: 41.

6) The bispecific molecule of any of the claims 1-5, wherein the first FN3 domain comprises the amino acid sequence of SEQ ID NO: 107 or 108, and the second FN3 domain comprises the amino acid sequence of SEQ ID NO: 114.

7) The bispecific molecule of any of the claims 1-6, wherein the first FN3 domain binds EGFR with one or more amino acid residues corresponding to residues D23, F27, Y28, V77 and G85 of P54AR4-83v2 (SEQ ID NO: 27).

8) The bispecific molecule of claim 7, wherein the second FN3 domain binds c-Met with one or more amino acid residues corresponding to residues R34, F38, M72 and I79 in P114AR7P95-A3 (SEQ ID NO: 41).

9) The bispecific molecule of any of the claims 1-8, wherein

a) the first FN3 domain comprises

i) an FG loop comprising the amino acid sequence of SEQ ID NO: 179 or the amino acid sequence of SEQ ID NO: 180; and

ii) a BC loop comprising the amino acid sequence of SEQ ID NO: 181; and

b) the second FN3 domain comprises

i) a C strand and a CD loop comprising the amino acid sequence of SEQ ID NO: 184; and

ii) an F strand and an FG loop comprising the amino acid sequence of SEQ ID NO: 185.

10) The bispecific molecule of any of the claims 1-9, wherein
    a) the first FN3 domain comprises the amino acid sequence of SEQ ID NO: 182 or the amino acid sequence of SEQ ID NO: 183; and
    b) the second FN3 domain comprises the amino acid sequence of SEQ ID NO: 186.
11) The bispecific molecule of any of the claims 5-10, wherein the first FN3 domain and/or the second FN3 domain comprises substitutions at one or more residue positions corresponding to positions 11, 14, 17, 37, 46, 73 and 86 in Tencon (SEQ ID NO: 1).
12) The bispecific molecule of claim 11, wherein the first FN3 domain comprises the amino acid sequence of SEQ ID NO: 187; and the second FN3 domain comprises the amino acid sequence of SEQ ID NO: 188.
13) The bispecific molecule of any of the claims 1-12, wherein the first FN3 domain comprises the sequence shown in one of SEQ ID NOs: 18-29, 107-110, 122-137 or 194-211, and the second FN3 domain comprises the sequence shown in one of SEQ ID NOs: 32-49, 111-114 or 212-223.
14) The bispecific molecule of claim 13, wherein the first FN3 domain and the second FN3 domain comprises the amino acid sequence of SEQ ID NOs:
    a) 27 and 32, respectively;
    b) 27 and 41, respectively;
    c) 27 and 40, respectively;
    d) 27 and 33, respectively;
    e) 107 and 41, respectively;
    f) 107 and 40, respectively;
    g) 107 and 33, respectively;
    h) 107 and 32, respectively;
    i) 107 and 114, respectively;
    j) 108 and 111, respectively;
    k) 108 and 112, respectively;
    l) 108 and 113, respectively;
    m) 108 and 114, respectively;
    n) 109 and 111, respectively;
    o) 109 and 112, respectively;
    p) 109 and 113, respectively;
    q) 109 and 114, respectively;
    r) 110 and 111, respectively;

s) 110 and 112, respectively;

t) 110 and 113, respectively; or

u) 110 and 114, respectively.

15) The bispecific molecule of claim 14, wherein the first FN3 domain and/or the second FN3 domain comprises one or more substitutions corresponding to substitutions L17A, N46V and E86I in Tencon (SEQ ID NO: 1).

16) The bispecific molecule of any of the claims 1-15, wherein the first FN3 domain and/or the second FN3 domain is isolated from a library designed based on Tencon sequence of SEQ ID NO: 1.

17) The bispecific molecule of any of the claims 1-16, wherein the first FN3 domain and the second FN3 domain are coupled by a linker.

18) The bispecific molecule of claim 17, wherein the linker comprises the amino acid sequence shown in one of SEQ ID NOs: 78-84 or 224.

19) The bispecific molecule of any of the claims 1-18, comprising the amino acid sequence shown in SEQ ID NOs: 50-72, 106, 118-121, 138-165 or 190-193, and optionally comprising a methionine (Met) linked to the N-terminus of the molecule.

20) The bispecific molecule of claim 19, further comprising a cysteine linked to the C-terminus of the molecule.

21) The bispecific molecule of any of the claims 1-20 coupled to a half-life extending moiety.

22) The bispecific molecule of claim 21, wherein the half-life extending moiety is an albumin binding molecule, a polyethylene glygol (PEG), an albumin, an albumin variant, or at least a portion of an Fc region of an immunoglobulin.

23) The bispecific molecule of claim 22, wherein the half-life extending moiety is the albumin variant of SEQ ID NO: 189.

24) An isolated polynucleotide encoding the bispecific molecule of claim 5.

25) A vector comprising the polynucleotide of claim 24.

26) An isolated host cell comprising the vector of claim 25.

27) A method of producing a bispecific molecule, comprising culturing the isolated host cell of claim 26 under conditions such that the bispecific molecule is expressed, and purifying the bispecific molecule.

28) A pharmaceutical composition comprising the bispecific molecule of any of the claims 1-23 and a pharmaceutically acceptable carrier.

29) A method of treating a subject having cancer, comprising administering a therapeutically effective amount of the bispecific molecule of claim 1 to a patient in need thereof for a time sufficient to treat cancer.

30) The method of claim 29, wherein cancer is associated with an EGFR activating mutation, an EGFR gene amplification, a c-Met activating mutation or a c-Met gene amplification.

31) The method of claim 30, wherein the EGFR activating mutation is G719A, G719X (X being any amino acid), L861X (X being any amino acid), L858R, E746K, L747S, E749Q, A750P, A755V, V765M, L858P or T790M substitution, deletion of E746-A750, deletion of R748-P753, insertion of Ala (A) between M766 and A767, insertion of Ser, Val and Ala (SVA) between S768 and V769, and insertion of Asn and Ser (NS) between P772 and H773.

32) The method of claim 29, wherein the subject is resistant or has acquired resistance to treatment with erlotinib, gefitinib, afatinib, CO-1686, AZD9192, or cetuximab.

33) The method of claim 29, wherein cancer is an epithelial cell cancer, breast cancer, ovarian cancer, lung cancer, non-small cell lung cancer (NSCLC), lung adenocarcinoma, small cell lung cancer, colorectal cancer, anal cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancer, pharynx cancer, cancer of the nose, pancreatic cancer, skin cancer, oral cancer, cancer of the tongue, esophageal cancer, vaginal cancer, cervical cancer, cancer of the spleen, testicular cancer, gastric cancer, cancer of the thymus, colon cancer, thyroid cancer, liver cancer, hepatocellular carcinoma (HCC) or sporadic or hereditary papillary renal cell carcinoma (PRCC).

34) The method of claim 29, comprising administering a second therapeutic agent.

35) The method of claim 33, wherein the second therapeutic agent is a chemotherapeutic agent or a targeted anti-cancer therapy.

36) The method of claim 35, wherein the second therapeutic agent is cisplatin, vinblastine, a tyrosine kinase inhibitor of EGFR, c-Met, HER2, HER3, HER4 or VEGFR, erlotinib,gefitinib or afatinib.

37) The method of claim 34, wherein the second therapeutic agent is administered simultaneously, sequentially or separately from the bispecific molecule.

38) An isolated fibronectin type III (FN3) domain that specifically binds epidermal growth factor receptor (EGFR) and blocks binding of epidermal growth factor (EGF) to EGFR, wherein the FN3 domain is isolated from a library designed based on the Tencon amino acid sequence of SEQ ID NO: 1.

39) The FN3 domain of claim 38, wherein the FN3 domain
    a) inhibits EGF-induced EGFR phosphorylation at EGFR residue Tyrosine 1173 with an IC_{50} value of less than about 2.5 x 10^{-6} M when measured in A431 cells using 50 ng/mL human EGF;
    b) inhibits EGF-induced EGFR phosphorylation at EGFR residue Tyrosine 1173 with an IC_{50} value between about 1.8 x 10^{-8} M to about 2.5 x 10^{-6} M when measured in A431 cells using 50 ng/mL human EGF;
    c) binds human EGFR with a dissociation constant (K_D) of less than about 1x10^{-8} M, wherein the K_D is measured using punder the conditions described in Example 3; or
    d) binds human EGFR with a K_D of between about 2x10^{-10} to about 1x10^{-8} M, wherein the K_D is measured using surface plasmon resonance as described in Example 3.
40) The FN3 domain of claim 38 or 39 comprising an amino acid sequence at least 87% identical to the amino acid sequence of SEQ ID NO: 27.
41) The FN3 domain of any of the claims 38-40, wherein the FN3 domain binds EGFR with one or more amino acid residues corresponding to residues D23, F27, Y28, V77 and G85 of P54AR4-83v2 (SEQ ID NO: 27).
42) The FN3 domain of any of the claims 38-41, wherein the FN3 domain comprises
    a) an FG loop comprising the amino acid sequence of SEQ ID NO: 179 or the amino acid sequence of SEQ ID NO: 180; and
    b) a BC loop comprising the amino acid sequence of SEQ ID NO: 181.
43) The FN3 domain of claim 42, comprising the amino acid sequence of SEQ ID NO: 182 or the amino acid sequence of SEQ ID NO: 183.
44) The FN3 domain of any of the claims 38-43, wherein the FN3 domain comprises the sequence shown in one of SEQ ID NOs: 18-29, 107-110, 122-137 or 194-211.
45) The FN3 domain of claim 44, wherein the FN3 domain comprises substitutions at one or more residue positions corresponding to positions 11, 14, 17, 37, 46, 73, and 86 in Tencon (SEQ ID NO: 1).
46) The FN3 domain of claim 45, wherein the FN3 domain comprises one or more substitutions corresponding to substitutions L17A, N46V, and E86I in the Tencon amino acid sequence of SEQ ID NO: 1.
47) An isolated polynucleotide encoding the FN3 domain of claim 40.
48) A vector comprising the polynucleotide of claim 47.
49) An isolated host cell comprising the vector of claim 48.

50) A method of producing an FN3 domain that specifically binds EGFR, comprising culturing the isolated host cell of claim 48 under conditions such that the FN3 domain that specifically binds EGFR is expressed, and purifying the FN3 domain.

51) An isolated fibronectin type III (FN3) domain that specifically binds hepatocyte growth factor receptor (c-Met) and blocks binding of hepatocyte growth factor (HGF) to c-Met.

52) The FN3 domain of claim 51, wherein the FN3 domain

a) inhibits HGF- induced c-Met phosphorylation at c-Met residue Tyrosine 1349 with an IC_{50} value of less than about 1.5 x 10^{-6} M when measured in NCI-H441 cells using 100 ng/mL recombinant human HGF;

b) inhibits HGF- induced c-Met phosphorylation at c-Met residue Tyrosine 1349 with an IC_{50} value between about 4 x 10^{-9} M and about 1.5 x 10^{-6} M when measured in NCI-H441 cells using 100 ng/mL recombinant human HGF;

c) binds human c-Met with a K_D of less than about 5 x10^{-8} M, wherein the K_D is measured under the conditions described in Example 3; or

d) binds human c-Met with a (K_D of between about 3x10^{-10} to about 5 x10^{-8} M, wherein the K_D is measured using surface plasmon resonance as described in Example 5.

53) The FN3 domain of claim 51 or 52, comprising an amino acid sequence at least 83% identical to the amino acid sequence of SEQ ID NO: 41.

54) The FN3 domain of any of the claims 51-53, wherein the FN3 domain binds c-Met with one or more amino acid residues corresponding to residues R34, F38, M72 and I79 in P114AR7P95-A3 (SEQ ID NO: 41).

55) The FN3 domain of any of the claims 51-54, wherein the FN3 domain comprises

a) a C strand and a CD loop comprising the amino acid sequence of SEQ ID NO: 184; and

b) an F strand and an FG loop comprising the amino acid sequence of SEQ ID NO: 185.

56) The FN3 domain of claim 55, comprising the amino acid sequence of SEQ ID NO: 186.

57) The FN3 domain of any of the claims 51-56, wherein the FN3 domain comprises the sequence shown in one of SEQ ID NOs: 32-49, 111-114 or 212-223.

58) The FN3 domain of claim 57, wherein the FN3 domain comprises substitutions at one or more residue positions corresponding to positions 11, 14, 17, 37, 46, 73, and 86 of the Tencon amino acid sequence of SEQ ID NO: 1.

59) The FN3 domain of claim 58, wherein the FN3 domain comprises one or more substitutions corresponding to substitutions L17A, N46V, and E86I of the Tencon amino acid sequence of SEQ ID NO: 1.

60) The FN3 domain of any of the claimm 51-59, wherein the FN3 domain is isolated from a library designed based on the Tencon amino acid sequence of SEQ ID NO: 1.

61) An isolated polynucleotide encoding the FN3 domain of claim 53.

62) A vector comprising the polynucleotide of claim 61.

63) An isolated host cell comprising the vector of claim 62.

64) A method of producing an FN3 domain specifically binding c-Met, comprising culturing the isolated host cell of claim 63 under conditions such that the FN3 domain specifically binding c-Met is expressed, and purifying the FN3 domain specifically binding c-Met.

65) A pharmaceutical composition comprising the FN3 domain of claim 38 or 51 and a pharmaceutically acceptable carrier.

66) A method of treating a subject having cancer, comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 65 to a patient in need thereof for a time sufficient to treat cancer.

67) The method of claim 66, wherein the subject is resistant or has acquired resistance to treatment with erlotinib, gefitinib, afatinib, CO-1686, AZD9192, or cetuximab.

68) The method of claim 66, wherein cancer is an epithelial cell cancer, breast cancer, ovarian cancer, lung cancer, non-small cell lung cancer (NSCLC), lung adenocarcinoma, small cell lung cancer, colorectal cancer, anal cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancer, pharynx cancer, cancer of the nose, pancreatic cancer, skin cancer, oral cancer, cancer of the tongue, esophageal cancer, vaginal cancer, cervical cancer, cancer of the spleen, testicular cancer, gastric cancer, cancer of the thymus, colon cancer, thyroid cancer, liver cancer, hepatocellular carcinoma (HCC) or sporadic or hereditary papillary renal cell carcinoma (PRCC).

69) Use of a bispecific FN3 comain containing molecule of any of the claims 1-33, an isolated fibronectin type III (FN3) domain that specifically binds epidermal growth factor receptor (EGFR) of any of the claims 38-46, or an isolated fibronectin type III (FN3) domain that specifically binds hepatocyte growth factor receptor (c-Met) of any of the claims 51-60 for therapy.

70) A bispecific FN3 domain containing molecule according to any of the claims 1-33, an isolated fibronectin type III (FN3) domain that specifically binds epidermal growth

factor receptor (EGFR) according to any of the claims 38-46, or an isolated fibronectin type III (FN3) domain that specifically binds hepatocyte growth factor receptor (c-Met) according to any of the claims 51-60 for use in treating cancer.

71) A bispecific FN3 domain containing molecule according to any of the claims 1-33, an isolated fibronectin type III (FN3) domain that specifically binds epidermal growth factor receptor (EGFR) according to any of the claims 38-46 for use according to claim 70, wherein the cancer is an epithelial cell cancer, breast cancer, ovarian cancer, lung cancer, non-small cell lung cancer (NSCLC), lung adenocarcinoma, small cell lung cancer, colorectal cancer, anal cancer, prostate cancer, kidney cancer, bladder cancer, head and neck cancer, pharynx cancer, cancer of the nose, pancreatic cancer, skin cancer, oral cancer, cancer of the tongue, esophageal cancer, vaginal cancer, cervical cancer, cancer of the spleen, testicular cancer, gastric cancer, cancer of the thymus, colon cancer, thyroid cancer, liver cancer, hepatocellular carcinoma (HCC) or sporadic or hereditary papillary renal cell carcinoma (PRCC).