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(54) BISPECIFIC AGONISTIC ANTIBODIES TO ACTIVIN A RECEPTOR LIKE TYPE 1 (ALK1)

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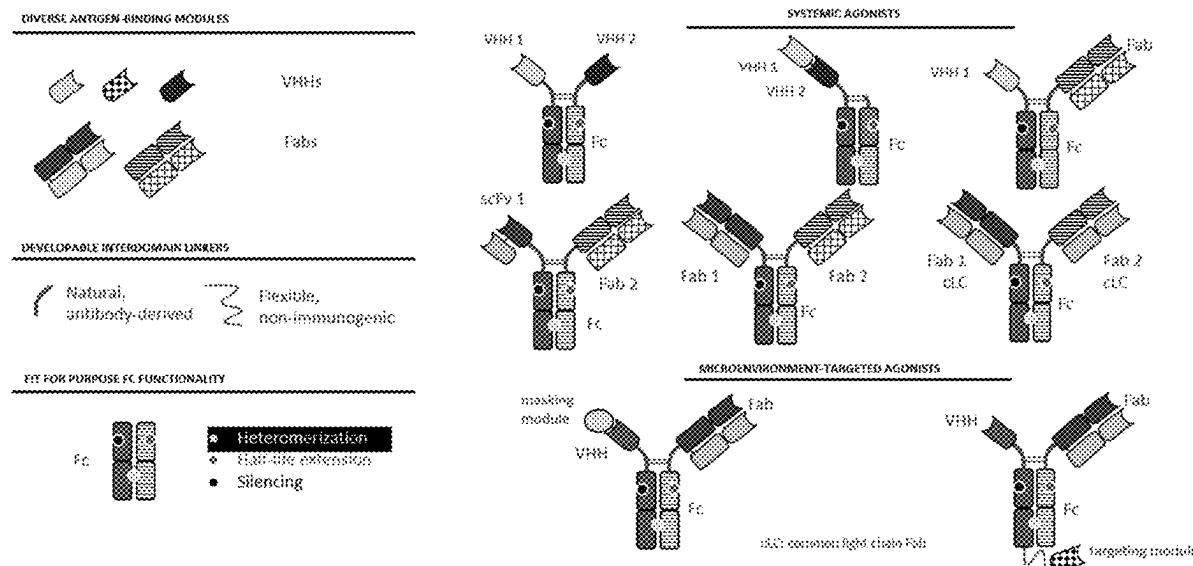
ABSTRACT

Provided herein are bispecific agonistic antibodies that bind to ALK1, BMPRII, ActRIIA, and/or ActRIIB, and methods of using the same.

Specification includes a Sequence Listing.

Related U.S. Application Data

- (63) Continuation of application No. 18/628,187, filed on Apr. 5, 2024.
(60) Provisional application No. 63/596,899, filed on Nov. 7, 2023, provisional application No. 63/537,318, filed



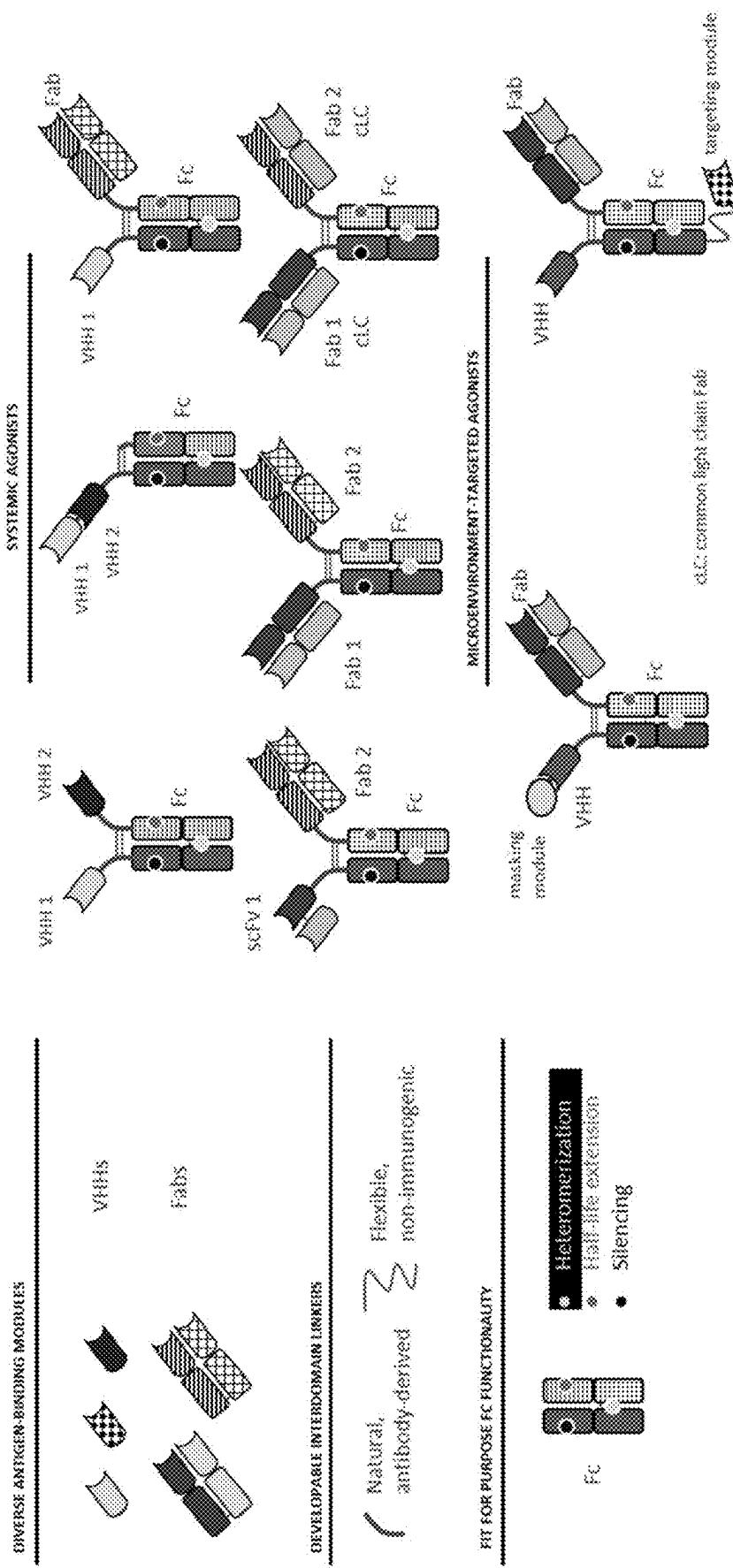


FIG. 1

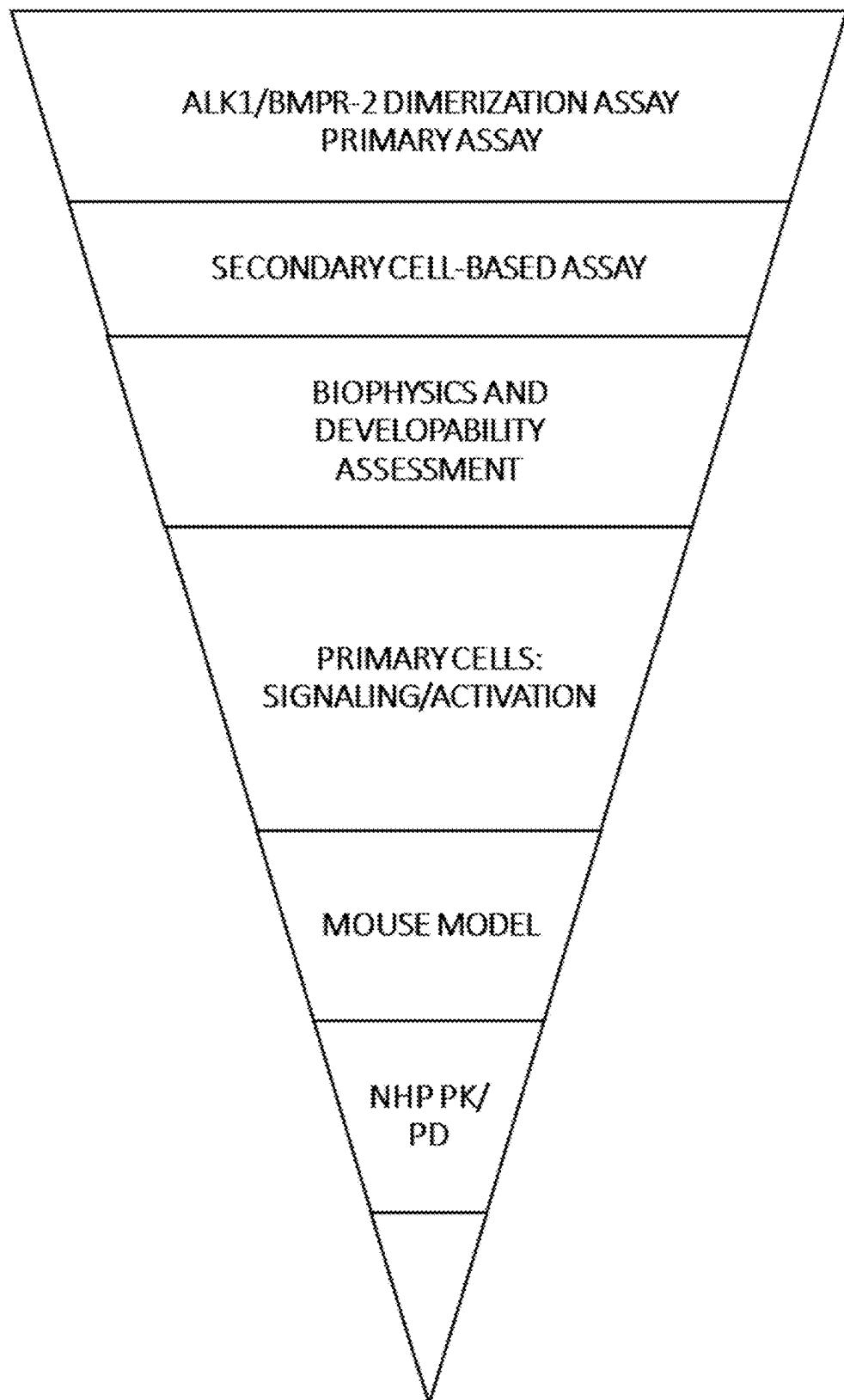


FIG. 2

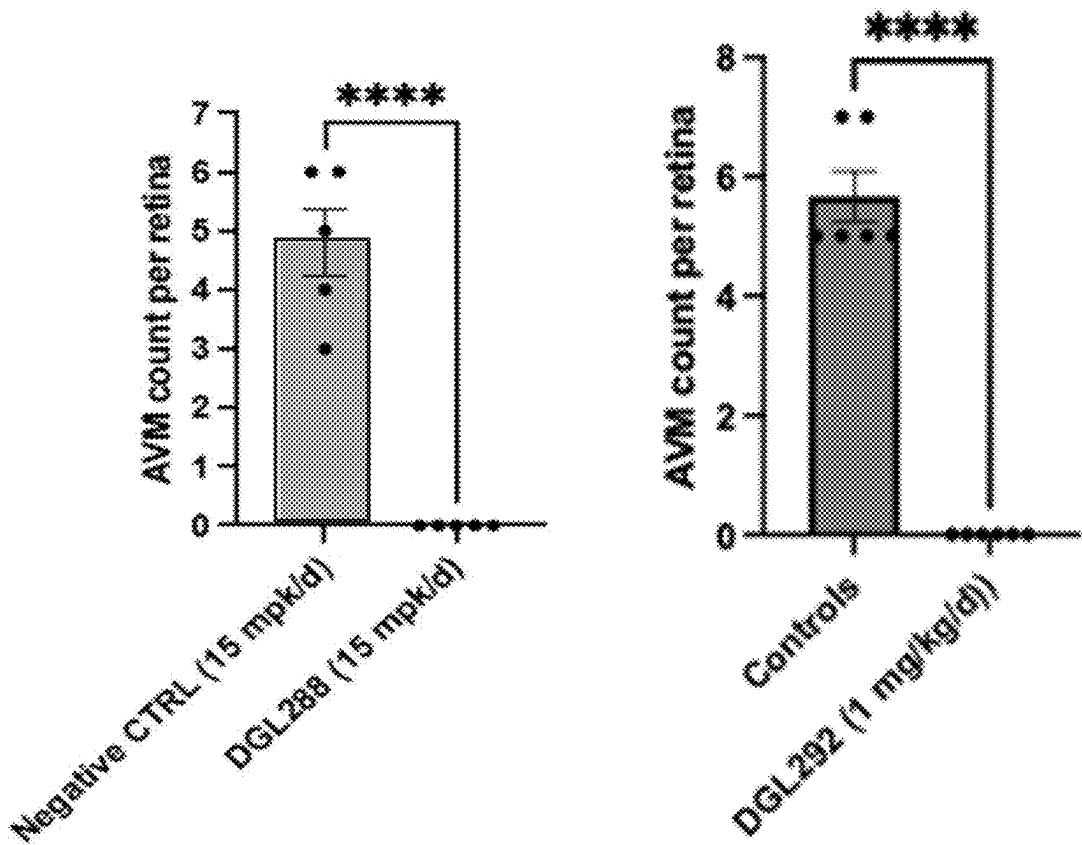


FIG. 3A

FIG. 3B

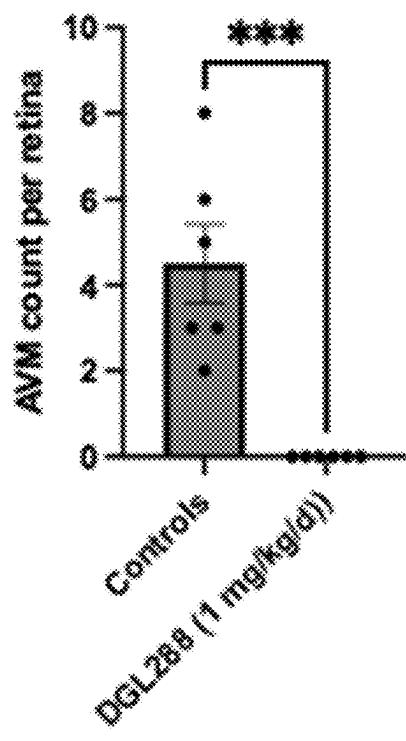


FIG. 3C

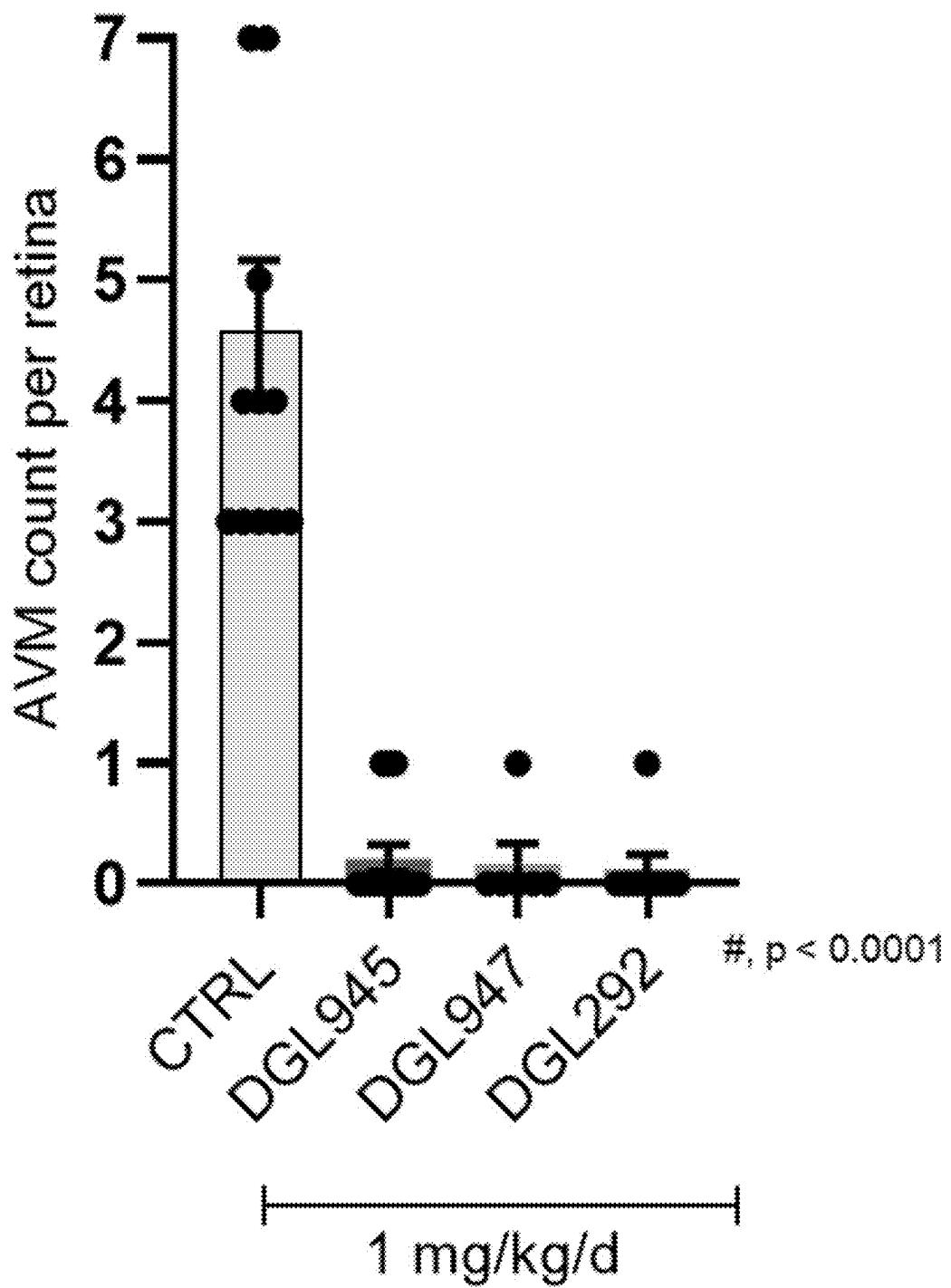


FIG. 4

BISPECIFIC AGONISTIC ANTIBODIES TO ACTIVIN A RECEPTOR LIKE TYPE 1 (ALK1)

RELATED APPLICATIONS

[0001] This application is a continuation of U.S. patent application Ser. No. 18/628,187, filed Apr. 5, 2024, which claims priority to U.S. Provisional Patent Application Serial Nos. 63/458,044, filed Apr. 7, 2023; 63/537,318, filed Sep. 8, 2023; and 63/596,899, filed Nov. 7, 2023, the entire disclosures of which are hereby incorporated herein by reference.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML file, created on Apr. 25, 2025, is named 764960_DGT9-005CON_ST26.xml, and is 263,152 bytes in size.

BACKGROUND

[0003] Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is an autosomal dominant genetic disease characterized by vascular malformations (arteriovenous malformations; AVMs) in multiple organs caused by an absent capillary network. The most common symptoms of HHT are epistaxis (nose bleeds), telangiectases, and visceral lesions. About 25-40% of patients have progressive disease and AVMs can result in acute life-threatening hemorrhages and emboli in patients. The majority (>85%) of HHT patients are heterozygous for loss of function (LOF) mutations in the endoglin (ENG, HHT1) or activin A receptor like type 1 (ALK1, HHT2) genes. HHT1 and HHT2 patients develop very similar clinical symptoms that result from sporadic vascular malformations, but tissues affected are different. HHT1 patients, accounting for about 61% of HHT, are more prone to pulmonary arteriovenous malformations (PAVMs) and cerebral arteriovenous malformations (CAVMs). Whereas HHT2 patients, accounting for about a third of patients (37%), are more prone to complications from liver AVMs and pulmonary hypertension. Hepatic involvement can lead to secondary portal hypertension which can require liver transplant and lead to heart failure. Pulmonary involvement in these patients can lead to pulmonary arterial hypertension (PAH). Activin receptor-like kinase 1 (ALK1) and endoglin are endothelial cell (EC)-restricted receptor of the large TGF- β family. Members of the TGF- β family act on many, if not all, cell types within the body, producing diverse and complex cellular outcomes, such as growth arrest, immune suppression, differentiation, apoptosis, and specification of developmental cell fate during embryogenesis and pathogenesis. Activation of the endothelial cell-restricted TGF- β type I receptor ALK1 results from the binding of several different ligands of the TGF- β family, including bone morphogenetic protein (BMP) 9, BMP10, and TGF- β .

[0004] TGF-beta signaling requires the recruitment of type I and type II receptors in a multimeric complex to initiate signaling. Endoglin is the type III receptor which delivers BMP9 and 10 to type I and type II receptors at endothelial cell membrane. A dimeric ligand molecule facilitates the assembly of a heteromeric complex of type II and type I receptors, wherein the constitutively active kinase

domain of the type II receptor trans-phosphorylates and activates the kinase domain of the type I receptor. The type I receptor is then able to initiate signaling via multiple signaling cascades, including the SMADs, which translocate to the nucleus and activate the transcription of target genes.

[0005] Defective signaling in ALK1 mediated pathway is also a hallmark of familial and sporadic PAH patients, which leads to endothelial dysfunction, i.e., apoptosis, proliferation, interaction with smooth muscle cells (SMC) and transdifferentiation. Over time, vasculature remodeling obstructs small pulmonary arteries, resulting in increased pulmonary vascular resistance and pulmonary pressures. This leads to reduced cardiac output, right heart failure, and ultimately death.

SUMMARY

[0006] The present disclosure improves upon the prior art by providing heteromeric antibodies which can effectively cross-link the ALK1 receptor to a receptor selected from BMPRII, ActRIIA, and ActRIIB and thereby activate SMAD signaling.

[0007] In one aspect, provided herein is a multispecific binding protein comprising a first binding moiety which binds specifically to human ALK1 and a second binding moiety which binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB, wherein: (a) the multispecific binding protein is capable of inducing signaling by inducing proximity between ALK1 and BMPRII, ActRIIA, or ActRIIB; and (b) at least one modified hinge region.

[0008] In some embodiments, the first modified hinge region comprises: (a) an upper hinge region of up to 7 amino acids in length or is absent; and (b) a lower hinge region, wherein the lower hinge region is linked to the N-terminus of a first constant region. In some embodiments, the multispecific binding protein further comprises a second modified hinge region linked to the N-terminus of a second constant region. In some embodiments, the second modified hinge region comprises (a) an upper hinge region of up to 7 amino acids in length or is absent; and (b) a lower hinge region, wherein the lower hinge region is linked to the N-terminus of the second constant region. In some embodiments, the upper hinge region of the first and the second modified hinge region are the same sequence. In some embodiments the upper hinge region of the first and the second modified hinge regions are different sequences.

[0009] In some embodiments the upper hinge region comprises an amino acid sequence derived from an upper hinge region of a human IgG antibody. In some embodiments, the IgG antibody is selected from IgG1, IgG2, IgG3, and IgG4. In some embodiments, the IgG antibody is IgG1. In some embodiments, the upper hinge region comprises an amino acid sequence of SEQ ID NO: 1. In some embodiments, the upper hinge region comprises an amino acid sequence of SEQ ID NO: 2. In some embodiments, the IgG antibody is IgG4. In some embodiments, the upper hinge region comprises an amino acid sequence of SEQ ID NO: 3. In some embodiments, the upper hinge is absent.

[0010] In some embodiments, the first heavy chain constant region and/or the second heavy chain constant region comprise a human IgG1, IgG2, IgG3, or IgG4. In some embodiments, the first heavy chain constant region and/or the second heavy chain constant region comprise an amino acid sequence of SEQ ID NO: 10.

[0011] In some embodiments, at least one heavy chain constant region comprises a substitution at amino acid position 234, according to EU numbering. In some embodiments, the substitution at amino acid position 234 is an alanine (A). In some embodiments, at least one heavy chain constant region comprises a substitution at amino acid position 235, according to EU numbering. In some embodiments, the substitution at amino acid position 235 is an alanine (A). In some embodiments, at least one heavy chain constant region comprises a substitution at amino acid position 237 according to EU numbering. In some embodiments, the substitution at amino acid position 237 is an alanine (A). In some embodiments, at least one heavy chain constant region comprises one or more substitutions at amino acid positions 234, 235, or 237, according to EU numbering. In some embodiments, the substitution at amino acid position 234 is an alanine (A), the substitution at amino acid position 235 is an alanine (A), and the substitution at amino acid position 237 is an alanine (A).

[0012] In some embodiments, the heavy chain constant region comprises heterodimerization mutations to promote heterodimerization of the first binding moiety with the second binding moiety. In some embodiments, the heterodimerization mutations are Knob-in-Hole (KIH) mutations. In some embodiments, the first heavy chain constant region comprises an amino acid substitution at position 366, 368, or 407 which produced a hole, and the second heavy chain constant region comprises an amino acid substitution at position 366 which produce a knob. In some embodiments, the first heavy chain constant region comprises the amino acid substitution T366S, L368A, or Y407V, and the second heavy chain constant region comprises the amino acid substitution T366W.

[0013] In some embodiments, the heterodimerization mutations are charge stabilization mutations. In some embodiments, the first heavy chain constant region comprises the amino acid substitution N297K, and the second heavy chain constant region comprises the amino acid substitution N297D. In some embodiments, the first heavy chain constant region comprises the amino acid substitution T299K, and the second heavy chain constant region comprises the amino acid substitution T299D.

[0014] In some embodiments, the heterodimerization mutations comprise an engineered disulfide bond. In some embodiments, the engineered disulfide bond is formed by a first heavy chain constant region comprising the amino acid substitution Y349C, and a second heavy chain constant region comprising the amino acid substitution S354C. In some embodiments, the engineered disulfide bond is formed by a C-terminal extension peptide fused to the C-terminus of each of the first heavy chain constant region and the second heavy chain constant region. In some embodiments, the first heavy chain constant region C-terminal extension comprises the amino acid sequence GEC, and the second heavy chain constant region C-terminal extension comprises the amino acid sequence SCDKT (SEQ ID NO:178).

[0015] In some embodiments, at least one heavy chain constant region comprises one or more mutations to promote increased half-life. In some embodiments, at least one heavy chain constant region comprises one or more substitutions at amino acid positions 252, 254, or 256, according to EU numbering. In some embodiments: the substitution at amino acid position 252 is a tyrosine (Y), the substitution at amino

acid position 254 is a threonine (T), and the substitution at amino acid position 256 is a glutamic acid (E).

[0016] In some embodiments, the first binding moiety that binds specifically to human ALK1 is selected from a single chain Fv (scFv), VHH, Fab, F(ab')2, or a single domain antibody. In some embodiments, the second binding moiety that binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB is selected from a single chain Fv (scFv), VHH, Fab, F(ab')2, or a single domain antibody.

[0017] In some embodiments, the multispecific binding protein comprises from N-terminus to C-terminus: (ai) a first polypeptide chain comprising a first antigen binding domain, a first modified hinge region, and a first constant region; and (bi) a second polypeptide chain comprising a second antigen binding domain, a second modified hinge region, and a second constant region; (aii) a first polypeptide chain comprising a second antigen binding domain, a first modified hinge region, and a first constant region; and (bii) a second polypeptide chain comprising a second modified hinge region, and a second constant region; or (aiii) a first polypeptide chain comprising a first modified hinge region, and a first constant region; and (biii) a second polypeptide chain comprising a second antigen binding domain, a first antigen binding domain, a second modified hinge region, and a second constant region. In some embodiments, (a) the first binding moiety comprises an VHH domain and the second moiety comprises a VHH domain; (b) the first binding moiety comprises a Fab domain and the second binding moiety comprises a VHH domain; (c) the first binding moiety comprises a VHH domain and the second binding moiety comprises a Fab domain; (d) the first binding moiety comprises a Fab domain and the second binding moiety comprises a Fab domain; (e) the first binding moiety comprises a Fab domain and the second binding moiety comprises an scFv; (f) the first binding moiety comprises a scFv and the second binding moiety comprises a Fab domain; (g) the first binding moiety comprises a scFv and the second binding moiety comprises a scFv; (h) the first binding moiety comprises a scFv and the second binding moiety comprises a VHH; or (i) the first binding moiety comprises a VHH and the second binding moiety comprises a scFv.

[0018] In some embodiments, the multispecific binding protein comprises a first and a second polypeptide chain, wherein: said first polypeptide chain comprises VH1-(HX1)n-VH2-C-(HX2)n, wherein: VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; HX1 is a linker; HX2 is an Fc region; and n is independently 0 or 1; and said second polypeptide chain comprises VL1-(LX1)n-VL2-C-(LX2)n, wherein: VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; LX1 is a linker; LX2 does not comprise an Fc region; and n is independently 0 or 1.

[0019] In some embodiments, VH1 binds specifically to human ALK1 and VH2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.

[0020] In some embodiments, VL1 binds specifically to human ALK1 and VL2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.

[0021] In some embodiments, VH1 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and VH2 binds specifically to human ALK1.

- [0022] In some embodiments, VL1 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and VL2 binds specifically to human ALK1.
- [0023] In some embodiments, linker HX1 comprises an amino acid sequence of PLAP (SEQ ID NO:2) or PAPNLLGGP (SEQ ID NO:157).
- [0024] In some embodiments, linker LX1 comprises an amino acid sequence of PLAP (SEQ ID NO:2) or PAPNLLGGP (SEQ ID NO:157).
- [0025] In some embodiments, linker HX1 comprises an amino acid sequence of PLAP (SEQ ID NO:2) and linker LX1 comprises an amino acid sequence of PLAP (SEQ ID NO:2) or PAPNLLGGP (SEQ ID NO:157).
- [0026] In some embodiments, the first and/or the second antigen binding domain is truncated at the C-terminal end adjacent to the upper hinge domain. In some embodiments, the C-terminal end adjacent to the upper hinge domain is truncated by at least one residue. In some embodiments, the C-terminal end adjacent to the upper hinge domain is truncated by at least two residues. In certain embodiments, the C terminal SS amino acids in a VH domain are truncated.
- [0027] In some embodiments, the multispecific binding protein comprises a first polypeptide chain of any one of SEQ ID NOS: 136-141 and a second polypeptide chain of any one of SEQ ID NOS: 142-145.
- [0028] In one aspect, the disclosure provides a multispecific binding protein comprising at least a first polypeptide chain, wherein:
- [0029] said first polypeptide chain comprises a first variable heavy chain domain (VH1) linked to a second variable heavy chain domain (VH2) via at least one modified hinge region; and
- [0030] the VH1 binds specifically to ALK1 and the VH2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.
- [0031] In some embodiments, one or both of VH1 and VH2 are VH domains or VHH domains.
- [0032] In some embodiments, the multispecific binding protein further comprises a second polypeptide chain, wherein said second polypeptide chain comprises a first variable light chain domain (VL1) linked to a second variable light chain domain (VL2), and wherein VL1 binds specifically to ALK1 and the VL2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.
- [0033] In some embodiments, the VL1 is linked to the VL2 via at least one modified hinge region.
- [0034] In some embodiments, one or both of VH1 and VH2 is truncated at the C-terminal end.
- [0035] In some embodiments, the C-terminal end is truncated by at least one residue.
- [0036] In some embodiments, the C-terminal end is truncated by at least two residues.
- [0037] In some embodiments, the SS amino acid residues of the C-terminal end are deleted.
- In some embodiments, the multispecific binding protein comprises a first polypeptide chain of
- [0038] VH1-HX1-VH2-C-Fc, wherein:
- [0039] VH1 is a first heavy chain variable domain;
- [0040] VH2 is a second heavy chain variable domain;
- [0041] C is a heavy chain constant domain;
- [0042] HX1 is a modified hinge region linker; and
- [0043] Fc is an Fc region; and
- [0044] a second polypeptide chain of VL1-LX1-VL2-C,

- [0045] wherein:
- [0046] VL1 is a first light chain variable domain;
- [0047] VL2 is a second light chain variable domain;
- [0048] C is a light chain constant domain; and
- [0049] LX1 is a modified hinge region linker.
- [0050] In some embodiments, the modified hinge region comprises or consists of an amino acid sequence of PLAP (SEQ ID NO:2) or PAPNLLGGP (SEQ ID NO:157).
- [0051] In some embodiments, the binding moiety which binds specifically to ALK1 is cross reactive with human ALK1 and mouse ALK1.
- [0052] In some embodiments, the binding moiety which binds specifically to ActRIIA is cross reactive with ActRIIB.
- [0053] In another aspect, provided herein is a multispecific binding protein comprising a first binding moiety which binds specifically to ALK1 and a second binding moiety which binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB, wherein: (a) the multispecific binding protein is capable of inducing signaling by inducing proximity between ALK1 and BMPRII, ActRIIA, or ActRIIB; and (b) at least one modified hinge region, wherein the at least one modified hinge region comprises: (i) an upper hinge region of up to 7 amino acids in length or is absent; and (ii) a lower hinge region, wherein the lower hinge region is linked to the N-terminus of the first heavy chain constant region.
- [0054] In another aspect, provided herein is a multispecific binding protein comprising at least a first polypeptide chain, wherein said first polypeptide chain comprises a first variable heavy chain domain (VH1) linked to a second variable heavy chain domain (VH2) via at least one modified hinge region, wherein: the VH1 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and the VH2 binds specifically to ALK1; or the VH1 binds specifically to ALK1 and the VH2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.
- [0055] In some embodiments, one or both of VH1 and VH2 are VH domains or VHH domains.
- [0056] In some embodiments, the multispecific binding protein further comprises a second polypeptide chain, wherein said second polypeptide chain comprises a first variable light chain domain (VL1) linked to a second variable light chain domain (VL2), wherein: the VL1 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and the VL2 binds specifically to a ALK1; or the VL1 binds specifically to ALK1 and the VL2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.
- [0057] In some embodiments, the VL1 is linked to the VL2 via at least one modified hinge region.
- [0058] In some embodiments, one or both of VH1 and VH2 is truncated at the C-terminal end.
- [0059] In some embodiments, the C-terminal end is truncated by at least one residue.
- [0060] In some embodiments, the C-terminal end is truncated by at least two residues.
- [0061] In some embodiments, the SS amino acid residues of the C-terminal end are deleted.
- [0062] In some embodiments, the multispecific binding protein comprises: a first polypeptide chain of VH1-HX1-VH2-C-Fc, wherein:
- [0063] VH1 is a first heavy chain variable domain;
- [0064] VH2 is a second heavy chain variable domain;
- [0065] C is a heavy chain constant domain;
- [0066] HX1 is a modified hinge region linker; and

[0067] Fc is an Fc region; and

[0068] a second polypeptide chain of VL1-LX1-VL2-C, wherein:

[0070] VL1 is a first light chain variable domain;

[0071] VL2 is a second light chain variable domain;

[0072] C is a light chain constant domain; and

[0073] LX1 is a modified hinge region linker.

[0074] In some embodiments, the modified hinge region comprises: i) an upper hinge region of up to 7 amino acids in length or is absent; and ii) a lower hinge region.

[0075] In some embodiments, the modified hinge region comprises or consists of an amino acid sequence of PLAP (SEQ ID NO:2) or PAPNLLGGP (SEQ ID NO:157).

[0076] In some embodiments, the VH binding to ALK1 comprises an HCDR1 amino acid sequence of SYAMS (SEQ ID NO:158), an HCDR2 amino acid sequence of NINQDGSEKNYVDSMRG (SEQ ID NO:159), and an HCDR3 amino acid sequence of EFDY (SEQ ID NO:160); and the VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDD-SLNGRV (SEQ ID NO:163).

[0077] In some embodiments, the VH binding to ALK1 comprises an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NINQDGSEKYYVDSMRG (SEQ ID NO:165), and an HCDR3 amino acid sequence of EYDY (SEQ ID NO:166); and the VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDD-SLNGRV (SEQ ID NO:163).

[0078] In some embodiments, the VH binding to ALK1 comprises an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NIKQDGSEKNYVDSMRG (SEQ ID NO:167), and an HCDR3 amino acid sequence of EFDF (SEQ ID NO:168); and the VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDD-SLNGRV (SEQ ID NO:163).

[0079] In some embodiments, the VH binding to BMPRII comprises an HCDR1 amino acid sequence of DYYMT (SEQ ID NO:169), an HCDR2 amino acid sequence of SISGGSTYYADSRKG (SEQ ID NO:170), and an HCDR3 amino acid sequence of DFGVAGWFGQYGMVD (SEQ ID NO:171); and the VL binding to BMPRII comprises an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

[0080] In some embodiments, the VH binding to BMPRII comprises an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYYADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGQFGMDV (SEQ ID NO:177); and the VL binding to BMPRII comprises an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

[0081] In some embodiments, the VH binding to BMPRII comprises an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYYADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGYYGMVD (SEQ ID NO:179); and the VL binding to BMPRII comprises an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

[0082] In some embodiments, the VH binding to ALK1 comprises an HCDR1 amino acid sequence of SYAMS (SEQ ID NO:158), an HCDR2 amino acid sequence of NINQDGSEKNYVDSMRG (SEQ ID NO:159), and an HCDR3 amino acid sequence of EFDY (SEQ ID NO:160); and the VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDD-SLNGRV (SEQ ID NO:163); and the VH binding to BMPRII comprises an HCDR1 amino acid sequence of DYYMT (SEQ ID NO:169), an HCDR2 amino acid sequence of SISGGSTYYADSRKG (SEQ ID NO:170), and an HCDR3 amino acid sequence of DFGVAGWFGQYGMVD (SEQ ID NO:171); and the VL binding to BMPRII comprises an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

[0083] In some embodiments, the VH binding to ALK1 comprises an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NINQDGSEKYYVDSMRG (SEQ ID NO:165), and an HCDR3 amino acid sequence of EYDY (SEQ ID NO:166); and the VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDD-SLNGRV (SEQ ID NO:163); and the VH binding to BMPRII comprises an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYYADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGQFGMDV (SEQ ID NO:177); and the VL binding to BMPRII comprises an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

[0084] In some embodiments, the VH binding to ALK1 comprises an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NIKQDGSEKNYVDSMRG (SEQ ID NO:167), and an HCDR3 amino acid sequence of EFDF (SEQ ID NO:168); and the VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDD-SLNGRV (SEQ ID NO:163); and the VH binding to BMPRII comprises an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYYADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGQYGMVD (SEQ ID NO:178); and the VL binding to BMPRII comprises an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

DFGVAGWFGYYGMDV (SEQ ID NO:179); and the VL binding to BMPRII comprises an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAG-NYNLV (SEQ ID NO:174).

[0085] In some embodiments, the VH binding to ALK1 comprises an amino acid sequence of EVQLLESGG-GLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK-GLEWVANINQDGSEKNYV DSMRGRFTISRDNSKNT-LYLQMNSLRAEDTAVYYCAREFDYWGQGTIVTSS (SEQ ID NO:180), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and the VL binding to ALK1 comprises an amino acid sequence of QSvlaQPP-SASGTPGQRVTISCGSSNI-G-SNYVWYQQLPGTAPKLLIYGNKNRPSGVPDFR SGSKSGTSASLAISGLRSEDEADYYCAAWDDSLN-GRVFGGGTKLTIVL (SEQ ID NO:181), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0086] In some embodiments, the VH binding to ALK1 comprises an amino acid sequence of EVQLLESGG-GLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK-GLEWVANINQDGSEKNYV DSMRGRFTISRDNSKNT-LYLQMNSLRAEDTAVYYCAREYDYWGQGTIVTSS (SEQ ID NO:182), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and the VL binding to ALK1 comprises an amino acid sequence of QSvlaQPP-SASGTPGQRVTISCGSSNI-G-SNYVWYQQLPGTAPKLLIYGNKNRPSGVPDFR SGSKSGTSASLAISGLRSEDEADYYCAAWDDSLN-GRVFGGGTKLTIVL (SEQ ID NO:181), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0087] In some embodiments, the VH binding to ALK1 comprises an amino acid sequence of EVQLLESGG-GLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK-GLEWVANIKQDGSEKNYV DSMRGRFTISRDNSKNT-LYLQMNSLRAEDTAVYYCAREFDYWGQGTIVTSS (SEQ ID NO:183), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and the VL binding to ALK1 comprises an amino acid sequence of QSvlaQPP-SASGTPGQRVTISCGSSNI-G-SNYVWYQQLPGTAPKLLIYGNKNRPSGVPDFR SGSKSGTSASLAISGLRSEDEADYYCAAWDDSLN-GRVFGGGTKLTIVL (SEQ ID NO:181), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0088] In some embodiments, the VH binding to BMPRII comprises an amino acid sequence of EVQLLESGG-GLVQPGGSLRLSCAASGFTFSDYYMTWIRQAPGK-GLEWVSSISGGSTYYADSR KGRFTISRDNSENT-LYLQMNSLRAEDTAVYYCARDFGVAGWFGQYGMDS VWGQGTIVTSS (SEQ ID NO:184), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at

least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and the VL binding to BMPRII comprises an amino acid sequence of QSVLQPPSASGTPGQRVTISCTGSSNI-GAGYDVWYQQLPGTAPKLLIYRSNQRPSGVPDFR FSGSKSGTSASLAISGLRSEDEADYYCSSYAG-
NYNLVFGGGTKLTIVL (SEQ ID NO:185), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; or In some embodiments, the VH binding to BMPRII comprises an amino acid sequence of EVQLLESGG-GLVQPGGSLRLSCAASGFTFSDYYMNWIRQAPGK-GLEWVSSISGGSTYYADSV KGRFTISRDNSENT-LYLQMNSLRAEDTAVYYCARDFGVAGWFGQYGMDS VWGQGTIVTSS (SEQ ID NO:186), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and the VL binding to BMPRII comprises an amino acid sequence of QSVLQPPSASGTPGQRVTISCTGSSNI-GAGYDVWYQQLPGTAPKLLIYRSNQRPSGVPDFR FSGSKSGTSASLAISGLRSEDEADYYCSSYAG-

NYNLVFGGGTKLTIVL (SEQ ID NO:185), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; or

[0089] In some embodiments, the VH binding to BMPRII comprises an amino acid sequence of EVQLLESGG-GLVQPGGSLRLSCAASGFTFSDYYMNWIRQAPGK-GLEWVSSISGGSTYYADSV KGRFTISRDNSENT-LYLQMNSLRAEDTAVYYCARDFGVAGWFGYYGMDS VWGQGTIVTSS (SEQ ID NO:187), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and the VL binding to BMPRII comprises an amino acid sequence of QSVLQPPSASGTPGQRVTISCTGSSNI-GAGYDVWYQQLPGTAPKLLIYRSNQRPSGVPDFR FSGSKSGTSASLAISGLRSEDEADYYCSSYAG-
NYNLVFGGGTKLTIVL (SEQ ID NO:185), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0090] In some embodiments, the VH binding to ALK1 comprises an amino acid sequence of EVQLLESGG-GLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGK-GLEWVANINQDGSEKNYV DSMRGRFTISRDNSKNT-LYLQMNSLRAEDTAVYYCAREFDYWGQGTIVTSS (SEQ ID NO:180), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; the VL binding to ALK1 comprises an amino acid sequence of QSvlaQPP-SASGTPGQRVTISCGSSNI-G-SNYVWYQQLPGTAPKLLIYGNKNRPSGVPDFR SGSKSGTSASLAISGLRSEDEADYYCAAWDDSLN-GRVFGGGTKLTIVL (SEQ ID NO:181), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, the VH binding to BMPRII comprises an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CASASGFTFSDYYMTWIRQAPGKGLEWVSSISGG-

STYYADSR KGRFTISRDNSENTLYLQMNSLRAED-TAVYYCARDGFGVAGWFGQYGMDFVWGQGTLVTVSS (SEQ ID NO:184), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and the VL binding to BMPRII comprises an amino acid sequence of QSVLTQPP-SASGTPGQRVTISCTGSSSNI-GAGYDVHWYQQLPGTAPKLLIYRSNQRPSGVPDFR FSGSKSGTSASLAISGLRSEDEADYYCSSYAG-NYNLVFGGGTKLTVL (SEQ ID NO:185), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0091] In some embodiments, the VH binding to ALK1 comprises an amino acid sequence of EVQLLESGG-GLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK-GLEWVANINQDGSEKYYV DSMRGRFTISRDNSKNT-LYLQMNSLRAEDTAVYYCAREYDYWGQGTLVTVSS (SEQ ID NO:182), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; the VL binding to ALK1 comprises an amino acid sequence of QSVLAQPP-SASGTPGQRVTISCGSSSNI-GSNYVYWWYQQLPGTAPKLLIYGNMNRPSGVPDFR SGSKSGTSASLAISGLRSEDEADYYCAAWDDSLN-GRVFGGGTKLTVL (SEQ ID NO:181), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and the VH binding to BMPRII comprises an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGFTSDYYMNWIRQAPGKGLEWVSSISGG-STYYADSV KGRFTISRDNSENTLYLQMNSLRAED-TAVYYCARDGFGVAGWFGQFGMDVWGQGTLVTVSS (SEQ ID NO:186), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and the VL binding to BMPRII comprises an amino acid sequence of QSVLTQPP-SASGTPGQRVTISCTGSSSNI-GAGYDVHWYQQLPGTAPKLLIYRSNQRPSGVPDFR FSGSKSGTSASLAISGLRSEDEADYYCSSYAG-NYNLVFGGGTKLTVL (SEQ ID NO:185), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0092] In some embodiments, the VH binding to ALK1 comprises an amino acid sequence of EVQLLESGG-GLVQPGGSLRLSCAASGFTFSSYWMSWVRQAPGK-GLEWVANIKQDGSEKNYV DSMRGRFTISRDNSKNT-LYLQMNSLRAEDTAVYYCAREDFWGQGTLVTVSS (SEQ ID NO:183), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; the VL binding to ALK1 comprises an amino acid sequence of QSVLAQPP-SASGTPGQRVTISCGSSSNI-GSNYVYWWYQQLPGTAPKLLIYGNMNRPSGVPDFR SGSKSGTSASLAISGLRSEDEADYYCAAWDDSLN-GRVFGGGTKLTVL (SEQ ID NO:181), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

97%, at least 98%, or at least 99% identity thereto; and the VH binding to BMPRII comprises an amino acid sequence of EVQLLESGGGLVQPGGSLRLSCAASGFTSDYYMNWIRQAPGKGLEWVSSISGG-STYYADSV KGRFTISRDNSENTLYLQMNSLRAED-TAVYYCARDGFGVAGWFGYGMDFVWGQGTLVTVSS (SEQ ID NO:187), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and the VL binding to BMPRII comprises an amino acid sequence of QSVLTQPP-SASGTPGQRVTISCTGSSSNI-GAGYDVHWYQQLPGTAPKLLIYRSNQRPSGVPDFR FSGSKSGTSASLAISGLRSEDEADYYCSSYAG-NYNLVFGGGTKLTVL (SEQ ID NO:185), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0093] In some embodiments, the first polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 136-142, and the second polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 143-146.

[0094] In some embodiments, the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 137, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0095] In some embodiments, the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 138, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0096] In some embodiments, the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 139, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0097] In some embodiments, the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 140, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0098] In some embodiments, the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 141, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0099] In some embodiments, the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 142, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0100] In some embodiments, the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 68, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 69, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0101] In some embodiments, the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 70, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 71, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0102] In some embodiments, the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 72, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 73, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0103] In some embodiments, the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 74, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 75, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0104] In one aspect, the disclosure provides a multispecific binding protein comprising a first polypeptide chain and a second polypeptide chain, wherein the first polypeptide chain and second polypeptide chain each comprise,

from N-terminus to C-terminus, a first single chain variable fragment (scFv) linked to a second scFv, wherein: the first scFv binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and the second scFv binds specifically to ALK1; or the first scFv binds specifically to ALK1 and the second scFv binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.

[0105] In some embodiments, the first scFv is linked to the second scFv via at least one modified hinge region.

[0106] In some embodiments, the scFv binding to ALK1 comprises: a VH domain comprising an HCDR1 amino acid sequence of SYAMS (SEQ ID NO:158), an HCDR2 amino acid sequence of NINQDGSEKNYVDSMRG (SEQ ID NO:159), and an HCDR3 amino acid sequence of EFDY (SEQ ID NO:160); and a VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163).

[0107] In some embodiments, the scFv binding to ALK1 comprises: a VH domain comprising an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NINQDGSEKYYVDSMRG (SEQ ID NO:165), and an HCDR3 amino acid sequence of EYDY (SEQ ID NO:166); and a VL domain comprising an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163).

[0108] In some embodiments, the scFv binding to ALK1 comprises: a VH domain comprising an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NIKQDGSEKNYVDSMRG (SEQ ID NO:167), and an HCDR3 amino acid sequence of EFDF (SEQ ID NO:168); and a VL domain comprising an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163).

[0109] In some embodiments, the scFv binding to BMPRII comprises: a VH domain comprising an HCDR1 amino acid sequence of DYYMT (SEQ ID NO:169), an HCDR2 amino acid sequence of SISGGSTYYADSRKG (SEQ ID NO:170), and an HCDR3 amino acid sequence of DFGVAGWFGQYGM DV (SEQ ID NO:171); and a VL domain comprising an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

[0110] In some embodiments, the scFv binding to BMPRII comprises: a VH domain comprising an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYYADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGQFGMDV (SEQ ID NO:177); and a VL domain comprising an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174); or

[0111] In some embodiments, the scFv binding to BMPRII comprises: a VH domain comprising an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino

acid sequence of SISGGSTYYADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGYYYGMDV (SEQ ID NO:179); and a VL domain comprising an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

[0112] In some embodiments, the scFv binding to ALK1 comprises: a VH domain comprising an HCDR1 amino acid sequence of SYAMS (SEQ ID NO:158), an HCDR2 amino acid sequence of NINQDGSEKYYVDSMRG (SEQ ID NO:159), and an HCDR3 amino acid sequence of EFDY (SEQ ID NO:160); and a VL domain comprising an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163); and the scFv binding to BMPRII comprises: a VH domain comprising an HCDR1 amino acid sequence of DYYMT (SEQ ID NO:169), an HCDR2 amino acid sequence of SISGGSTYYADSRKG (SEQ ID NO:170), and an HCDR3 amino acid sequence of DFGVAGWFGQYGMDF (SEQ ID NO:171); and a VL domain comprising an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

[0113] In some embodiments, the scFv binding to ALK1 comprises: a VH domain comprising an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NINQDGSEKYYVDSMRG (SEQ ID NO:165), and an HCDR3 amino acid sequence of EYDY (SEQ ID NO:166); and a VL domain comprising an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163); and the scFv binding to BMPRII comprises: a VH domain comprising an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYYADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGQFGMDV (SEQ ID NO:177); and a VL domain comprising an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

[0114] In some embodiments, the scFv binding to ALK1 comprises: a VH domain comprising an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NIKQDGSEKYYVDSMRG (SEQ ID NO:167), and an HCDR3 amino acid sequence of EFDF (SEQ ID NO:168); and a VL domain comprising an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163); and the scFv binding to BMPRII comprises: a VH domain comprising an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYYADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGYYYGMDV (SEQ ID NO:179); and a VL domain comprising an LCDR1 amino acid sequence of

TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

[0115] In some embodiments, the scFv binding to ALK1 comprises: a VH domain comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CAASGFTFSSYAMSWVRQAPGKGLEWVAN-INQDGSEKNYV DSMRGRTISRDNSKNT-LYLQMNSLRAEDTAVYYCAREFDYWGQGTLVTVSS (SEQ ID NO:180), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and a VL domain comprising an amino acid sequence of QSVLQAQPP-SASGTPGQRTISCGSSSNIG-SNYVWYQQLPGTAPKLLIYGNKNRPSGVPDFR SGSKSGTSASLAISGLRSEDEADYYCAAWDDSLN-GRVFGGGTKLTVL (SEQ ID NO:181), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0116] In some embodiments, the scFv binding to BMPRII comprises: a VH domain comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CAASGFTFSYYMTWIRQAPGKGLEWVSSISGG-STYYADSR KGRFTISRDNSENTLYLQMNSLRAED-TAVYYCARDFGVAGWFGQYGMDFVWGQGTLVTVSS (SEQ ID NO:184), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto; and a VL domain comprising an amino acid sequence of QSVLTAQPP-SASGTPGQRTISCTGSSSNI-GAGYDVHWYQQLPGTAPKLLIYRSNQRPSGVPDFR FSGSKSGTSASLAISGLRSEDEADYYCSSYAG-NYNLVFGGGTKLTVL (SEQ ID NO:185), or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0117] In some embodiments, the scFv binding to ALK1 comprises an amino acid sequence of SEQ ID NO: 120, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0118] In some embodiments, the scFv binding to ALK1 comprises an amino acid sequence of SEQ ID NO: 122, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0119] In some embodiments, the scFv binding to BMPRII comprises an amino acid sequence of SEQ ID NO: 121, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0120] In some embodiments, the scFv binding to ALK1 comprises an amino acid sequence of SEQ ID NO: 123, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0121] In some embodiments, the first and second polypeptide chain each comprise an amino acid sequence of any one of SEQ ID Nos: 60-63, or an amino acid sequence with at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identity thereto.

[0122] In some embodiments, wherein the multispecific binding protein is capable of inducing signaling by inducing proximity between ALK1 and BMPRII, ActRIIA, or ActRIIB.

[0123] In some embodiments, the multispecific binding protein has greater agonist activity compared to a multispecific binding protein that lacks at least one modified hinge region.

[0124] In some embodiments, the multispecific binding protein induces at least about 35% of the activity of BMP9.

[0125] In some embodiments, the activity of BMP9 is determined by measuring phosphorylated SMAD1 (pS-MAD1) levels in cells incubated with the multispecific binding protein and/or in cells incubated with BMP9.

[0126] In some embodiments, the melting temperature onset of unfolding (Tonset) of the multispecific binding protein is at least about 55° C.

[0127] In some embodiments, the melting temperature thermal transition midpoint (Tm) of the multispecific binding protein is at least about 64° C.

[0128] In some embodiments, the Tonset and Tm of the multispecific binding protein is determined by differential scanning calorimetry (DSC).

[0129] In some embodiments, the multispecific binding protein is capable of stimulating expression of ID1 in a cell.

[0130] In some embodiments, expression of ID1 in the cell is at least 50% relative to ID1 expression from a cell incubated with BMP9.

[0131] In some embodiments, the first polypeptide chain further comprises a heavy chain constant region.

[0132] In some embodiments, the heavy chain constant region comprises a substitution at amino acid position 234, according to EU numbering.

[0133] In some embodiments, the substitution at amino acid position 234 is an alanine (A).

[0134] In some embodiments, the heavy chain constant region comprises a substitution at amino acid position 235, according to EU numbering.

[0135] In some embodiments, the substitution at amino acid position 235 is an alanine (A).

[0136] In some embodiments, the heavy chain constant region comprises a substitution at amino acid position 237 according to EU numbering.

[0137] In some embodiments, the substitution at amino acid position 237 is an alanine (A).

[0138] In some embodiments, the heavy chain constant region comprises one or more substitutions at amino acid positions 234, 235, or 237, according to EU numbering.

[0139] In some embodiments, the substitution at amino acid position 234 is an alanine (A), the substitution at amino acid position 235 is an alanine (A), and the substitution at amino acid position 237 is an alanine (A).

[0140] In some embodiments, the heavy chain constant region comprises heterodimerization mutations to promote heterodimerization of the first binding moiety with the second binding moiety.

[0141] In some embodiments, the heterodimerization mutations are Knob-in-Hole (KIH) mutations.

[0142] In some embodiments, the first heavy chain constant region comprises an amino acid substitution at position 366, 368, or 407 which produced a hole, and the second heavy chain constant region comprises an amino acid substitution at position 366 which produce a knob.

[0143] In some embodiments, the first heavy chain constant region comprises the amino acid substitution T366S, L368A, or Y407V, and the second heavy chain constant region comprises the amino acid substitution T366W.

[0144] In some embodiments, the heterodimerization mutations are charge stabilization mutations.

[0145] In some embodiments, the first heavy chain constant region comprises the amino acid substitution N297K, and the second heavy chain constant region comprises the amino acid substitution N297D.

[0146] In some embodiments, the first heavy chain constant region comprises the amino acid substitution T299K, and the second heavy chain constant region comprises the amino acid substitution T299D.

[0147] In some embodiments, the heterodimerization mutations comprise an engineered disulfide bond.

[0148] In some embodiments, the engineered disulfide bond is formed by a first heavy chain constant region comprising the amino acid substitution Y349C, and a second heavy chain constant region comprising the amino acid substitution S354C.

[0149] In some embodiments, the engineered disulfide bond is formed by a C-terminal extension peptide fused to the C-terminus of each of the first heavy chain constant region and the second heavy chain constant region.

[0150] In some embodiments, the first heavy chain constant region C-terminal extension comprises the amino acid sequence GEC, and the second heavy chain constant region C-terminal extension comprises the amino acid sequence SCDKT (SEQ ID NO:178).

[0151] In some embodiments, at least one heavy chain constant region comprises one or more mutations to promote increased half-life.

[0152] In some embodiments, at least one heavy chain constant region comprises one or more substitutions at amino acid positions 252, 254, or 256, according to EU numbering.

[0153] In some embodiments, the substitution at amino acid position 252 is a tyrosine (Y), the substitution at amino acid position 254 is a threonine (T), and the substitution at amino acid position 256 is a glutamic acid (E).

[0154] In some embodiments, at least one heavy chain constant region comprises one or more substitutions at amino acid positions 428 or 434, according to EU numbering.

[0155] In some embodiments, at least one heavy chain constant region comprises a M428L and N434S substitution, according to EU numbering.

[0156] In one aspect, the disclosure provides a pharmaceutical composition comprising the multispecific binding protein described herein and a pharmaceutically acceptable carrier.

[0157] In one aspect, the disclosure provides an isolated nucleic acid molecule encoding the multispecific binding protein described herein.

[0158] In one aspect, the disclosure provides an expression vector comprising the nucleic acid molecule described herein.

[0159] In one aspect, the disclosure provides a host cell comprising the expression vector described herein.

[0160] In one aspect, the disclosure provides a method for treating a disease or disorder in a subject, comprising administering to a subject in need thereof the multispecific binding protein described herein.

[0161] In some embodiments, the disease or disorder is a vascular disease or disorder.

[0162] In some embodiments, the vascular disease or disorder is hereditary hemorrhagic telangiectasia (HHT).

[0163] In some embodiments, the vascular disease or disorder is pulmonary arterial hypertension (PAH).

[0164] In some embodiments, the multispecific binding protein is for use as a medicament.

[0165] In one aspect, the disclosure provides a method for inducing signaling between ALK1 and BMPRII, ActRIIA, or ActRIIB in a subject, comprising administering to the subject the multispecific binding protein described herein.

[0166] In some embodiments, the multispecific binding protein is capable of inducing signaling by inducing proximity between ALK1 and BMPRII, ActRIIA, or ActRIIB.

[0167] In some embodiments, the multispecific binding protein has greater agonist activity compared to a multispecific binding protein that lacks at least one modified hinge region.

[0168] In some embodiments, the multispecific binding protein induces at least about 35% of the activity of BMP9.

[0169] In some embodiments, the activity of BMP9 is determined by measuring phosphorylated SMAD1 (pSMAD1) levels in cells incubated with the multispecific binding protein and/or in cells incubated with BMP9.

BRIEF DESCRIPTION OF THE DRAWINGS

[0170] FIG. 1 is an illustration depicting certain exemplary embodiments of the formats of the bispecific antibodies described herein.

[0171] FIG. 2 is a schematic diagram depicting the workflow for characterization of the bispecific antibodies of the present disclosure.

[0172] FIG. 3A-3C are graphs depicting arteriovenous malformations (AVMs) in the retina in a HHT mouse model. FIG. 3A illustrates mice treated with control (no bispecific antibody) compared to DGL288 (15 mg/kg/day). Mice treated with DGL288 did not form detectable AVMs compared to control. FIG. 3B illustrates that mice treated with 1 mg/kg/day of DGL292 did not form AVMs compared to the mice treated with control. FIG. 3C demonstrates that DGL288 given at a dose of 1 mg/kg/day also did not form AVMs compared to mice treated with control.

[0173] FIG. 4 is a graph depicting arteriovenous malformations (AVMs) in the retina in a HHT mouse model. Mice were treated with control (no bispecific antibody) compared to DGL292, DGL945, and DGL947 (1 mg/kg/day). Mice treated with DGL292, DGL945, and DGL947 did not form detectable AVMs compared to control.

DETAILED DESCRIPTION

[0174] Before the present disclosure is described, it is to be understood that this disclosure is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended

to be limiting, since the scope of the present disclosure will be limited only by the appended claims.

[0175] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0176] Although any methods and materials similar or equivalent to those described herein can be used in the practice of the present disclosure, exemplary methods and materials are now described. All publications mentioned herein are incorporated herein by reference to describe in their entirety.

[0177] As used herein, the terms "antibody" and "antibodies" include full-length antibodies, antigen-binding fragments of full-length antibodies, and molecules comprising antibody CDRs, VH regions, and/or VL regions. Examples of antibodies include, without limitation, monoclonal antibodies, recombinantly produced antibodies, monospecific antibodies, multispecific antibodies (including bispecific antibodies), human antibodies, humanized antibodies, chimeric antibodies, immunoglobulins, synthetic antibodies, tetrameric antibodies comprising two heavy chain and two light chain molecules, an antibody light chain monomer, an antibody heavy chain monomer, an antibody light chain dimer, an antibody heavy chain dimer, an antibody light chain-antibody heavy chain pair, intrabodies, heteroconjugate antibodies, antibody-drug conjugates, single domain antibodies, monovalent antibodies, single chain antibodies or single-chain Fvs (scFv), camelized antibodies, affibodies, common light chain antibodies, Fab fragments, F(ab')² fragments, disulfide-linked Fvs (sdFv), anti-idiotypic (anti-Id) antibodies (including, e.g., anti-anti-Id antibodies), dual variable domains (DVD), and antigen-binding fragments of any of the above. In certain embodiments, antibodies described herein refer to polyclonal antibody populations. Antibodies can be of any type (e.g., IgG, IgE, IgM, IgD, IgA or IgY), any class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2), or any subclass (e.g., IgG2a or IgG2b) of immunoglobulin molecule. In certain embodiments, antibodies described herein are IgG antibodies, or a class (e.g., human IgG1 or IgG4) or subclass thereof. As used herein, the terms "VH" and "VL" refer to antibody heavy and light chain variable domain, respectively, as described in Kabat et al., (1991) Sequences of Proteins of Immunological Interest (NIH Publication No. 91-3242, Bethesda), which is herein incorporated by reference in its entirety.

[0178] As used herein, the term "VHH" refers to the heavy chain variable domain of a camelid heavy chain-only antibody (HCAb) and humanized variants thereof, as described in Hamers-Casterman C. et al., Nature (1993) 363:446-8. 10.1038/363446a0, which is incorporated by reference herein in its entirety.

[0179] As used herein, the term "VH/VL Pair" refers to a combination of a VH and a VL that together form the binding site for an antigen.

[0180] As used herein, the term "heavy chain" when used in reference to an antibody can refer to any distinct type, e.g., alpha (α), delta (δ), epsilon (ϵ), gamma (γ), and mu (μ), based on the amino acid sequence of the constant domain, which give rise to IgA, IgD, IgE, IgG, and IgM classes of antibodies, respectively, including subclasses of IgG, e.g., IgG1, IgG2, IgG3, and IgG4.

[0181] As used herein, the term "full-length antibody heavy chain" refers to an antibody heavy chain comprising,

from N to C terminal, a VH, a CH1 region, a hinge region, a CH2 domain and a CH3 domain.

[0182] As used herein, the term “light chain” when used in reference to an antibody can refer to any distinct type, e.g., kappa (κ) or lambda (λ) based on the amino acid sequence of the constant domains. Light chain amino acid sequences are well known in the art. In specific embodiments, the light chain is a human light chain. As used herein, the term “complementarity determining region” or “CDR” refers to sequences of amino acids within antibody variable regions, which confer antigen specificity and binding affinity. In general, there are three CDRs in each heavy chain variable region (CDR-H1, CDR-H2, CDR-H3) and three CDRs in each light chain variable region (CDR-L1, CDR-L2, CDR-L3). “Framework regions” or “FR” are known in the art to refer to the non-CDR portions of the variable regions of the heavy and light chains. In general, there are four FRs in each heavy chain variable region (FR-H1, FR-H2, FR-H3, and FR-H4), and four FRs in each light chain variable region (FR-L1, FR-L2, FR-L3, and FR-L4).

[0183] The precise amino acid sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), “Sequences of Proteins of Immunological Interest,” 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (“Kabat” numbering scheme), Al-Lazikani et al., (1997) JMB 273, 927-948 (“Chothia” numbering scheme), MacCallum et al., J. Mol. Biol. 262:732-745 (1996), “Antibody-antigen interactions: Contact analysis and binding site topography,” J. Mol. Biol. 262, 732-745. (“Contact” numbering scheme), Lefranc M. P. et al., “IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains,” Dev. Comp. Immunol., 2003 January; 27(1):55-77 (“IMGT” numbering scheme), and Honegger A. and Pluckthun A., “Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool,” J. Mol. Biol., 2001 Jun. 8; 309(3):657-70, (AHo numbering scheme).

[0184] The boundaries of a given CDR or FR may vary depending on the scheme used for identification. For example, the Kabat scheme is based on sequence alignments, while the Chothia scheme is based on structural information. Numbering for both the Kabat and Chothia schemes is based upon the most common antibody region sequence lengths, with insertions accommodated by insertion letters, for example, “30a,” and deletions appearing in some antibodies. The two schemes place certain insertions and deletions (“indels”) at different positions, resulting in differential numbering. The Contact scheme is based on analysis of complex crystal structures and is similar in many respects to the Chothia numbering scheme.

[0185] As used herein, the term “single chain variable fragment” (scFv) refers to a fusion protein comprising at least one antibody fragment comprising a variable region of a light chain and at least one antibody fragment comprising a variable region of a heavy chain, wherein the light and heavy chain variable regions are contiguously linked via a short flexible polypeptide linker, and capable of being expressed as a single chain polypeptide, and wherein the scFv retains the specificity of the intact antibody from which it is derived. Unless specified, as used herein an scFv may have the VL and VH variable regions in either order, e.g.,

with respect to the N-terminal and C-terminal ends of the polypeptide, the scFv may comprise VL-linker-VH or may comprise VH-linker-VL.

[0186] The term “human antibody,” as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human mAbs of the disclosure may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3. However, the term “human antibody,” as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (e.g., mouse), have been grafted onto human FR sequences. The term includes antibodies recombinantly produced in a non-human mammal, or in cells of a non-human mammal. The term is not intended to include antibodies isolated from or generated in a human subject.

[0187] The term “multispecific antigen-binding molecules,” as used herein refers to bispecific, trispecific or multispecific antigen-binding molecules, and antigen-binding fragments thereof. Multispecific antigen-binding molecules may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for epitopes of more than one target polypeptide. A multispecific antigen-binding molecule can be a single multifunctional polypeptide, or it can be a multimeric complex of two or more polypeptides that are covalently or non-covalently associated with one another. The term “multispecific antigen-binding molecules” includes antibodies of the present disclosure that may be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, non-covalent association or otherwise) to one or more other molecular entities, such as a protein or fragment thereof to produce a bi-specific or a multispecific antigen-binding molecule with a second binding specificity. According to the present disclosure, the term “multispecific antigen-binding molecules” also includes bispecific, trispecific or multispecific antibodies or antigen-binding fragments thereof. In certain exemplary embodiments, an antibody of the present disclosure is functionally linked to another antibody or antigen-binding fragment thereof to produce a bispecific antibody with a second binding specificity.

[0188] The term “valency” or “valent”, as used herein, denotes the presence of a number of binding sites in an antibody molecule. For example, the term bivalent indicates the presence of two binding sites. In some embodiments, the antibody molecule could be multivalent. As such, the term trivalent indicates three binding sites; the term tetravalent indicates four binding sites. In some embodiments, there may be more than four binding sites. In some embodiments, the binding sites may bind to the same antigen. In some embodiments, the binding sites bind to different antigens.

[0189] In some embodiments, the multivalent antibody molecules of the invention are multi-chain molecules with one or more binding sites in each chain.

[0190] For example, in one embodiment, the multivalent binding molecule is a bivalent molecule with one binding site (e.g., a VHH or scFV) in a first chain and a second binding site in a second chain. In another embodiment, the

multivalent binding molecule is a bivalent molecule with two binding sites in a first chain and no binding sites in the second chain.

[0191] In another embodiment, the multivalent binding molecule is a trivalent molecule with one binding site (e.g., a VH or scFV) in a first chain and a second and third binding site in a second chain. In another embodiment, the multivalent binding molecule is a trivalent molecule with three binding sites in a first chain and no binding sites in a second chain.

[0192] In another embodiment, the multivalent binding molecule is a tetravalent molecule with two binding sites in a first chain and two binding sites in a second chain. In another embodiment, the multivalent binding molecule is a tetravalent molecule with three binding sites in a first chain and one binding site in a second chain. In another embodiment, the multivalent binding molecule is a tetravalent molecule with four binding sites in a first chain and no binding sites in a second chain.

[0193] In exemplary embodiments, the heteromeric antibodies of the present disclosure are bispecific antibodies. Bispecific antibodies can be monoclonal, e.g., human or humanized, antibodies that have binding specificities for at least two different antigens.

[0194] Methods for making bispecific antibodies are well-known. Traditionally, the recombinant production of bispecific antibodies was based on the co-expression of two immunoglobulin heavy chain/light chain pairs, where the two heavy chains have different specificities (Milstein et al., *Nature* 305:537 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, the hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. More modern techniques for generating bispecific antibodies employ heterodimerization domains that favor desired pairing of heavy chain from the antibody with a first specificity to the heavy chain of an antibody with a second specificity.

[0195] Antibody variable domains with the desired binding specificities can be fused to immunoglobulin constant domain sequences. The fusion typically is with an immunoglobulin heavy chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It may have the first heavy chain constant region (CH1) containing the site necessary for light chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transformed into a suitable host organism. For further details of generating bispecific antibodies see, for example Suresh et al., *Meth. Enzymol.* 121:210 (1986).

[0196] As used herein, the term “Fc” refers to a polypeptide comprising a CH2 domain and a CH3 domain, wherein the C-terminus of the CH2 domain is linked (directly or indirectly) to the N-terminus of the CH3 domain. The term “Fc polypeptide” includes an antibody heavy chain linked to an antibody light chain by disulfide bonds (e.g., to form a half-antibody).

[0197] In certain embodiments, an Fc chain begins in the hinge region just upstream of the papain cleavage site and ends at the C-terminus of the antibody. Accordingly, a complete Fc chain comprises at least a hinge domain, a CH2

domain, and a CH3 domain. In certain embodiments, an Fc chain comprises at least one of: a hinge (e.g., upper, middle, and/or lower hinge region) domain, a CH2 domain, a CH3 domain, a CH4 domain, or a variant, portion, or fragment thereof. In certain embodiments, an Fc domain comprises a complete Fc chain (i.e., a hinge domain, a CH2 domain, and a CH3 domain). In certain embodiments, an Fc chain comprises a hinge domain (or portion thereof) fused to a CH3 domain (or portion thereof). In certain embodiments, an Fc chain comprises a CH2 domain (or portion thereof) fused to a CH3 domain (or portion thereof). In certain embodiments, an Fc chain consists of a CH3 domain or portion thereof. In certain embodiments, an Fc chain consists of a hinge domain (or portion thereof) and a CH3 domain (or portion thereof). In certain embodiments, an Fc chain consists of a CH2 domain (or portion thereof) and a CH3 domain. In certain embodiments, an Fc chain consists of a hinge domain (or portion thereof) and a CH2 domain (or portion thereof). In certain embodiments, an Fc chain lacks at least a portion of a CH2 domain (e.g., all or part of a CH2 domain). An Fc chain herein generally refers to a polypeptide comprising all or part of the Fc chain of an immunoglobulin heavy-chain. This includes, but is not limited to, polypeptides comprising the entire CH1, hinge, CH2, and/or CH3 domains as well as fragments of such peptides comprising only, e.g., the hinge, CH2, and CH3 domain. The Fc chain may be derived from an immunoglobulin of any species and/or any subtype, including, but not limited to, a human IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM antibody. The Fc domain encompasses native Fc and Fc variant molecules. As with Fc variants and native Fc's, the term Fc chain includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means. In some embodiment, the Fc chain comprises the carboxy-terminal portions of both heavy chains held together by disulfides. In certain embodiments, an Fc chain consists of a CH2 domain and a CH3 domain.

[0198] In some embodiments, an Fc polypeptide comprises part or all of a wild-type hinge sequence (generally at its N-terminal). In some embodiments, an Fc polypeptide does not comprise a functional or wild-type hinge sequence.

[0199] As used herein, the term “CH1 domain” refers to the first constant domain of an antibody heavy chain (e.g., amino acid positions 118-215 of human IgG1, according to the EU index). The term includes naturally occurring CH1 domains and engineered variants of naturally occurring CH1 domains (e.g., CH1 domains comprising one or more amino acid insertions, deletions, substitutions, or modifications relative to a naturally occurring CH1 domain).

[0200] As used herein, the term “CH2 domain” refers to the second constant domain of an antibody heavy chain (e.g., amino acid positions 231-340 of human IgG1, according to the EU index). The term includes naturally occurring CH2 domains and engineered variants of naturally occurring CH2 domains (e.g., CH2 domains comprising one or more amino acid insertions, deletions, substitutions, or modifications relative to a naturally occurring CH2 domain).

[0201] As used herein, the term “CH3 domain” refers to the third constant domain of an antibody heavy chain (e.g., amino acid positions 341-447 of human IgG1, according to the EU index). The term includes naturally occurring CH3 domains and engineered variants of naturally occurring CH3 domains (e.g., CH3 domains comprising one or more amino

acid insertions, deletions, substitutions, or modifications relative to a naturally occurring CH3 domain).

[0202] As used herein, the term “hinge region” refers to the portion of an antibody heavy chain comprising the cysteine residues (e.g., the cysteine residues at amino acid positions 226 and 229 of human IgG1, according to the EU index) that mediate disulfide bonding between two heavy chains in an intact antibody. The term includes naturally occurring hinge regions and engineered variants of naturally occurring hinge regions (e.g., hinge regions comprising one or more amino acid insertions, deletions, substitutions, or modifications relative to a naturally occurring hinge regions). An exemplary full-length IgG1 hinge region comprises amino acid positions 216-230 of human IgG1, according to the EU index. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable regions and/or constant domains in a single polypeptide molecule. In some embodiments, the hinge region is an immunoglobulin-like hinge region. In some embodiments, the immunoglobulin-like hinge region can be from or derived from any IgG1, IgG2, IgG3, or IgG4 subtype, or from IgA, IgE, IgD or IgM, including chimeric forms thereof, e.g., a chimeric IgG1/2 hinge region.

[0203] In some embodiments, the hinge region can be from the human IgG1 subtype extending from amino acid 216 to amino acid 230 according to the numbering system of the EU index, or from amino acid 226 to amino acid 243 according to the numbering system of Kabat. Those skilled in the art may differ in their understanding of the exact amino acids corresponding to the various domains of the IgG molecule. Thus, the N-terminal or C-terminal of the domains outlined above may extend or be shortened by 1, 2, 3, 4, 5, 6, 7, 8, 9, or even 10 amino acids.

[0204] The term “upper hinge” as used herein typically refers to the last residue of the CH1 domain up to but not including the first inter-heavy chain cysteine. The upper hinge can sometimes be defined as the N-terminal sequence from position 216 to position 225 according to the Kabat EU numbering system of an IgG1 antibody (Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institute of Health, Bethesda, Md., 1991). The term “middle hinge” refers to the region extending from the first inter-heavy chain cysteine to a proline residue adjacent to the carboxyl-end of the last middle hinge cysteine. The middle hinge can be the N-terminal sequence from position 226 to position 230 according to the Kabat EU numbering system. The term “lower hinge” refers to a highly conserved 7-8 amino acids. The lower hinge can be defined as the sequence from position 231 to 238 according the Kabat EU numbering system of an IgG1 antibody. In some embodiments, the antibody according to the present invention effectively comprises an upper, a middle, and a lower hinge.

[0205] As used herein, the term “a modified hinge region” refers to a hinge region in which alterations are made in one or more of the characteristics of the hinge, including, but not limited to, flexibility, length, conformation, charge and hydrophobicity relative to a wild-type hinge. The modified hinge regions disclosed herein may be generated by methods well known in the art, such as, for example introducing a modification into a wild-type hinge. In some embodiments, the hinge region may be modified by one or more amino acids. Modifications which may be utilized to generate a

modified hinge region include, but are not limited to, amino acid insertions, deletions, substitutions, and rearrangements. Said modifications of the hinge and the modified hinge regions disclosed are referred to herein jointly as “hinge modifications of the invention”, “modified hinge(s) of the invention” or simply “hinge modifications” or “modified hinge(s).” The modified hinge regions disclosed herein may be incorporated into a molecule of choice including, but not limited to, antibodies and fragments thereof. In some embodiments, the hinge region may be truncated and contain only a portion of the full hinge region.

[0206] As demonstrated herein, molecules comprising a modified hinge may exhibit altered (e.g., enhanced) agonistic activity when compared to a molecule having the same amino acid sequence except for the modified hinge, such as, for example, a molecule having the same amino acid sequence except comprising a wild type hinge. In some embodiments, the antibody comprises a modified hinge region wherein the upper hinge region is up to 7 amino acids in length. In some embodiments, the upper hinge region is absent. In some embodiments, the modified hinge is a modified IgG1 linker. In some embodiments, the modified IgG1 hinge is derived from the sequence PLAPDKTHT (SEQ ID NO: 1). In some embodiments, the modified IgG1 hinge comprises the sequence PLAP (SEQ ID NO: 2). In some embodiments, the modified IgG1 hinge comprises the sequence DKTHT (SEQ ID NO: 5). In some embodiments, the modified hinge is a modified IgG4 hinge. In some embodiments, the modified IgG1 hinge comprises the sequence EKSYGPP (SEQ ID NO: 4). In some embodiments, the modified hinge is a Gly/Ser hinge. In some embodiments, the Gly/Ser hinge comprises the sequence GGGGSGGGGSGGGGSGGGGS (SEQ ID NO: 3). In some embodiments, the C-terminal residues of the variable domain adjacent to the upper hinge are truncated. In some embodiments, at least one residue of the variable domain adjacent to the upper hinge is truncated. In some embodiments, at least two residues of the variable domain adjacent to the upper hinge is truncated.

[0207] The modified hinge region of the disclosure may be used as a linker to attach one or more antigen binding domains of the disclosure. In certain embodiments, a first variable heavy chain domain (VH1) linked to a second variable heavy chain domain (VH2) via at least one modified hinge region. In certain embodiments, a first variable light chain domain (VL1) linked to a second variable light chain domain (VL2) via at least one modified hinge region. The VH1 and VL1 associate to form a first antigen binding domain and the VH2 and VL2 associate to form a second antigen binding domain. In other embodiments, a first scFv is linked to a second scFv via at least one modified hinge region.

[0208] In certain embodiments, the multispecific binding proteins of the disclosure (i.e., multispecific binding proteins having at least a first antigen binding protein and a second antigen binding protein) have greater agonist activity compared to a multispecific binding protein that lacks at least one modified hinge region. For example, but in no way limiting, a multispecific binding protein having a VH1 linked to a VH2 via at least one modified hinge region and/or a VL1 linked to a VL2 via at least one modified hinge region may possess greater agonist activity of a target receptor pair (e.g., ALK1 and any one of BMPRII, ActRIIA, and

ActRIIB), than the same multispecific binding protein that does not have the at least one modified hinge region.

[0209] As used herein, the term "EU index" refers to the EU numbering convention for the constant regions of an antibody, as described in Edelman, G M. et al., Proc. Natl. Acad. USA, 63, 78-85 (1969) and Kabat et al., Sequences of Proteins of Immunological Interest, U.S. Dept. Health and Human Services, 5th edition, 1991, each of which is herein incorporated by reference in its entirety. All numbering of amino acid positions of the Fc polypeptides, or fragments thereof, used herein is according to the EU index. As used herein, the term "linker" refers to 0-100 contiguous amino acid residues. The linkers are, present or absent, and same or different. Linkers comprised in a protein or a polypeptide may all have the same amino acid sequence or may have different amino acid sequences.

[0210] In some embodiments, the term "linker" refers to 1-100 contiguous amino acid residues. Typically, a linker provides flexibility and spatial separation between two amino acids or between two polypeptide domains. A linker may be inserted between VH, VL, CH and/or CL domains to provide sufficient flexibility and mobility for the domains of the light and heavy chains depending on the format of the molecule. A linker is typically inserted at the transition between variable domains between variable and knockout domain, or between variable and constant domains, respectively, at the amino sequence level. The transition between domains can be identified because the approximate sizes of the immunoglobulin domains are well understood. The precise location of a domain transition can be determined by locating peptide stretches that do not form secondary structural elements such as beta-sheets or alpha-helices as demonstrated by experimental data or as can be determined by techniques of modeling or secondary structure prediction.

[0211] As used herein, the term "specifically binds," "specifically binding," "binding specificity" or "specifically recognized" refers that an antigen binding protein or antigen-binding fragment thereof that exhibits appreciable affinity for an antigen (e.g., a BMPR Type I receptor or BMPR Type II receptor antigen) and does not exhibit significant cross reactivity to a target that is not a BMPR Type I receptor or a BMPR Type II receptor protein. As used herein, the term "affinity" refers to the strength of the interaction between an antigen binding protein or antigen-binding fragment thereof antigen binding site and the epitope to which it binds. In certain exemplary embodiments, affinity is measured by surface plasmon resonance (SPR), e.g., in a Biacore instrument. As readily understood by those skilled in the art, an antigen binding protein affinity may be reported as a dissociation constant (KD) in molarity (M). The antigen binding protein or antigen-binding fragment thereof of the disclosure have KD values in the range of about 10^{-5} M to about 10^{-12} M (i.e., low micromolar to picomolar range), about 10^{-7} M to 10^{-11} M, about 10^{-8} M to about 10^{-10} M, about 10^{-9} M. In certain embodiments, the antigen binding protein or antigen-binding fragment thereof has a binding affinity of about 10^{-5} M, 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M, 10^{-10} M, 10^{-11} M, or 10^{-12} M. In certain embodiments, the antigen binding protein or antigen-binding fragment thereof has a binding affinity of about 10^{-7} M to about 10^{-9} M (nanomolar range).

[0212] Specific binding can be determined according to any art-recognized means for determining such binding. In some embodiments, specific binding is determined by com-

petitive binding assays (e.g., ELISA) or Biacore assays. In certain embodiments, the assay is conducted at about 20° C., 25° C., 30° C., or 37° C.

[0213] As used herein, "administer" or "administration" refers to the act of injecting or otherwise physically delivering a substance as it exists outside the body (e.g., an isolated binding polypeptide provided herein) into a patient, such as by, but not limited to, pulmonary (e.g., inhalation), mucosal (e.g., intranasal), intradermal, intravenous, intramuscular delivery and/or any other method of physical delivery described herein or known in the art. When a disease, or a symptom thereof, is being managed or treated, administration of the substance typically occurs after the onset of the disease or symptoms thereof. When a disease, or symptom thereof, is being prevented, administration of the substance typically occurs before the onset of the disease or symptoms thereof and may be continued chronically to defer or reduce the appearance or magnitude of disease-associated symptoms.

[0214] As used herein, the term "composition" is intended to encompass a product containing the specified ingredients (e.g., an isolated binding polypeptide provided herein) in, optionally, the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in, optionally, the specified amounts. "Effective amount" means the amount of active pharmaceutical agent (e.g., an isolated binding polypeptide of the present disclosure) sufficient to effectuate a desired physiological outcome in an individual in need of the agent. The effective amount may vary among individuals depending on the health and physical condition of the individual to be treated, the taxonomic group of the individuals to be treated, the formulation of the composition, assessment of the individual's medical condition, and other relevant factors.

[0215] As used herein, the terms "subject" and "patient" are used interchangeably. As used herein, a subject can be a mammal, such as a non-primate (e.g., cows, pigs, horses, cats, dogs, rats, mice, etc.) or a primate (e.g., monkey and human). In certain embodiments, the term "subject," as used herein, refers to a vertebrate, such as a mammal. Mammals include, without limitation, humans, non-human primates, wild animals, feral animals, farm animals, sport animals, and pets.

[0216] As used herein, the term "therapy" refers to any protocol, method and/or agent that can be used in the prevention, management, treatment and/or amelioration of a disease or a symptom related thereto. In some embodiments, the term "therapy" refers to any protocol, method and/or agent that can be used in the modulation of an immune response to an infection in a subject or a symptom related thereto. In some embodiments, the terms "therapies" and "therapy" refer to a biological therapy, supportive therapy, and/or other therapies useful in the prevention, management, treatment and/or amelioration of a disease or a symptom related thereto, known to one of skill in the art such as medical personnel. In other embodiments, the terms "therapies" and "therapy" refer to a biological therapy, supportive therapy, and/or other therapies useful in the modulation of an immune response to an infection in a subject or a symptom related thereto known to one of skill in the art such as medical personnel.

[0217] As used herein, the terms "treat," "treatment" and "treating" refer to the reduction or amelioration of the progression, severity, and/or duration of a disease or a

symptom related thereto, resulting from the administration of one or more therapies (including, but not limited to, the administration of one or more prophylactic or therapeutic agents, such as an isolated binding polypeptide provided herein). The term “treating,” as used herein, can also refer to altering the disease course of the subject being treated. Therapeutic effects of treatment include, without limitation, preventing occurrence or recurrence of disease, alleviation of symptom(s), diminishment of direct or indirect pathological consequences of the disease, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis.

[0218] The term “about” or “approximately” means within about 20%, such as within about 10%, within about 5%, or within about 1% or less of a given value or range.

BMPR Type I Receptors and BMPR Type II Receptors

[0219] Bone morphogenetic protein (BMP) Type I and Type II receptors are serine-threonine kinase transmembrane signal transduction proteins that regulate a vast array of ligand-dependent cell-fate decisions with temporal and spatial fidelity during development and postnatal life. The activation of the receptors, induced by first binding to their ligand (BMPs) and then heterodimerizing, triggers intracellular signaling that is initiated by phosphorylation of receptor-regulated SMAD1, 5, and 8 (R-SMADs). These activated R-SMADs form heteromeric complexes with SMAD4, which engage in specific transcriptional responses.

[0220] As used herein, the term “ALK1” refers to the activin A receptor like type 1, a BMP Type I receptor. Alternative terms for ALK1 include ACVRLK1, Serine/threonine-protein kinase receptor R3, TGF-B superfamily receptor type 1, and HHT2. The ALK1 protein is encoded by the gene ACVRL1. The ALK1 protein comprises human, murine, and further mammalian homologues. Sequence(s) for human ALK1 are accessible via UniProt Identifier P37023 (ACVL1 HUMAN), for instance human isoform P37023-1. Sequence(s) for murine ALK1 are accessible via UniProt Identifier Q61288 (ACVL1 MOUSE). The term “ALK1” may encompass different isoforms and variants that may exist for different species and are all comprised by the term ALK1. In addition, the term “ALK1” may include synthetic variants of the ALK1 protein produced, e.g. by introducing at least one mutation. The protein ALK1 may furthermore be subject to various modifications, e.g. synthetic or naturally occurring modifications. Naturally occurring mutations in the ALK1 gene are associated with hereditary hemorrhagic telangiectasia (HHT) type 2, wherein patients suffer pulmonary hypertension, daily epistaxis, strokes, and emboli.

[0221] The term “BMPRII” refers to the protein Bone morphogenetic protein receptor type 2. Alternative names comprise BMP type-2 receptor, Bone morphogenetic protein receptor type II, BMP type II receptor, BMR2, PPH1, BMPR3, BRK-3, POVD1, T-ALK, BMPRII and BMPR-II. The BMPRII protein is encoded by the gene BMPR2. The BMPRII protein comprises human, murine, and further mammalian homologues. Sequence(s) for human BMPRII are accessible via UniProt Identifier Q13873 (BMPRII HUMAN), for instance human isoform 1 (identifier: QI 3873-1), and human isoform 2 (identifier: Q13873-2). Sequence(s) for murine BMPRII are accessible via UniProt Identifier 035607 (BMPRII MOUSE). Different isoforms and variants may exist for the different species and are all

comprised by the term BMPRII. In addition, synthetic variants of the BMPRII protein may be generated, e.g. by introducing at least one mutation, and are comprised by the term BMPRII. The protein BMPRII may furthermore be subject to various modifications, e.g. synthetic or naturally occurring modifications.

[0222] As used herein, the term “ActRIIA” refers to a family of activin receptor type IIA (ActRIIA) proteins from any species and variants derived from such ActRIIA proteins by mutagenesis or other modification. Reference to ActRIIA herein is understood to be a reference to any one of the currently identified forms. Members of the ActRIIA family are generally transmembrane proteins, composed of a ligand-binding extracellular domain comprising a cysteine-rich region, a transmembrane domain, and a cytoplasmic domain with predicted serine/threonine kinase activity. The term “ActRIIA” includes polypeptides comprising any naturally occurring polypeptide of an ActRIIA family member as well as any variants thereof (including mutants, fragments, fusions, and peptidomimetic forms) that retain a useful activity.

[0223] As used herein, the term “ActRIIB” refers to a family of activin receptor type IIB (ActRIIB) proteins from any species and variants derived from such ActRIIB proteins by mutagenesis or other modification. Reference to ActRIIB herein is understood to be a reference to any one of the currently identified forms. Members of the ActRIIB family are generally transmembrane proteins, composed of a ligand-binding extracellular domain comprising a cysteine-rich region, a transmembrane domain, and a cytoplasmic domain with predicted serine/threonine kinase activity. The term “ActRIIA” includes polypeptides comprising any naturally occurring polypeptide of an ActRIIB family member as well as any variants thereof (including mutants, fragments, fusions, and peptidomimetic forms) that retain a useful activity. Examples of such variant ActRIIB polypeptides are provided throughout the present disclosure as well as in International Patent Application Publication Nos. WO 2006/012627 and WO 2008/097541, which are incorporated herein by reference in its entirety.

ALK1/BMPRII, ActRIIA or ActRIIB Bispecific Antibodies

[0224] Bispecific antibodies as provided herein promote the heterodimerization of ALK1 and a BMP Type II receptor, such as BMPRII, ActRIIA, and ActRIIB. Bispecific antibodies according to the current invention can be produced with high yields. The bispecific antibodies or their binding domains can be easily matured, or screening approaches can be used to detect binders with optimized binding capabilities. For bispecific antibodies, each binding site can be optimized individually. Finally, even in the absence of downstream signaling, e.g. due to a genetic defect, an antibody approach could still be able to rescue the ALK1/BMPRII, ALK1/ActRIIA, or the ALK1/ActRIIB signaling cascade.

[0225] The antibodies disclosed herein specifically bind to ALK1 and BMPRII, ActRIIA, or ActRIIB; i.e., they bind to their targets with an affinity that is higher (e.g., at least two-fold higher) than their binding affinity for an irrelevant antigen (e.g., bovine serum albumin (BSA), casein).

[0226] As used herein, the term “inducing proximity” between ALK1 and BMPRII, ActRIIA, or ActRIIB refers to bringing ALK1 and any one of BMPRII, ActRIIA, or ActRIIB together such that the ALK1/BMPRII, ALK1/

ActRIIA, or the ALK1/ActRIIB signaling cascade is stimulated. In certain embodiments, the proximity induced by the multispecific binding proteins of the disclosure is the same or similar to the proximity induced when BMP9 brings ALK1 and BMPRII together. Stimulation of the ALK1/BMPRII, ALK1/ActRIIA, or the ALK1/ActRIIB signaling cascade may be detected through any of the downstream results of said signaling cascade, including, but not limited to, detection of phosphorylated SMAD proteins (e.g. pSMAD1, pSMAD5, and/or pSMAD8), and detection of gene expression associated with said signaling cascade. Genes that have been previously shown to be upregulated from the ALK1/BMPRII, ALK1/ActRIIA, or the ALK1/ActRIIB signaling cascade include, but are not limited to, ID1, ID3, and TMEM100.

[0227] The bispecific antibodies of the disclosure are exemplified by numerous ALK1/BMPRII bispecific antibodies in the working examples, however the technical effect of the exemplified bispecific antibodies (i.e., inducing agonism) is expected to extend to ALK1/ActRIIA and ALK1/ActRIIB bispecific antibodies as well. One of skill in the art will appreciate that the technical effect of inducing proximity between ALK1 and BMPRII with a ALK1/BMPRII bispecific antibody, and the subsequent activation of the receptor complex, will extend to ALK1/ActRIIA and ALK1/ActRIIB bispecific antibodies that also induce proximity between ALK1 and ActRIIA and ALK1 and ActRIIB.

[0228] The bispecific antibodies of the disclosure may employ at least one modified hinge region. The modified hinge region serves as a linker to connect different domains of the bispecific antibody. In certain embodiments, the modified hinge region links a first variable heavy chain domain (VH1) to a second variable heavy chain domain (VH2), and/or the modified hinge region links a first variable light chain domain (VL1) linked to a second variable light chain domain (VL2). In another embodiment, the modified hinge region links a first scFv to a second scFv. In certain embodiments, the modified hinge region comprises; i) an upper hinge region of up to 7 amino acids in length or is absent; and ii) a lower hinge region. In certain embodiments, the modified hinge region comprises or consists of an amino acid sequence of PLAP (SEQ ID NO:2) or PAPNLLGGP (SEQ ID NO:157).

[0229] The bispecific antibodies of the disclosure (e.g., multispecific binding proteins) have greater agonist activity compared to a bispecific antibody that lacks at least one modified hinge region. Agonist activity may be measured using a specific receptor potency assay (e.g., Pathhunter U2OS dimerization assay (DiscoverX) Potency assays (e.g., Pathhunter) involve a cell line (e.g., U2OS) that expresses the target receptors of interest. The binding of the bispecific antibodies to the receptors triggers a signaling cascade leading to the expression of a reporter gene which can be quantified.

[0230] The bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 35% of the activity of BMP9. In certain embodiments, bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 40% of the activity of BMP9. In certain embodiments, bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 40% of the activity of BMP9. In certain embodiments, bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 45% of the activity of

BMP9. In certain embodiments, bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 50% of the activity of BMP9. In certain embodiments, bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 55% of the activity of BMP9. In certain embodiments, bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 60% of the activity of BMP9. In certain embodiments, bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 65% of the activity of BMP9. In certain embodiments, bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 70% of the activity of BMP9. In certain embodiments, bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 75% of the activity of BMP9. In certain embodiments, bispecific antibodies of the disclosure (e.g., multispecific binding proteins) induce at least about 80% of the activity of BMP9.

[0231] In certain embodiments, the activity of BMP9 is determined by measuring phosphorylated SMAD1 (pSMAD1) levels, measuring phosphorylated SMAD5 (pSMAD5) levels, and/or measuring phosphorylated SMAD8 (pSMAD8) levels in cells incubated with the multispecific binding protein and/or in cells incubated with BMP9. Phosphorylated SMAD levels (i.e., pSMAD1, pSMAD5, and pSMAD8) may be detected using an enzyme-linked immunosorbent assay (ELISA). Briefly, a first population of cells (e.g., HUVEC cells) is incubated with a bispecific antibody of the disclosure and a second population of cells (e.g., HUVEC cells) is incubated with BMP9. Following an incubation time, cells are lysed and the cell lysate is analyzed using an antibody against the phosphorylated SMAD protein (i.e., pSMAD1, pSMAD5, or pSMAD8). Antibody binding is detected (such as through a fluorescent signal) and quantified. The level of the phosphorylated SMAD protein in the first population of cells is then compared to the level of the phosphorylated SMAD protein in the second population of cells to determine the % activity of the bispecific antibody relative to BMP9.

[0232] The bispecific antibodies of the disclosure (e.g., multispecific binding proteins) are capable of stimulating expression of a gene selected from ID1, ID3, and TMEM100 in a cell. The expression of ID1, ID3, and/or TMEM100 in the cell is at least 50% relative to ID1, ID3, and/or TMEM100 expression from a cell incubated with BMP9. In certain embodiments, the expression of ID1, ID3, and/or TMEM100 in the cell is at least equal to ID1, ID3, and/or TMEM100 expression from a cell incubated with BMP9. In certain embodiments, the expression of ID1, ID3, and/or TMEM100 in the cell is at least 1.5-fold greater than ID1, ID3, and/or TMEM100 expression from a cell incubated with BMP9. In certain embodiments, the expression of ID1, ID3, and/or TMEM100 in the cell is at least 2-fold greater than ID1, ID3, and/or TMEM100 expression from a cell incubated with BMP9. In certain embodiments, the expression of ID1, ID3, and/or TMEM100 in the cell is at least 3-fold greater than ID1, ID3, and/or TMEM100 expression from a cell incubated with BMP9. In certain embodiments, the expression of ID1, ID3, and/or TMEM100 in the cell is at least 4-fold greater than ID1, ID3, and/or TMEM100 expression from a cell incubated with BMP9. In certain embodiments, the expression of ID1, ID3, and/or TMEM100 in the cell is at least 5-fold greater than ID1, ID3,

and/or TMEM100 expression from a cell incubated with BMP9. In certain embodiments, the expression of ID1, ID3, and/or TMEM100 in the cell is at least 6-fold greater than ID1, ID3, and/or TMEM100 expression from a cell incubated with BMP9.

[0233] Detection of ID1, ID3, and TMEM100 expression may be achieved using standard molecular biology techniques and PCR. Briefly, a first population of cells (e.g., HUVEC cells or HMEC-1 cells) is incubated with a bispecific antibody of the disclosure and a second population of cells (e.g., HUVEC cells or HMEC-1 cells) is incubated with BMP9. Following an incubation time, mRNA from the cells is isolated, cDNA is generated, and PCR is performed to detect the levels of ID1, ID3, and/or TMEM100 relative to a control gene, such as GAPDH. The level of ID1, ID3, and/or TMEM100 in the first population of cells is then compared to the level of ID1, ID3, and/or TMEM100 in the second population of cells.

Thermostability

[0234] Certain bispecific antibodies of the disclosure (e.g., multispecific binding proteins) possess improved thermostability relative to other antibodies of the disclosure. For example, bispecific antibodies designated DGL947 (comprising a first polypeptide chain of SEQ ID NO: 139 and a second polypeptide chain of SEQ ID NO: 146) and DGL949 (comprising a first polypeptide chain of SEQ ID NO: 141 and a second polypeptide chain of SEQ ID NO: 146) possess improved thermostability relative to bispecific antibodies designated DGL945 and DGL1146. As used herein,

[0235] “improved thermostability” refers to a higher melting temperature. The melting temperature may be the melting temperature onset of unfolding (Tonset) and/or the melting temperature thermal transition midpoint (Tm).

[0236] In certain embodiments, the melting temperature onset of unfolding (Tonset) of the bispecific antibodies of the disclosure is at least about 50° C., at least about 51° C., at least about 52° C., at least about 53° C., at least about 54° C., at least about 55° C., at least about 56° C., at least about 57° C., at least about 58° C., at least about 59° C., or at least about 60° C.

[0237] In certain embodiments, the melting temperature thermal transition midpoint (Tm) of the bispecific antibodies of the disclosure is at least about 63° C., at least about 64° C., at least about 65° C., at least about 66° C., at least about 67° C., at least about 68° C., at least about 69° C., at least about 70° C., at least about 71° C., or at least about 72° C.

[0238] The Tonset and Tm of the bispecific antibodies of the disclosure is determined by differential scanning calorimetry (DSC).

[0239] In some embodiments according to the first aspect, the bispecific antibodies specifically bind an extracellular domain of ALK1 and/or an extracellular domain of BMPRII, ActRIIA, OR ActRIIB. In some embodiments, the ALK1 is human ALK1 or a fragment thereof, and/or the BMPRII, ActRIIA, or ActRIIB is human BMPRII, ActRIIA, or ActRIIB or a fragment thereof. In some embodiments, the bispecific antibody binds an extracellular domain of human ALK1 or a fragment thereof and/or an extracellular domain of human BMPRII or a fragment thereof.

[0240] In some embodiments, the bispecific antibody binds to ALK1 with a Kd of at most about 10⁻⁴ M to about 10⁻¹³ M (e.g., 10⁻⁴ M, 10^{-4.5} M, 10⁻⁵ M, 10^{-5.5} M, 10⁻⁶ M,

10^{-6.5} M, 10⁻⁷ M, 10^{-7.5} M, 10⁻⁸ M, 10^{-8.5} M, 10⁻⁹ M, 10^{-9.5} M, 10⁻¹⁰ M, 10^{-10.5} M, 10⁻¹¹ M, 10^{-11.5} M, 10⁻¹² M, 10^{-12.5} M, 10⁻¹³ M).

[0241] In some embodiments, the bispecific antibody binds to BMPRII, ActRIIA, or ActRIIB with a Kd of at most about 10⁻⁴ M to about 10⁻¹³ M (e.g., 10⁻⁴ M, 10^{-4.5} M, 10⁻⁵ M, 10^{-5.5} M, 10⁻⁶ M, 10^{-6.5} M, 10⁻⁷ M, 10^{-7.5} M, 10⁻⁸ M, 10^{-8.5} M, 10⁻⁹ M, 10^{-9.5} M, 10⁻¹⁰ M, 10^{-10.5} M, 10⁻¹¹ M, 10^{-11.5} M, 10⁻¹² M, 10^{-12.5} M, 10⁻¹³ M).

[0242] In some embodiments, the bispecific antibody binds to ALK1 and BMPRII or ALK1 and ActRIIA or ALK1 and ActRIIB with a Kd of at most about 10⁻⁴ M to about 10⁻¹³ M (e.g., 10⁻⁴ M, 10^{-4.5} M, 10⁻⁵ M, 10^{-5.5} M, 10⁻⁶ M, 10^{-6.5} M, 10⁻⁷ M, 10^{-7.5} M, 10⁻⁸ M, 10^{-8.5} M, 10⁻⁹ M, 10^{-9.5} M, 10⁻¹⁰ M, 10^{-10.5} M, 10⁻¹¹ M, 10^{-11.5} M, 10⁻¹² M, 10^{-12.5} M, 10⁻¹³ M).

[0243] The Kd of antibody binding to an antigen can be assayed using any method known in the art including, for example, immunoassays such as enzyme-linked immunospecific assay (ELISA), Bimolecular Interaction Analysis (BIA) (e.g., Sjolander & Urbaniczky, Anal. Chem. 63:2338-2345, 1991; Szabo, et al., Curr. Opin. Struct. Biol. 5:699-705, 1995), and fluorescence-activated cell sorting (FACS) for quantification of antibody binding to cells that express an antigen. BIA is a technology for analyzing bispecific interactions in real time, without labeling any of the interactants (e.g., BIACORE™). Changes in the optical phenomenon surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

[0244] In some embodiments, the antibody according to the current invention, in addition to binding domains for ALK1 and BMPRII, ActRIIA, or ActRIIB further comprises a binding domain for a ligand of the ALK1/BMPRII, ALK1/ActRIIA, or ALK1/ActRIIB receptor, or for another molecule involved in ALK1/BMPRII, ALK1/ActRIIA, or ALK1/ActRIIB signaling.

[0245] In some embodiments, the binding moiety which binds specifically to ALK1 is cross reactive with human ALK1 and mouse ALK1.

[0246] In some embodiments, the binding moiety which binds specifically to ActRIIA is cross reactive with ActRIIB.

[0247] Except if there is an obvious incompatibility for a person skilled in the art, each of the embodiments describing the binding capabilities can be combined with each of the embodiments describing the format of the antibody.

Binding Domains

[0248] One component of the multispecific binding protein of the present disclosure is a binding domain or binding specificity which binds a first cell surface target and a second cell surface target. In certain embodiments, the first cell surface target is a first receptor subunit, and the second cell surface target is the receptor subunit.

[0249] Any type of binding moiety that specifically binds to a specific receptor subunit can be employed in the multispecific binding proteins disclosed herein. In certain embodiments, the binding moiety comprises an antibody variable domain. Exemplary binding moieties comprising an antibody variable domain include, without limitation, a VH, a VL, a VHH, a VH/VL pair, an scFv, a diabody, or a Fab. Other suitable binding moiety formats include, without limitation, lipocalins (see e.g., Gebauer M. et al., 2012, Method Enzymol. 503:157-188, which is incorporated by reference herein in its entirety), adnectins (see e.g., Lipovsek

D., 2011, Protein Eng. Des. Sel. 24:3-9, which is incorporated by reference herein in its entirety), avimers (see e.g., Silverman J, et al., 2005, Nat. Biotechnol. 23:1556-1561, which is incorporated by reference herein in its entirety), fynomers (see e.g., Schlatter D, et al., 2012, mAbs 4:497-508, which is incorporated by reference herein in its entirety), kunitz domains (see e.g., Hosse R. J. et al., 2006, Protein Sci. 15:14-27, which is incorporated by reference herein in its entirety), knottins (see e.g., Kintzing J. R. et al., 2016, Curr. Opin. Chem. Biol. 34:143-150, which is incorporated by reference herein in its entirety), affibodies (see e.g., Feldwisch J. et al., 2010 J. Mol. Biol. 398:232-247, which is incorporated by reference herein in its entirety), and DARPins (see e.g., Pluckthun A., 2015, Annu. Rev. Pharmacol. Toxicol. 55:489-511, which is incorporated by reference herein in its entirety).

[0250] In certain embodiments, the binding domain comprises the heavy and/or light chain variable regions of a conventional antibody or antigen binding fragment thereof (e.g., a Fab or scFv), wherein the term “conventional antibody” is used herein to describe heterotetrameric antibodies containing heavy and light immunoglobulin chains arranged according to the “Y” configuration. Such conventional antibodies may derive from any suitable species including but not limited to antibodies of llama, alpaca, camel, mouse, rat, rabbit, goat, hamster, chicken, monkey, or human origin. In certain exemplary embodiments, the conventional antibody comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) wherein the VH and/or VL domains or one or more complementarity determining regions (CDRs) thereof are derived from the same antibodies. In certain embodiments, the conventional antibody antigen binding region may be referred to as a “Fab” (Fragment antigen-binding). The Fab comprises one constant and one variable domain from each of heavy chain and light chain. The variable heavy and light chains contain the CDRs responsible for antigen binding.

[0251] In other embodiments, the specific receptor subunit binding subunit comprises at least a CDR or VHH domain of a VHH antibody or Nanobody®. VHH antibodies, which are camelid-derived heavy chain antibodies, are composed of two heavy chains and are devoid of light chains (Hamers-Casterman, et al. Nature. 1993; 363; 446-8). Each heavy chain of the VHH antibody has a variable domain at the N-terminus, and these variable domains are referred to in the art as “VHH” domains in order to distinguish them from the variable domains of the heavy chains of the conventional antibodies i.e., the VH domains. Similar to conventional antibodies, the VHH domains of the molecule comprise HCDR1, HCDR2 and HCDR3 regions which confer antigen binding specificity and therefore VHH antibodies or fragments such as isolated VHH domains, are suitable as components of the multispecific binding proteins of the present disclosure.

Multispecific Binding Proteins

[0252] In certain embodiments, the first and second binding domains disclosed herein can be paired together or operatively linked to generate a multispecific binding protein which is capable of cross-linking a first and a second subunits of the given receptor (e.g., a BMP Type I receptor and a BMP type II receptor). In some embodiments, the first specific binding domain (e.g., VHH or scFv) is operatively linked (directly or indirectly) to the N and/or C terminus of

a first Fc domain or polypeptide, and the second specific binding domain is operatively linked to the N and/or C terminus of second Fc domain or polypeptide, such that the first Fc domain and the second Fc domain facilitate heterodimerization of the first and second specific binding domains.

[0253] In certain exemplary embodiments, the multispecific binding proteins of the disclosure are agonistic to any given signaling pathway, i.e., they are not antagonistic to the ALK1 pathway. In some embodiments, agonism may be measured using a specific receptor potency assay (e.g., Pathhunter U2OS dimerization assay (DiscoverX) Potency assays (e.g., Pathhunter) involve a cell line (e.g., U2OS) that expresses the target receptors of interest. The binding of the bispecific antibodies to the receptors triggers a signaling cascade leading to the expression of a reporter gene which can be quantified.

[0254] In certain embodiments, the multispecific binding protein comprises a dual variable domain format. “Dual variable domain” (“DVD”) binding proteins of the disclosure comprise two or more antigen binding sites and are tetravalent or multivalent binding proteins. The DVDs of the disclosure are multispecific, i.e., capable of binding ALK1 and one of BMPRII, ActRIIA, and ActRIIB. A DVD binding protein comprising two heavy chain DVD polypeptides and two light chain DVD polypeptides is referred to as a “DVD immunoglobulin” or “DVD-Ig”. Each half of a DVD-Ig comprises a heavy chain DVD polypeptide and a light chain DVD polypeptide, and two or more antigen binding sites. Each binding site comprises a heavy chain variable domain and a light chain variable domain with a total of six CDRs involved in antigen binding per antigen binding site.

[0255] A description of the design, expression, and characterization of DVD-Ig molecules is provided in PCT Publication No. WO 2007/024715; U.S. Pat. No. 7,612,181; and Wu et al., Nature Biotechnol., 25: 1290-1297 (2007). An example of such DVD-Ig molecules comprises a heavy chain that comprises the structural formula VD1-(X1)n-VD2-C-(X2)n, wherein VD1 is a first heavy chain variable domain, VD2 is a second heavy chain variable domain, C is a heavy chain constant domain, X1 is a linker with the proviso that it is not CH1, X2 is an Fc region, and n is 0 or 1; and a light chain that comprises the structural formula VD1-(X1)n-VD2-C-(X2)n, wherein VD1 is a first light chain variable domain, VD2 is a second light chain variable domain, C is a light chain constant domain, X1 is a linker with the proviso that it is not CH1, and X2 does not comprise an Fc region; and n is 0 or 1. Such a DVD-Ig may comprise two such heavy chains and two such light chains, wherein each chain comprises variable domains linked in tandem without an intervening constant region between variable regions, wherein a heavy chain and a light chain associate to form tandem functional antigen binding sites, and a pair of heavy and light chains may associate with another pair of heavy and light chains to form a tetrameric binding protein with four functional antigen binding sites. In another example, a DVD-Ig molecule may comprise heavy and light chains that each comprise three variable domains (VD1, VD2, VD3) linked in tandem without an intervening constant region between variable domains, wherein a pair of heavy and light chains may associate to form three antigen binding sites, and wherein a pair of heavy and light chains

may associate with another pair of heavy and light chains to form a tetrameric binding protein with six antigen binding sites.

[0256] In an embodiment, the disclosure provides a binding protein comprising first and second polypeptide chains, wherein said first polypeptide chain comprises a first VD1-(X1)n-VD2-C-(X2)n, wherein: VD1 is a first heavy chain variable domain; VD2 is a second heavy chain variable domain; C is a heavy chain constant domain; X1 is a linker with the proviso that it is not CH1; X2 is an Fc region; and n is independently 0 or 1; and wherein said second polypeptide chain comprises a second VD1-(X1)n-VD2-C-(X2)n, wherein: VD1 is a first light chain variable domain; VD2 is a second light chain variable domain; C is a light chain constant domain; X1 is a linker with the proviso that it is not CH1; X2 does not comprise an Fc region; and n is independently 0 or 1.

[0257] With respect to constructing DVD-Ig or other binding protein molecules, a “linker” is used to denote a single amino acid or a polypeptide (“linker polypeptide”) comprising two or more amino acid residues joined by peptide bonds and used to link one or more antigen binding portions. Such linker polypeptides are well known in the art (see, e.g., Hollinger et al., Proc. Natl. Acad. Sci. USA, 90: 6444-6448 (1993); Poljak, R. J., Structure, 2: 1121-1123 (1994)). Flexible linkers may be employed, which are generally composed of small, non-polar (e.g. Gly) or polar (e.g. Ser or Thr) amino acids. Exemplary flexible linkers include, but are not limited to, GGGGSG (SEQ ID NO: 188), GGSGGG (SEQ ID NO: 189), GGGGSGGGGS (SEQ ID NO: 190), GGSGGGGGSG (SEQ ID NO: 191), GGSGGGGGSGS (SEQ ID NO: 192), GGSGGGGGSGGGGS (SEQ ID NO: 193), GGGGSGGGGGSGGGG (SEQ ID NO: 194), GGGGSGGGGGSGGGGS (SEQ ID NO: 195), and RADAAGGGGGSGGGGGSGGGGGSGGGGS (SEQ ID NO: 196).

[0258] Alternatively, rigid linkers may be employed to join one or more antigen binding proteins. Said rigid linkers may allow for the maintenance of fixed distances between linked antigen binding proteins, thereby promoting the activity of each individual protein. Rigid linkers may employ one or more proline amino acids to confer the rigidity. Exemplary rigid linkers include, but are not limited to, ASTKGP (SEQ ID NO: 197), ASTKGPSVFLPLAP (SEQ ID NO: 198), TVAAP (SEQ ID NO: 199), RTVAAP (SEQ ID NO: 200), TVAAPSVFIFPP (SEQ ID NO: 201), RTVAAPSVFIFPP (SEQ ID NO: 202), AKTTPKLEEGEFSEAR (SEQ ID NO: 203), AKTTPKLEEGEFSEARV (SEQ ID NO: 204), AKTTPKLGG (SEQ ID NO: 205), SAKTTPKLGG (SEQ ID NO: 206), SAKTTP (SEQ ID NO: 207), RADAAP (SEQ ID NO: 208), RADAAPTVS (SEQ ID NO: 209), RADAAAAGGPGS (SEQ ID NO: 210), SAKTTPKLEEGEFSEAR (SEQ ID NO: 211), ADAAAP (SEQ ID NO: 212), ADAAPTVSIFPP (SEQ ID NO: 213), QPKAAP (SEQ ID NO: 214), QPKAAPSVTLFP (SEQ ID NO: 215), AKTTPP (SEQ ID NO: 216), AKTTPPSVT-PLAP (SEQ ID NO: 217), AKTTAP (SEQ ID NO: 218), AKTTAPSVPYPLAP (SEQ ID NO: 219), GENKVEYAPAL-MALS (SEQ ID NO: 220), GPAKELTPLKEAKVS (SEQ ID NO: 221), and GHEAAAVMQVQYPAS (SEQ ID NO: 222).

[0259] In certain embodiments, the linker comprises a modified hinge region as described herein.

[0260] In certain embodiments, the linker comprises or consists of PLAP (SEQ ID NO:2), PAPNLLGGP (SEQ ID NO:157), PLAPDKTHT (SEQ ID NO:1), EKSYGPP (SEQ ID NO:4), or DKTHT (SEQ ID NO:5).

[0261] In certain embodiments, the multispecific binding protein comprises a first and a second polypeptide chain, wherein:

[0262] said first polypeptide chain comprises VH1-(HX1)n-VH2-C-(HX2)n, wherein:

[0263] VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; HX1 is a linker; HX2 is an Fc region; and n is independently 0 or 1; and

[0264] said second polypeptide chain comprises VL1-(LX1)n-VL2-C-(LX2)n, wherein:

[0265] VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; LX1 is a linker; LX2 does not comprise an Fc region; and n is independently 0 or 1.

[0266] In certain embodiments, VH1 binds specifically to human ALK1 and VH2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.

[0267] In certain embodiments, VL1 binds specifically to human ALK1 and VL2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.

[0268] In certain embodiments, VH1 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and VH2 binds specifically to human ALK1.

[0269] In certain embodiments, VL1 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and VL2 binds specifically to human ALK1.

[0270] In certain embodiments, linker HX1 comprises an amino acid sequence of PLAP (SEQ ID NO:2) or PAPNLLGGP (SEQ ID NO:157).

[0271] In certain embodiments, linker LX1 comprises an amino acid sequence of PLAP (SEQ ID NO:2) or PAPNLLGGP (SEQ ID NO:157).

[0272] In certain embodiments, linker HX1 comprises an amino acid sequence of PLAP (SEQ ID NO:2) and linker LX1 comprises an amino acid sequence of PLAP (SEQ ID NO:2) or PAPNLLGGP (SEQ ID NO:157).

[0273] In certain embodiments, the multispecific binding protein comprises two polypeptide chains of VH1-(HX1)n-VH2-C-(HX2)n and two polypeptide chains of VL1-(LX1)n-VL2-C-(LX2)n.

[0274] In certain embodiments, for (HX1)n, n is 1 and for (HX2)n, n is 1.

[0275] In certain embodiments, for (LX1)n, n is 1 and for (LX2)n, n is 0.

[0276] In certain embodiments, the multispecific binding protein comprises a first and a second polypeptide chain, wherein:

[0277] said first polypeptide chain comprises VH1-(HX1)n-VH2-C-Fc, wherein:

[0278] VH1 is a first heavy chain variable domain; VH2 is a second heavy chain variable domain; C is a heavy chain constant domain; HX1 is a linker; Fc is an Fc region; and n is independently 0 or 1; and

[0279] said second polypeptide chain comprises VL1-(LX1)n-VL2-C, wherein:

[0280] VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; LX1 is a linker; and n is independently 0 or 1.

Non-DVD-Ig Formats

[0281] In another aspect of the disclosure, the multispecific binding protein comprises from N-terminus to C-terminus:

[0282] ai) a first polypeptide chain comprising a first antigen binding domain, a first linker (e.g., a modified hinge region), and a first constant region; and

[0283] bi) a second polypeptide chain comprising a second antigen binding domain, a second linker (e.g., a modified hinge region), and a second constant region;

[0284] aii) a first polypeptide chain comprising a second antigen binding domain, a first antigen binding domain, a first linker (e.g., a modified hinge region), and a first constant region; and

[0285] bii) a second polypeptide chain comprising a second linker (e.g., a modified hinge region) or the absence of a linker, and a second constant region;

[0286] aiii) a first polypeptide chain comprising a first linker (e.g., a modified hinge region) or the absence of a linker, and a first constant region; and

[0287] biii) a second polypeptide chain comprising a second antigen binding domain, a first antigen binding domain, a second linker (e.g., a modified hinge region), and a second constant region; or

[0288] av) a first polypeptide chain comprising a first antigen binding domain, an optional first linker (e.g., a modified hinge region), a second antigen binding domain, an optional second linker (e.g., a modified hinge region), and a first constant region; and

[0289] biv) a second polypeptide chain comprising a third antigen binding domain, an optional third linker (e.g., a modified hinge region), a fourth antigen binding domain, an optional fourth linker (e.g., a modified hinge region), and a second constant region.

[0290] In certain embodiments, the first antigen binding domain comprises an scFv, VHH, Fab, F(ab')2, or a single domain antibody.

[0291] In certain embodiments, the second antigen binding domain comprises an scFv, VHH, Fab, F(ab')2, or a single domain antibody.

[0292] In certain embodiments, the third antigen binding domain comprises an scFv, VHH, Fab, F(ab')2, or a single domain antibody.

[0293] In certain embodiments, the fourth antigen binding domain comprises an scFv, VHH, Fab, F(ab')2, or a single domain antibody.

[0294] In certain embodiments, any one or more of the first antigen binding domain, second antigen binding domain, third antigen binding domain, and fourth antigen binding domain comprise an scFv, VHH, Fab, F(ab')2, or a single domain antibody.

[0295] In certain embodiments, the first antigen binding domain, second antigen binding domain, third antigen binding domain, and fourth antigen binding domain each comprise an scFv.

[0296] The Fc polypeptides employed in the multispecific binding proteins of the disclosure generally comprise a CH2 domain and a CH3 domain, wherein the C-terminus of the CH2 domain is linked (directly or indirectly) to the N-terminus of the CH3 domain. Any naturally occurring or variant CH2 and/or CH3 domain can be used. For example, in certain embodiments, the CH2 and/or CH3 domain is a naturally occurring CH2 or CH3 domain from an IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2 antibody heavy chain, e.g.,

a human IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2 antibody heavy chain. The CH2 and CH3 domains can be from the same or different antibody heavy chains. In certain embodiments, the Fc polypeptide comprises a CH2 and CH3 domain-containing portion from a single antibody heavy chain. In certain embodiments, the CH2 and/or CH3 domain is a variant of a naturally occurring CH2 or CH3 domain, respectively. In certain embodiments, the CH2 and/or CH3 domain is a variant comprising one or more amino acid insertions, deletion, substitutions, or modifications relative to a naturally occurring CH2 or CH3 domain, respectively. In certain embodiments, the CH2 and/or CH3 domain is a chimera of one or more CH2 or CH3 domains, respectively. In certain embodiments, the CH2 domain comprises amino acid positions 231-340 of a naturally occurring hinge region (e.g., human IgG1), according to the EU index. In certain embodiments, the CH3 domain comprises amino acid positions 341-447 of a naturally occurring hinge region (e.g., human IgG1), according to the EU index.

[0297] In certain embodiments, the Fc polypeptides further comprise a hinge region, wherein the C-terminus of hinge region is linked (directly or indirectly) to the N-terminus of the CH2 domain. For example, in certain embodiments, the hinge region is a naturally occurring hinge region from an IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2 antibody heavy chain, e.g., a human IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2 antibody heavy chain. The hinge region can be from the same or different antibody heavy chain than the CH2 and/or CH3 domains. In certain embodiments, the hinge region is a variant comprising one or more amino acid insertions, deletion, substitutions, or modifications relative to a naturally occurring hinge region. In certain embodiments, the hinge region is a chimera of one or more hinge regions. In certain embodiments, the hinge region comprises amino acid positions 226-229 of a naturally occurring hinge region (e.g., human IgG1), according to the EU index. In certain embodiments, the hinge region comprises amino acid positions 216-230 of a naturally occurring hinge region (e.g., human IgG1), according to the EU index. In certain embodiments, the hinge region comprises amino acid positions 216-230 of a naturally occurring hinge region (e.g., human IgG1), according to the EU index. In certain embodiments, the hinge region is a variant IgG4 hinge region comprising a serine (S) at amino acid position 228, according to the EU index.

[0298] In certain embodiments, the Fc polypeptides further comprise a CH1 domain, wherein the C-terminus of CH1 domain is linked (directly or indirectly) to the N-terminus of the hinge region. For example, in certain embodiments, the CH1 domain is a naturally occurring CH1 domain from an IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2 antibody heavy chain, e.g., a human IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2 antibody heavy chain. The CH1 domain can be from the same or different antibody heavy chain than the hinge region, CH2 domain and/or CH3 domain. In certain embodiments, the CH1 domain is a variant comprising one or more amino acid insertions, deletions, substitutions, or modifications relative to a naturally occurring CH1 domain. In certain embodiments, the CH1 domain is a chimera of one or more CH1 domain. In certain embodiments, the CH1 domain comprises amino acid positions 118-215 of a naturally occurring hinge region (e.g., human IgG1), according to the EU index.

[0299] In certain embodiment, the Fc polypeptide lacks a CH1 domain or comprises mutations in a CH1 domain or heavy chain variable domain that prevent association of the heavy chain with an antibody light chain. In certain embodiments, the antibody heavy chain lacks a portion of a hinge region.

Heterodimerization Motifs

[0300] In certain exemplary embodiments, the first and second Fc domains are further engineered to enhance heterodimerization of the first specific and second specific binding domains and minimize the effects of incorrect chain pairing (i.e., pairing of a BMP Type I receptor and a BMP Type II receptor).

[0301] Any art-recognized approach that addresses the problem of incorrect chain pairing can be employed to improve desired multispecific antibody production. For instance, US2010/0254989 A1 describes the construction of bispecific cMet-ErbB1 antibodies, where the VH and VL of the individual antibodies are fused genetically via a GlySer linker. For bispecific antibodies including an Fc domain, mutations may be introduced into the Fc to promote the correct heterodimerization of the Fc portion. Several such approaches are reviewed in Klein et al. (*mAbs* (2012) 4:6, 1-11), the contents of which are incorporated herein by reference in their entirety.

[0302] In certain embodiments, the first specific and second specific binding specificities of the multispecific antibody are heterodimerized through knobs-into-holes (KiH) pairing of Fc domains. This dimerization technique utilizes “protuberances” or “knobs” with “cavities” or “holes” engineered into the interface of CH3 domains. Where a suitably positioned and dimensioned knob or hole exists at the interface of either the first or second CH3 domain, it is only necessary to engineer a corresponding hole or knob, respectively, at the adjacent interface, thus promoting and strengthening Fc domain pairing in the CH3/CH3 domain interface. The IgG Fc domain that is fused to the VHH is provided with a knob, and the IgG Fc domain of the conventional antibody is provided with a hole designed to accommodate the knob, or vice-versa. A “knob” refers to an at least one amino acid side chain, typically a larger side chain, that protrudes from the interface of the CH3 portion of a first Fc domain. The protrusion creates a “knob” which is complementary to and received by a “hole” in the CH3 portion of a second Fc domain. The “hole” is an at least one amino acid side chain, typically a smaller side chain, which recedes from the interface of the CH3 portion of the second Fc domain. This technology is described, for example, in U.S. Pat. Nos. 5,821,333; 5,731,168 and 8,216,805; Ridgway et al. *Protein Engineering* (1996) 9:617-621; and Carter P. J. *Immunol. Methods* (2001) 248: 7-15, which are herein incorporated by reference.

[0303] Exemplary amino acid residues that may act as the knob include arginine (R), phenylalanine (F), tyrosine (Y) or tryptophan (W). An existing amino acid residue in the CH3 domain may be replaced or substituted with a knob amino acid residue. Preferred amino acids to substitute may include any amino acids with a small side chain, such as alanine (A), asparagine (N), aspartic acid (D), glycine (G), serine (S), threonine (T), or valine (V).

[0304] Exemplary amino acid residues that may act as the hole include alanine (A), serine (S), threonine (T), or valine (V). An existing amino acid residue in the CH3 domain may

be replaced or substituted with a hole amino acid residue. Preferred amino acids to substitute may include any amino acids with a large side chain, such as arginine (R), phenylalanine (F), tyrosine (Y) or tryptophan (W).

[0305] The CH3 domain is preferably derived from a human IgG1 antibody. Exemplary amino acid substitutions to the CH3 domain include Y349C, S354C, T366S, T366Y, T366W, F405A, F405W, Y407T, Y407A, Y407V, T394S, or combinations thereof. A preferred exemplary combination is S354C, T366Y or T366W for the knob mutation on a first CH3 domain and Y349C, T366S, L368A, Y407T or Y407V for the hole mutation on a second CH3 domain.

[0306] In certain embodiments, the two Fc domains of the antigen binding construct are heterodimerized through Fab arm exchange (FAE). A human IgG1 possessing a P228S hinge mutation may contain an F405L or K409R CH3 domain mutation. Mixing of the two antibodies with a reducing agent leads to FAE. This technology is described in U.S. Pat. No. 9,212,230 and Labrijn A. F. *PNAS* (2013) 110(13):5145-5150, which are incorporated herein by reference.

[0307] In other embodiments, the two Fc domains of the antigen binding construct are heterodimerized through electrostatic steering effects. This dimerization technique utilizes electrostatic steering to promote and strengthen Fc domain pairing in the CH3/CH3 domain interface. The charge complementarity between two CH3 domains is altered to favor heterodimerization (opposite charge pairing) over homodimerization (same charge pairing). In this method, the electrostatic repulsive forces prevent homodimerization. Certain exemplary amino acid residue substitutions which confer electrostatic steering effects include K409D, K392D, and/or K370D in a first CH3 domain and D399K, E356K, and/or E357K in a second CH3 domain. This technology is described in US Patent Publication No. 2014/0154254 A1 and Gunasekaran K. *JBC* (2010) 285(25): 19637-19646, which are incorporated herein by reference.

[0308] In other embodiments, the charge complementarity is formed by a first Fc domain comprising a N297K and/or a T299K mutation, and a second Fc domain comprising a N297D and/or a T299D mutation.

[0309] In an aspect of the invention, the two Fc domains of the antigen binding construct are heterodimerized through hydrophobic interaction effects. This dimerization technique utilizes hydrophobic interactions instead of electrostatic ones to promote and strengthen Fc domain pairing in the CH3/CH3 domain interface. Exemplary amino acid residue substitution may include K409W, K360E, Q347E, Y349S, and/or S354C in a first CH3 domain and D399V, F405T, Q347R, E357W, and/or Y349C in a second CH3 domain. Preferred pairs of amino acid residue substitutions between a first CH3 domain and a second CH3 domain include K409W:D399V, K409W:F405T, K360E:Q347R, Y349S: E357W, and S354C:Y349C. This technology is described in US Patent Publication No. 2015/0307628 A1.

[0310] In an aspect of the invention, heterodimerization can be mediated through the use of leucine zipper fusions. Leucine zipper domains fused to the C terminus of each CH3 domain of the antibody chains force heterodimerization. This technology is described in Wranik B. *JBC* (2012) 287(52):43331-43339.

[0311] In an aspect of the invention, heterodimerization can be mediated through the use of a Strand Exchange Engineered Domain (SEED) body. CH3 domains derived

from an IgG and IgA format force heterodimerization. This technology is described in Muda M. PEDS (2011) 24(5): 447-454.

[0312] In other embodiments, the heterodimerization motif may comprise non-native, disulfide bonds formed by engineered cysteine residues. In certain embodiments, the first set of disulfide may comprise a Y349C mutation in the first Fc domain and a S354C mutation in the second Fc domain. In other embodiment, an engineered disulfide bond may be introduced by fusion a C-terminal extension peptide with an engineered cysteine residue to the C-terminus of each of the two Fc domains. In certain embodiments, the first Fc domain may comprise the substitution of the carboxyl-terminal as “PGK” with “GEC”, and the second Fc domain may comprise the substitution of the carboxyl terminal amino acids “PGK” with “KSCDKT” (SEQ ID NO:223).

[0313] In yet another approach, the multispecific antibodies may employ the CrossMab principle (as reviewed in Klein et al.), which involves domain swapping between heavy and light chains so as to promote the formation of the correct pairings. Yet another approach involves engineering the interfaces between the paired VH-VL domains or paired CH1-CL domains of the heavy and light chains so as to increase the affinity between the heavy chain and its cognate light chain (Lewis et al. Nature Biotechnology (2014) 32: 191-198).

[0314] An alternative approach to the production of multispecific antibody preparations having the correct antigen specificity has been the development of methods that enrich for antibodies having the correct heavy chain-light chain pairings. For example, Spiess et al. (Nature Biotechnology (2013) 31: 753-758) describe a method for the production of a MET-EGFR bispecific antibody from a co-culture of bacteria expressing two distinct half-antibodies.

[0315] Methods have also been described wherein the constant region of at least one of the heavy chains of a bispecific antibody is mutated so as to alter its binding affinity for an affinity agent, for example Protein A. This allows correctly paired heavy chain heterodimers to be isolated based on a purification technique that exploits the differential binding of the two heavy chains to an affinity agent (see US2010/0331527, WO2013/136186).

[0316] International patent application no. PCT/EP2012/071866 (WO2013/064701) addresses the problem of incorrect chain pairing using a method for multispecific antibody isolation based on the use of anti-idiotypic binding agents, in particular anti-idiotypic antibodies. The anti-idiotype binding agents are employed in a two-step selection method in which a first agent is used to capture antibodies having a VH-VL domain pairing specific for a first antigen and a second agent is subsequently used to capture antibodies also having a second VH-VL domain pairing specific for a second antigen.

[0317] In yet another embodiment, the multispecific antibody employs a first binding specificity having a conventional Fab binding region and a second binding specificity comprising a single domain antibody (VHH) binding region. The heterodimerization method employed forces the binding of the heavy chain region of the Fab and the full, heavy chain only, of the VHH. Because the VHH chain does not associate with light chains, the light chain region of the Fab portion will only associate with its corresponding heavy chain.

[0318] In certain other embodiments, the multispecific binding protein described herein further comprises a com-

mon light chain. The term “common light chain” as used herein refers to a light chain which is capable of pairing with a first heavy chain of an antibody which binds to a first antigen in order to form a binding site specifically binding to said first antigen and which is also capable of pairing with a second heavy chain of an antibody which binds to a second antigen in order to form a binding site specifically binding to said second antigen. A common light chain is a polypeptide comprising in N-terminal to C-terminal direction an antibody light chain variable domain (VL), and an antibody light chain constant domain (CL), which is herein also abbreviated as “VL-CL”. Multispecific binding proteins with a common light chain require heterodimerization of the distinct heavy chains. In certain embodiments, the heterodimerization methods listed above may be used with a common light chain. In certain exemplary embodiments, the heterodimerization motif may comprise non-native, disulfide bonds formed by engineered cysteine residues. Adding disulfide bonds, both between the heavy and light chain of an antibody has been shown to improve stability. Additionally, disulfide bonds have also been used as a solution to improve light-chain pairing within bispecific antibodies (Geddie M. L. et al, mABs (2022) 14(1)).

[0319] Unless otherwise stated, all antibody constant region numbering employed herein corresponds to the EU numbering scheme, as described in Edelman et al. (Proc. Natl. Acad. Sci. 63(1): 78-85. 1969).

[0320] Additional methods of heterodimerization of heavy and/or light chains and the generation and purification of asymmetric antibodies are known in the art. See, for example, Klein C. mAbs (2012) 4(6): 653-663, and U.S. Pat. No. 9,499,634, each of which is incorporated herein by reference.

Effector Function Mutations

[0321] As discussed above, multispecific binding proteins of the disclosure can be provided in various isotypes and with different constant regions. The Fc region of the multispecific binding primarily determines its effector function in terms of Fc binding, antibody-dependent cell-mediated cytotoxicity (ADCC) activity, complement dependent cytotoxicity (CDC) activity, and antibody-dependent cell phagocytosis (ADCP) activity. These “cellular effector functions”, as distinct from effector T cell function, involve the recruitment of cells bearing Fc receptors to the site of the target cells, resulting in killing of the antibody-bound cell.

[0322] An antibody according to the present invention may be one that exhibits reduced effector function. In certain embodiments, the one or more mutations reduces one or more of antibody dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), or complement dependent cytotoxicity (CDC). In certain embodiments, an antibody according to the present invention may lack ADCC, ADCP and/or CDC activity. In either case, an antibody according to the present invention may comprise, or may optionally lack, an Fc region that binds to one or more types of Fc receptor. Use of different antibody formats, and the presence or absence of FcR binding and cellular effector functions, allow the antibody to be tailored for use in particular therapeutic purposes as discussed elsewhere herein.

[0323] In certain embodiments, the first and the second Fc domain comprise one or more mutations that reduces Fc effector function. In certain embodiments, the first Fc

domain and the second Fc domain each comprise a L234A and L235A mutation. These IgG1 mutations are also known as the “LALA” mutations and are described in further detail in Xu et al. (Cell Immunol. 2000; 200:16-26). In certain embodiments the first Fc domain and the second Fc domain each comprise a L234A, L235A, G237A, and/or P329G mutation. The Fc domain amino acid positions referred to herein are based on EU antibody numbering. Alternatively, an antibody may have a constant region which is effector null. An antibody may have a heavy chain constant region that does not bind Fcγ receptors, for example the constant region may comprise a L235E mutation. Another optional mutation for a heavy chain constant region is S228P, which increases stability. A heavy chain constant region may be an IgG4 comprising both the L235E mutation and the S228P mutation. This “IgG4-PE” heavy chain constant region is effector null. A disabled IgG1 heavy chain constant region is also effector null. A disabled IgG1 heavy chain constant region may contain alanine at position 234, 235 and/or 237 (EU index numbering), e.g., it may be an IgG1 sequence comprising the L234A, L235A and/or G237A mutations (“LALAGA”).

[0324] Human IgG1 constant regions containing specific mutations or altered glycosylation on residue Asn297 (e.g., N297Q, N297D, and N297K, EU index numbering) have been shown to reduce binding to Fc receptors.

[0325] In other embodiments, it may be desirable to enhance the binding of the Fc region of a multispecific antibody to human Fc gamma receptor IIIA (FcγRIIA) relative to that of the Fc region of a corresponding naturally occurring antibody. In certain embodiments, a constant region may be engineered for enhanced ADCC and/or CDC and/or ADCP. The potency of Fc-mediated effects may be enhanced by engineering the Fc domain by various established techniques. Such methods increase the affinity for certain Fc-receptors, thus creating potential diverse profiles of activation enhancement. This can be achieved by modification of one or several amino acid residues. Example mutations are one or more of the residues selected from 239, 332 and 330 for human IgG1 constant regions (or the equivalent positions in other IgG isotypes). An antibody may thus comprise a human IgG1 constant region having one or more mutations independently selected from S239D, 1332E and A330L (EU index numbering).

[0326] Increased affinity for Fc receptors can also be achieved by altering the natural glycosylation profile of the Fc domain by, for example, generating under fucosylated or de-fucosylated variants. Non-fucosylated antibodies harbor a tri-mannosyl core structure of complex-type N-glycans of Fc without fucose residue. These glycoengineered antibodies that lack core fucose residue from the Fc N-glycans may exhibit stronger ADCC than fucosylated equivalents due to enhancement of FcγRIIA binding capacity. For example, to increase ADCC, residues in the hinge region can be altered to increase binding to FcγRIIA. Thus, an antibody may comprise a human IgG heavy chain constant region that is a variant of a wild-type human IgG heavy chain constant region. In certain embodiments, the variant human IgG heavy chain constant region binds to human Fcγ receptors selected from the group consisting of FcγRIIB and FcγRIIA with higher affinity than the wild type human IgG heavy chain constant region binds to the human FcγRIIA. The antibody may comprise a human IgG heavy chain constant region that is a variant of a wild type human IgG heavy chain

constant region, wherein the variant human IgG heavy chain constant region binds to human FcγRIIB with higher affinity than the wild type human IgG heavy chain constant region binds to human FcγRIIB. The variant human IgG heavy chain constant region can be a variant human IgG1, a variant human IgG2, or a variant human IgG4 heavy chain constant region. In one embodiment, the variant human IgG heavy chain constant region comprises one or more amino acid mutations selected from G236D, P238D, S239D, S267E, L328F, and L328E (EU index numbering system). In another embodiment, the variant human IgG heavy chain constant region comprises a set of amino acid mutations selected from the group consisting of: S267E and L328F; P238D and L328E; P238D and one or more substitutions selected from the group consisting of E233D, G237D, H268D, P271G, and A330R; P238D, E233D, G237D, H268D, P271G, and A330R; G236D and S267E; S239D and S267E; V262E, S267E, and L328F; and V264E, S267E, and L328F (EU index numbering system).

[0327] The enhancement of CDC may be achieved by amino acid changes that increase affinity for C1q, the first component of the classic complement activation cascade. Another approach is to create a chimeric Fc domain created from human IgG1 and human IgG3 segments that exploit the higher affinity of IgG3 for C1q. Antibodies of the present invention may comprise mutated amino acids at residues 329, 331 and/or 322 to alter the C1q binding and/or reduced or abolished CDC activity. In another embodiment, the antibodies or antibody fragments disclosed herein may contain Fc regions with modifications at residues 231 and 239, whereby the amino acids are replaced to alter the ability of the antibody to fix complement. In one embodiment, the antibody or fragment has a constant region comprising one or more mutations selected from E345K, E430G, R344D and D356R, in particular a double mutation comprising R344D and D356R (EU index numbering system).

[0328] The functional properties of the multispecific binding proteins may be further tuned by combining amino acid substitutions that alter Fc binding affinity with amino acid substitutions that affect binding to FcRn. Binding proteins with amino acid substitutions that affect binding to FcRn (also referred to herein as “FcRn variants”) may in certain situations also increase serum half-life in vivo as compared to an unmodified binding protein. As will be appreciated, any combination of Fc and FcRn variants may be used to tune clearance of the antigen-antibody complex. Suitable FcRn variants that may be combined with any of the Fc variants described herein that include without limitation N434A, N434S, M428L, V308F, V259I, M428L/N434S, V259I/V308F, Y436I/M428L, Y436I/N434S, Y436V/N434S, Y436V/M428L, M252Y, M252Y/S254T/T256E, and V259I/V308F/M428L.

Expression of Antigen-Binding Proteins

[0329] In one aspect, polynucleotides encoding the binding proteins (e.g., antigen-binding proteins and antigen-binding fragments thereof) disclosed herein are provided. Methods of making binding proteins comprising expressing these polynucleotides are also provided.

[0330] Polynucleotides encoding the binding proteins disclosed herein are typically inserted in an expression vector for introduction into host cells that may be used to produce the desired quantity of the binding proteins. Accordingly, in certain aspects, the disclosure provides expression vectors

comprising polynucleotides disclosed herein and host cells comprising these vectors and polynucleotides.

[0331] The term "vector" or "expression vector" is used herein to mean vectors used in accordance with the present disclosure as a vehicle for introducing into and expressing a desired gene in a cell. As known to those skilled in the art, such vectors may readily be selected from the group consisting of plasmids, phages, viruses and retroviruses. In general, vectors compatible with the disclosure will comprise a selection marker, appropriate restriction sites to facilitate cloning of the desired gene and the ability to enter and/or replicate in eukaryotic or prokaryotic cells.

[0332] Numerous expression vector systems may be employed for the purposes of this disclosure. For example, one class of vector utilizes DNA elements which are derived from animal viruses such as bovine papilloma virus, polyoma virus, adenovirus, vaccinia virus, baculovirus, retroviruses (RSV, MMTV or MOMLV), or SV40 virus. Others involve the use of polycistronic systems with internal ribosome binding sites. Additionally, cells which have integrated the DNA into their chromosomes may be selected by introducing one or more markers which allow selection of transfected host cells. The marker may provide for prototrophy to an auxotrophic host, biocide resistance (e.g., antibiotics) or resistance to heavy metals such as copper. The selectable marker gene can either be directly linked to the DNA sequences to be expressed or introduced into the same cell by co-transformation. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include signal sequences, splice signals, as well as transcriptional promoters, enhancers, and termination signals. In some embodiments, the cloned variable region genes are inserted into an expression vector along with the heavy and light chain constant region genes (e.g., human constant region genes) synthesized as discussed above.

[0333] In other embodiments, the binding proteins may be expressed using polycistronic constructs. In such expression systems, multiple gene products of interest such as heavy and light chains of antibodies may be produced from a single polycistronic construct. These systems advantageously use an internal ribosome entry site (IRES) to provide relatively high levels of polypeptides in eukaryotic host cells. Compatible IRES sequences are disclosed in U.S. Pat. No. 6,193,980, which is incorporated by reference herein in its entirety for all purposes. Those skilled in the art will appreciate that such expression systems may be used to effectively produce the full range of polypeptides disclosed in the instant application.

[0334] More generally, once a vector or DNA sequence encoding a binding protein, e.g. an antibody or fragment thereof, has been prepared, the expression vector may be introduced into an appropriate host cell. That is, the host cells may be transformed. Introduction of the plasmid into the host cell can be accomplished by various techniques well known to those of skill in the art. These include, but are not limited to, transfection (including electrophoresis and electroporation), protoplast fusion, calcium phosphate precipitation, cell fusion with enveloped DNA, microinjection, and infection with intact virus. See, Ridgway, A. A. G. "Mammalian Expression Vectors" Chapter 24.2, pp. 470-472 Vectors, Rodriguez and Denhardt, Eds. (Butterworths, Boston, Mass. 1988). Plasmid introduction into the host can be by electroporation. The transformed cells are grown under conditions appropriate to the production of the light chains

and heavy chains, and assayed for heavy and/or light chain protein synthesis. Exemplary assay techniques include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), or fluorescence-activated cell sorter analysis (FACS), immunohistochemistry and the like.

[0335] As used herein, the term "transformation" shall be used in a broad sense to refer to the introduction of DNA into a recipient host cell that changes the genotype.

[0336] Along those same lines, "host cells" refers to cells that have been transformed with vectors constructed using recombinant DNA techniques and encoding at least one heterologous gene. In descriptions of processes for isolation of polypeptides from recombinant hosts, the terms "cell" and "cell culture" are used interchangeably to denote the source of antibody unless it is clearly specified otherwise. In other words, recovery of polypeptide from the "cells" may mean either from spun down whole cells, from supernatant of lysed cells culture, or from the cell culture containing both the medium and the suspended cells.

[0337] In one embodiment, a host cell line used for antibody expression is of mammalian origin. Those skilled in the art can determine particular host cell lines which are best suited for the desired gene product to be expressed therein. Exemplary host cell lines include, but are not limited to, GS-CHO and CHO-K1 (Chinese Hamster Ovary lines), DG44 and DUXB11 (Chinese Hamster Ovary lines, DHFR minus), HELA (human cervical carcinoma), CV-1 (monkey kidney line), COS (a derivative of CV-1 with SV40 T antigen), R1610 (Chinese hamster fibroblast) BALBC/3T3 (mouse fibroblast), HEK (human kidney line), SP2/O (mouse myeloma), BFA-1c1BPT (bovine endothelial cells), RAJI (human lymphocyte), 293 (human kidney). In one embodiment, the cell line provides for altered glycosylation, e.g., afucosylation, of the antibody expressed therefrom (e.g., PER.C6® (Crucell) or FUT8-knock-out CHO cell lines (POTELLIGENT® cells) (Biowa, Princeton, N.J.)). In one embodiment, NS0 cells may be used. CHO cells are particularly useful. Host cell lines are typically available from commercial services, e.g., the American Tissue Culture Collection, or from authors of published literature.

[0338] In vitro production allows scale-up to give large amounts of the desired polypeptides. Techniques for mammalian cell cultivation under tissue culture conditions are known in the art and include homogeneous suspension culture, e.g., in an airlift reactor or in a continuous stirrer reactor, or immobilized or entrapped cell culture, e.g., in hollow fibers, microcapsules, on agarose microbeads or ceramic cartridges. If necessary and/or desired, the solutions of polypeptides can be purified by the customary chromatography methods, for example gel filtration, ion-exchange chromatography, chromatography over DEAE-cellulose and/or (immuno-) affinity chromatography.

[0339] Genes encoding the binding proteins featured in the disclosure can also be expressed in non-mammalian cells such as bacteria or yeast or plant cells. In this regard, it will be appreciated that various unicellular non-mammalian microorganisms such as bacteria can also be transformed, i.e., those capable of being grown in cultures or fermentation. Bacteria, which are susceptible to transformation, include members of the enterobacteriaceae, such as strains of *Escherichia coli* or *Salmonella*; *Bacillaceae*, such as *Bacillus subtilis*; *Pneumococcus*; *Streptococcus*, and *Hemophilus influenzae*. It will further be appreciated that, when expressed in bacteria, the binding proteins can become part

of inclusion bodies. In some embodiments, the binding proteins are then isolated, purified and assembled into functional molecules. In some embodiments, the binding proteins of the disclosure are expressed in a bacterial host cell. In some embodiments, the bacterial host cell is transformed with an expression vector comprising a nucleic acid molecule encoding a binding protein of the disclosure.

[0340] In addition to prokaryotes, eukaryotic microbes may also be used. *Saccharomyces cerevisiae*, or common baker's yeast, is the most commonly used among eukaryotic microbes, although a number of other strains are commonly available. For expression in *Saccharomyces*, the plasmid YRp7, for example (Stinchcomb et al., *Nature*, 282:39 (1979); Kingsman et al., *Gene*, 7:141 (1979); Tschemper et al., *Gene*, 10:157 (1980)), is commonly used. This plasmid already contains the TRP1 gene which provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example ATCC No. 44076 or PEP4-1 (Jones, *Genetics*, 85:12 (1977)). The presence of the trpI lesion as a characteristic of the yeast host cell genome then provides an effective environment for detecting transformation by growth in the absence of tryptophan.

Formulations/Pharmaceutical Compositions

[0341] In certain embodiments, a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of an antigen-binding protein described herein is provided. Some embodiments include pharmaceutical compositions comprising a therapeutically effective amount of any one of the binding proteins as described herein, or a binding protein-drug conjugate, in admixture with a pharmaceutically or physiologically acceptable formulation agent selected for suitability with the mode of administration.

[0342] Acceptable formulation materials are typically non-toxic to recipients at the dosages and concentrations employed.

[0343] In some embodiments, the pharmaceutical composition can contain formulation materials for modifying, maintaining, or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption, or penetration of the composition. Suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine, or lysine), antimicrobials, antioxidants (such as ascorbic acid, sodium sulfite, or sodium hydrogensulfite), buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates, or other organic acids), bulking agents (such as mannitol or glycine), chelating agents (such as ethylenediamine tetraacetic acid (EDTA)), complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin, or hydroxypropyl-beta-cyclodextrin), fillers, monosaccharides, disaccharides, and other carbohydrates (such as glucose, mannose, or dextrins), proteins (such as serum albumin, gelatin, or immunoglobulins), coloring, flavoring and diluting agents, emulsifying agents, hydrophilic polymers (such as polyvinylpyrrolidone), low molecular weight polypeptides, salt-forming counterions (such as sodium), preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid, or hydrogen peroxide), solvents (such as glycerin, propylene glycol, or polyethylene glycol), sugar alcohols (such as mannitol or sorbitol), suspending agents, surfactants or wetting agents

(such as pluronic; PEG; sorbitan esters; polysorbates such as polysorbate 20 or polysorbate 80; triton; tromethamine; lecithin; cholesterol or tyloxapal), stability enhancing agents (such as sucrose or sorbitol), tonicity enhancing agents (such as alkali metal halides, e.g., sodium or potassium chloride, or mannitol sorbitol), delivery vehicles, diluents, excipients and/or pharmaceutical adjuvants (see, e.g., REMINGTON'S PHARMACEUTICAL SCIENCES (18th Ed., A. R. Gennaro, ed., Mack Publishing Company 1990), and subsequent editions of the same, incorporated herein by reference for any purpose).

[0344] In some embodiments the optimal pharmaceutical composition will be determined by a skilled artisan depending upon, for example, the intended route of administration, delivery format, and desired dosage. Such compositions can influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the binding protein.

[0345] In some embodiments the primary vehicle or carrier in a pharmaceutical composition can be either aqueous or non-aqueous in nature. For example, a suitable vehicle or carrier for injection can be water, physiological saline solution, or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. Neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. Other exemplary pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which can further include sorbitol or a suitable substitute. In one embodiment of the disclosure, binding protein compositions can be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents in the form of a lyophilized cake or an aqueous solution. Further, the binding protein can be formulated as a lyophilizate using appropriate excipients such as sucrose.

[0346] In some embodiments, the pharmaceutical compositions of the disclosure can be selected for parenteral delivery or subcutaneous delivery. Alternatively, the compositions can be selected for inhalation or for delivery through the digestive tract, such as orally. The preparation of such pharmaceutically acceptable compositions is within the skill of the art.

[0347] In some embodiments, the formulation components are present in concentrations that are acceptable to the site of administration. For example, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0348] When parenteral administration is contemplated, the therapeutic compositions for use can be in the form of a pyrogen-free, parenterally acceptable, aqueous solution comprising the desired binding protein in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which a binding protein is formulated as a sterile, isotonic solution, properly preserved. Yet another preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads, or liposomes, that provides for the controlled or sustained release of the product which can then be delivered via a depot injection. Hyaluronic acid can also be used, and this can have the effect of promoting sustained duration in

the circulation. Other suitable means for the introduction of the desired molecule include implantable drug delivery devices.

[0349] In one embodiment, a pharmaceutical composition can be formulated for inhalation. For example, a binding protein can be formulated as a dry powder for inhalation. Binding protein inhalation solutions can also be formulated with a propellant for aerosol delivery. In yet another embodiment, solutions can be nebulized.

[0350] It is also contemplated that certain formulations can be administered orally. In one embodiment of the disclosure, multispecific binding proteins that are administered in this fashion can be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. For example, a capsule can be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of the binding protein. Diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders can also be employed.

[0351] Another pharmaceutical composition can involve an effective quantity of multispecific binding proteins in a mixture with non-toxic excipients that are suitable for the manufacture of tablets. By dissolving the tablets in sterile water, or another appropriate vehicle, solutions can be prepared in unit-dose form. Suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

[0352] Additional pharmaceutical compositions of the disclosure will be evident to those skilled in the art, including formulations involving binding proteins in sustained- or controlled-delivery formulations. Techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. Additional examples of sustained-release preparations include semipermeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules. Sustained release matrices can include polyesters, hydrogels, poly lactides, copolymers of L-glutamic acid and gamma ethyl-L-glutamate, poly(2-hydroxyethyl-methacrylate), ethylene vinyl acetate, or poly-D(-)-3-hydroxybutyric acid. Sustained-release compositions can also include liposomes, which can be prepared by any of several methods known in the art.

[0353] In some embodiments, pharmaceutical compositions are to be used for in vivo administration typically must be sterile. This can be accomplished by filtration through sterile filtration membranes. Where the composition is lyophilized, sterilization using this method can be conducted either prior to, or following, lyophilization and reconstitution. The composition for parenteral administration can be stored in lyophilized form or in a solution. In addition, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper that can be pierced by a hypodermic injection needle.

[0354] Once the pharmaceutical composition has been formulated, it can be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. Such formulations can be stored either in a ready-to-use form or in a form (e.g., lyophilized) requiring reconstitution prior to administration.

[0355] The disclosure also encompasses kits for producing a single dose administration unit. The kits can each contain both a first container having a dried multispecific binding protein and a second container having an aqueous formulation. Also included within the scope of this disclosure are kits containing single and multi-chambered pre-filled syringes (e.g., liquid syringes and lyosyringes).

[0356] The effective amount of a binding protein pharmaceutical composition to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon the molecule delivered, the indication for which the binding protein is being used, the route of administration, and the size (body weight, body surface, or organ size) and condition (the age and general health) of the patient. Accordingly, the clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect.

[0357] Dosing frequency will depend upon the pharmacokinetic parameters of the binding protein in the formulation being used. Typically, a clinician will administer the composition until a dosage is reached that achieves the desired effect. The composition can therefore be administered as a single dose, as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. Appropriate dosages can be ascertained through use of appropriate dose-response data.

[0358] The route of administration of the pharmaceutical composition is in accord with known methods, e.g., orally; through injection by intravenous, intraperitoneal, intracerebral (intraparenchymal), intracerebroventricular, intramuscular, intraocular, intraarterial, intraportal, or intralesional routes; by sustained release systems; or by implantation devices. Where desired, the compositions can be administered by bolus injection or continuously by infusion, or by implantation device.

[0359] In some embodiments, the composition can also be administered locally via implantation of a membrane, sponge, or other appropriate material onto which the desired molecule has been absorbed or encapsulated. Where an implantation device is used, the device can be implanted into any suitable tissue or organ, and delivery of the desired molecule can be via diffusion, timed-release bolus, or continuous administration.

[0360] Multispecific binding proteins disclosed herein can be formulated as an aerosol for topical application, such as by inhalation (see, e.g., U.S. Pat. Nos. 4,044,126, 4,414,209 and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma and are herein incorporated by reference in their entireties). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflations,

alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will, in one embodiment, have diameters of less than 50 microns, in one embodiment less than 10 microns.

[0361] A multispecific binding protein disclosed herein can be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the heterodimeric protein alone or in combination with other pharmaceutically acceptable excipients can also be administered.

[0362] Transdermal patches, including iontophoretic and electrophoretic devices, are well known to those of skill in the art, and can be used to administer a heterodimeric protein. For example, such patches are disclosed in U.S. Pat. Nos. 6,267,983, 6,261,595, 6,256,533, 6,167,301, 6,024, 975, 6,010,715, 5,985,317, 5,983,134, 5,948,433, and 5,860, 957, all of which are herein incorporated by reference in their entireties.

[0363] In certain embodiments, a pharmaceutical composition comprising a multispecific binding protein described herein is a lyophilized powder, which can be reconstituted for administration as solutions, emulsions and other mixtures. It may also be reconstituted and formulated as solids or gels. The lyophilized powder is prepared by dissolving heterodimeric protein described herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. In certain embodiments, the lyophilized powder is sterile. The solvent may contain an excipient which improves the stability or other pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agents. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, in one embodiment, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. In one embodiment, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4° C. to room temperature. Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, the lyophilized powder is added to sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined. Multispecific binding proteins provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, see, e.g., U.S. Pat. Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674,

5,759,542 and 5,709,874, all of which are herein incorporated by reference in their entireties. In a specific embodiment, a heterodimeric protein described herein is targeted to a tumor.

Methods of Treatment/Use

[0364] Another aspect of the disclosure is a multispecific antibody and/or an antigen-binding protein as described herein for use as a medicament.

[0365] In a particular embodiment, a method of treating a disorder through the activation of BMP Type I receptors and BMP Type II receptors is provided, the method comprising administering to a subject in need thereof an effective amount of an antigen-binding protein described herein.

[0366] The binding proteins can be employed in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays for the detection and quantitation of one or more target antigens. The binding proteins will bind the one or more target antigens with an affinity that is appropriate for the assay method being employed.

[0367] For diagnostic applications, in some embodiments, binding proteins can be labeled with a detectable moiety. The detectable moiety can be any one that is capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety can be a radioisotope, such as ³H, ¹⁴C, ³²P, ³⁵, ¹²⁵I, ⁹⁹Tc, ¹¹¹In, or ⁶⁷Ga; a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin; or an enzyme, such as alkaline phosphatase, β-galactosidase, or horseradish peroxidase.

[0368] The binding proteins are also useful for in vivo imaging. A binding protein labeled with a detectable moiety can be administered to an animal, e.g., into the bloodstream, and the presence and location of the labeled antibody in the host assayed. The binding protein can be labeled with any moiety that is detectable in an animal, whether by nuclear magnetic resonance, radiology, or other detection means known in the art.

[0369] The disclosure also relates to a kit comprising a binding protein and other reagents useful for detecting target antigen levels in biological samples. Such reagents can include a detectable label, blocking serum, positive and negative control samples, and detection reagents. In some embodiments, the kit comprises a composition comprising any binding protein, polynucleotide, vector, vector system, and/or host cell described herein. In some embodiments, the kit comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing a condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper that can be pierced by a hypodermic injection needle). In some embodiments, the label or package insert indicates that the composition is used for preventing, diagnosing, and/or treating the condition of choice. Alternatively, or additionally, the article of manufacture or kit may further comprise a second (or third) container comprising a pharmaceutically acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buff-

ered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0370] In some embodiments, the present disclosure relates to a method of preventing and/or treating a disease or disorder (e.g., cancer). In some embodiments, the method comprises administering to a patient a therapeutically effective amount of at least one of the binding proteins, or pharmaceutical compositions related thereto, described herein. In some embodiments, the patient is a human.

[0371] The contents of the articles, patents, and patent applications, and all other documents and electronically available information mentioned or cited herein, are hereby incorporated by reference in their entirety to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference. Applicants reserve the right to physically incorporate into this application any and all materials and information from any such articles, patents, patent applications, or other physical and electronic documents.

[0372] While the present disclosure has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the disclosure. It will be readily apparent to those skilled in the art that other suitable modifications and adaptations of the methods described herein may be made using suitable equivalents without departing from the scope of the embodiments disclosed herein. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present disclosure. All such modifications are intended to be within the scope of the claims appended hereto. Having now described certain embodiments in detail, the same will be more clearly understood by reference to the

following examples, which are included for purposes of illustration only and are not intended to be limiting.

EXAMPLES

Example 1. Bispecific Antibodies to BMPR Type I and Type II Receptors with Optimized Hinges, Linkers and Valencies

[0373] Bispecific antibodies targeting the BMPR Type I receptor ALK1 and BMPR Type II receptor BMPRII were designed, with sequences provided below. Some constructs include upper hinge variants: hinge 1=no upper hinge; hinge 3=an upper hinge sequence of PLAP (SEQ ID NO: 2); hinge 6=an upper hinge sequence of DKTHT (SEQ ID NO: 5).

[0374] Three-dimensional structures of BMP10 in complex with ALK1 and BMPRII (PDB ID 7PPC) was used in combination with structural models from AlphaFold2 AF-P37023-F1-model_v4 (ALK1), AF-Q13873-F1-model_v4 (BMPRII) and a model from Agnew et al. (DOI: 10.1038/s41467-021-25248-5) to construct a model of the intra and extra cellular domains of the BMPRII/ALK1/BMP9 active tetrameric receptor complex that enables phosphorylation of the GS domain and activation of SMADs. We predicted that tetravalent format of agonistic antibodies would facilitate the predicted tetrameric receptor assembly, required for signaling of ALK1/BMPRII complex.

[0375] The DIAGONAL platform predicted epitopes on ALK1 and BMPRII that binders could target to engage the receptor in this tetravalent format. Those predictions were used to design CDRs of the binding modules of the DGL molecules and connecting linkers compatible with the geometrical constraints of tetravalent antibody formats.

[0376] Antibodies were transiently transfected using the Expi293 (Thermo) system according to the manufacturer's instructions. Cells were harvested six days post transfection and harvested using batch purification with mabSelect resin. Purity of the final product was assessed using SDS-PAGE and analytical gel filtration.

TABLE 1

Hinge variant and Fc domain sequences		
	SEQ ID NO	SEQUENCE
Hinge 2	1	PLAPDKTHT
Hinge 3	2	PLAP
Hinge 4	3	GGGGSGGGSGGGGGGGG
Hinge 5	4	EKSYGPP
Hinge 6	5	DKTHT
Middle and Lower Hinge	6	CPPCPAPELLG
Hinge 3 + Middle and Lower	7	PLAPCPPCPAPELLG
Hinge 6 + Middle and Lower	8	DKTHTCPPCPAPELLG
Hinge 5 + Middle and Lower	9	EKSYGPPCPPCPAPELLG
Wildtype Fc domain	10	GPSVFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP

TABLE 1-continued

Hinge variant and Fc domain sequences		
	SEQ ID NO	SEQUENCE
		APIEKTIKAKGQPREPQVYTLPPSRDELTKN QVS LTCLVKGFYPSDI AVEWESNGQPENNYK TPPPVLDSDGSFFLYSKLTVDKSRWQQGNVF SCS VMHEALHNHYTQKSLSLSPG
Hinge 3 + Fc domain	11	PLAPCPCPAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPAPIEKTIKAKGQPRE PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPG
Hinge 6 + Fc domain	12	DKTHTCPCPAPELLGGPSVFLFPPKPKDT LMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQD WLN GKEYKCKVSNKALPAPIEKTIKAKGQPR EPQVYTLPPSRDELTKNQVSLTCLVKGFYPSD IAVEWESNGQPENNYKTTPPVLDSDGSFFLYS KLTVVDKSRWQQGNVFSCSVMHEALHNHYTQ KSLSLSPG
Hinge 5 + Fc domain	13	EKS YGPPCPCPAPELLGGPSVFLFPPKPK DTLMISRTPEVTCVVVDVSHEDPEVKFNWYV DG VEVHNAKTKPREEQYNSTYRVVSVLTVLH QDW LNGKEYKCKVSNKALPAPIEKTIKAKGQ PREPQVYTLPPSRDELTKNQVSLTCLVKGFY PSDI AVEWESNGQPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPG
Middle + Lower hinge and Fc domain	14	CPPCPAPELLGGPSVFLFPPKPKDTLMISR PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNA KTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTIKAKGQPREPQVYTL PPSRDELTKNQVSLTCLVKGFYPSDI AVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSP G

TABLE 2

Bispecific antibodies to ALK1 and BMPRII constructs		
Antibody Designation	Amino acid sequence	
DGL284	GDEMGTIDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPG KAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQ QS YSTPRTFGQGTKVDIKEKGKSSGSGSESKASQVQLQESGPGLVKP QTLSLTCVSGGSISDDYYWSWIQRTPKGLEWIGIYYSGITYNN PSL KSRVTISVDTSKNQFSLKLSVTAADTAVYYCAREGCNDGV CYN GVFDYWGQQLTVTVSSGGGGSSGGGGSSGGGGSSGGGG GGGSGGTQSAALTQ PASVSGSPGQSI TISCTGTSSDVGGYKSVSWYQ QHPGKAPKLM IYDVS NRP SGS VSDRFS GS KSGNTASLTISGLQA EDEA DYYCSSTSSSLWFGGTTKLT VLGEGKSSGSGSESKASQVQLVQ SGAEVKKPGPSV KVSKC ASGGTFSSYAI SWVRQAPGQGLEWMGR II PILGITANYA QKFQGRVTM TEDTSTD TAYMELSSLRSE DTAVYYCATDL WGVGADWGQQLTVTVSSGGGGGGGGGGGDKTH TCPPCPAPEL LGGPSVFLFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKA LPAPIEKTIKAKGQPREPQVYTLPPSREELTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGS (SEQ ID NO: 15)	
DGL266	EVQLLESGGGLVQPGGSLRLSCAASGFTSIYAMSWVRQAPGKGL WVSAISGSGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARDFDYWGQGT LVTVTSSGGGGSGGGGSQSVLTQPP	

TABLE 2-continued

<u>Bispecific antibodies to ALK1 and BMPRII constructs</u>		
Antibody Designation	Amino acid sequence	
	SASGTPGQRTVISCGSSSNIGSNVYVYQQLPGTAPKLLIYGNINRP SGVPDRFGSKSGTSASLAIISGLRSEDEADYYCAAWDDSLNGRVFG GGTKLTVLGGGGSGGGGGGGSGVECPAPPVAGPSVFLFP PKPDTLMI SRTPEVTCVVVDVSHEPVEQFNWYVDGVEVHNAKTKP REEQFNSTRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTIKST KGQPREPVYTLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWESNG QPENNYKTTPPMLSDGSFFLVSKLTVDKSRWQQGVFSCVMHEA LHNHYTQKSLSLSPG (SEQ ID NO: 16) EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVANINQDGSEKNVYDSMRGRFTISRDNISKNTLYLQMNLSRAEDTA VYYCAREFDYWQGQTLTVTSSGGGGSGGGGSQVLAQPM PSASGTPGQRTISCSGSSSNIGSNVYVYQQLPGTAPKLLIYGNINK RPSGPVDRFGSKSGTSASLAIISGLRSEDEADYYCAAWDDSLNGRV FGGGTKLTVLGGGGSGGGGGGGSGVECPCPAPPVAGPSVFLF PPPKDTLMI SRTPEVTCVVVDVSHEPVEQFNWYVDGVEVHNAKT KPREEQFNSTRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKQPREPVYTLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWE SNGQPENNYKTTPPMLSDGSFFLVSKLTVDKSRWQQGVFSCVMHEA MHEALHNHYTQKSLSLSPG (SEQ ID NO: 17) EVQLLESGGGLVQPGGSLRLSCAASGFTPSDYYMTWIRQAPGKLE WVSSISGGSTYYADSRKGRTFISRDNSENLYLQMNLSRAEDTAVYY CARDFGVAGWFGQYGMWDVWQGTLTVTSSGGGGSGGGGGGG SQSVLITQPPSASGTPGQRTVISCTGSSSNIGAGYDVHNYQQLPGTA PKLLIYRSNQRPSGPDRFGSKSGTSASLAIISGLRSEDEADYYCSSY AGNYNLVFGGGTTLTVLGGGGSGGGGGSGVECPCPAPPVA GPSVFLFPKPDKTLMI SRTPEVTCVVVDVSHEPVEQFNWYVDGVE VHNAKTKPREEQFNSTRVSVLTVVHQDWLNGKEYKCKVSNKGLP APIEKTIKSTKGQPREPVQVCTLPPSREEMTKNQVSLSCAVKGFYPSDI AVEWESNGQPENNYKTTPPMLSDGSFFLVSKLTVDKSRWQQGVFSCVMHEA FSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 19)	
DGL267	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVANINQDGSEKNVYDSMRGRFTISRDNISKNTLYLQMNLSRAEDTA VYYCAREFDYWQGQTLTVTSSGGGGSGGGGSQVLAQPM PSASGTPGQRTISCSGSSSNIGSNVYVYQQLPGTAPKLLIYGNINK RPSGPVDRFGSKSGTSASLAIISGLRSEDEADYYCAAWDDSLNGRV FGGGTKLTVLGGGGSGGGGGGGSGVECPCPAPPVAGPSVFLF PPPKDTLMI SRTPEVTCVVVDVSHEPVEQFNWYVDGVEVHNAKT KPREEQFNSTRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKQPREPVYTLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWE SNGQPENNYKTTPPMLSDGSFFLVSKLTVDKSRWQQGVFSCVMHEA MHEALHNHYTQKSLSLSPG (SEQ ID NO: 18) EVQLLESGGGLVQPGGSLRLSCAASGFTPSDYYMTWIRQAPGKLE WVSSISGGSTYYADSRKGRTFISRDNSENLYLQMNLSRAEDTAVYY CARDFGVAGWFGQYGMWDVWQGTLTVTSSGGGGSGGGGGGG SQSVLITQPPSASGTPGQRTVISCTGSSSNIGAGYDVHNYQQLPGTA PKLLIYRSNQRPSGPDRFGSKSGTSASLAIISGLRSEDEADYYCSSY AGNYNLVFGGGTTLTVLGGGGSGGGGGSGVECPCPAPPVA GPSVFLFPKPDKTLMI SRTPEVTCVVVDVSHEPVEQFNWYVDGVE VHNAKTKPREEQFNSTRVSVLTVVHQDWLNGKEYKCKVSNKGLP APIEKTIKSTKGQPREPVQVCTLPPSREEMTKNQVSLSCAVKGFYPSDI AVEWESNGQPENNYKTTPPMLSDGSFFLVSKLTVDKSRWQQGVFSCVMHEA FSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 19)	
DGL268	EVQLLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKLE WVSAISGSGGTYYADSVKGRFTISRDNISKNTLYLQMNLSRAEDTA YYCARDFDYWGQGTLTVTSSGGGGSGGGGGSGGGSGQVLTQPP SASGTPGQRTISCSGSSSNIGSNVYVYQQLPGTAPKLLIYGNINRP SGVPDRFGSKSGTSASLAIISGLRSEDEADYYCAAWDDSLNGRVFG GGTKLTVLGGGGSGGGGGSGVECPCPAPPVAGPSVFLFP PKPDTLMI SRTPEVTCVVVDVSHEPVEQFNWYVDGVEVHNAKTKP REEQFNSTRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTIKST KGQPREPVYTLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWESNG QPENNYKTTPPMLSDGSFFLVSKLTVDKSRWQQGVFSCVMHEA LHNHYTQKSLSLSPG (SEQ ID NO: 20) EVQLLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKLE WVSAISGSGGTYYADSVKGRFTISRDNISKNTLYLQMNLSRAEDTA YYCARDFDYWGQGTLTVTSSGGGGSGGGGGSGQVLTQPP SASGTPGQRTISCSGSSSNIGSNVYVYQQLPGTAPKLLIYGNINRP SGVPDRFGSKSGTSASLAIISGLRSEDEADYYCAAWDDSLNGRVFG GGTKLTVLGGGGSGGGGGSGVECPCPAPPVAGPSVFLFP PKPDTLMI SRTPEVTCVVVDVSHEPVEQFNWYVDGVEVHNAKTKP REEQFNSTRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTIKST KGQPREPVQVCTLPPSREEMTKNQVSLSCAVKGFYPSDIAVEWESNG QPENNYKTTPPMLSDGSFFLVSKLTVDKSRWQQGVFSCVMHEA LHNHYTQKSLSLSPG (SEQ ID NO: 21)	
DGL269	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMNWRQAPGKGL EWVSSISSSSSYIYADSVKGRFTISRDNISKNTLYLQMNLSRAEDTA YYCARAVAAGGMFWGLDQWQGQTLTVTSSGGGGSGGGGG GSQSVLITQPPSASGTPGQRTISCSGSSRNIGSNVHNYQQLPGTA PKLLIYRSNQRPSGPDRFGSKSGTSASLAIISGLRSEDEADYYCQS YDSSLNDHVVFGGGTTLTVLGGGGSGGGGGSGVECPCPAP	

TABLE 2-continued

<u>Bispecific antibodies to ALK1 and BMPRII constructs</u>		
Antibody Designation	Amino acid sequence	
	PVAGPSVFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNK GLPAPIEKTI STKTGQPREPVYTLPPCREEMTKNQVSLWCLVKGFY PSDIAVEWESNGQPENNYKTTPMLDSDGSSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 22) EVQLLESGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKGL EWVSSI SSSSYI YYADSVKGRTFTISRDNSKNTLYLQMNSLRAEDTA YYCARAVAAGGMFWGLDQWQGQTLLVTVTSSGGGGGGGGGGGG GSQSVLTQPPSASGTPGQRVTISCSGSRSNIGSNVHWYQQLPGTA PKLLIYGNNSRPGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQS YDSSLNDHVVFGGGTKLTVLGGGGSGGGGGGGSGVCECPCCPAP PVAGPSVFLFPPPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVD GVEVHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNK GLPAPIEKTI STKTGQPREPVQVCTLPPSREEMTKNQVSLSCAVKG SDIAVEWESNGQPENNYKTTPMLDSDGSSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 23)	
DGL270	EVQLLESGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKGL WVANINQDGSEKNEYVDSMRGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREFDYWGQGTLVTVTSSGGGGGGGGGGGGGGGGGGGG PSASGTPGQRVTISCSGSSSNIGSNVYWWYQQLPGTAPKLLIYGNNK RPSGVPDFRSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNDRV FGGGTKLTVLGGGGSGGGGGGGGGVCECPCCPAPPVAGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKGQPREPVYTLPPCREEMTKNQVSLWCLVKGFYPSDIAVEWE SNGOPENNYKTTPMLDSDGSSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG (SEQ ID NO: 24) EVQLLESGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKGL WVANINQDGSEKNEYVDSMRGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREFDYWGQGTLVTVTSSGGGGGGGGGGGGGGGGGGGG PSASGTPGQRVTISCSGSSSNIGSNVYWWYQQLPGTAPKLLIYGNNK RPSGVPDFRSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNDRV FGGGTKLTVLGGGGSGGGGGGGGGVCECPCCPAPPVAGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKT KPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTI SKTKGQPREPVYTLPPCREEMTKNQVSLSCAVKGFYPSDIAVEWE SNGOPENNYKTTPMLDSDGSSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPG (SEQ ID NO: 25)	
DGL271	EVQLLESGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKGL WVSSISGGSTYYADSRKGRTFTISRDNSENTLYLQMNSLRAEDTA CARDPGVAGWFGQYGMWDVWQGTLVTVTSSGGGGGGGGGGGG SQSVLTQPPSASGTPGQRVTISCTGSSNI GAGYDVHWYQQLPGTA PKLLIYRSNQRPGVPDRFSGSKSGTSASLAISGLRSEDEADYYCSSY AGNYNLVFGGGTKLTVLGGGGGGGGGGGGGGGGGGVCECPCCPAPPVA GPSVFLFPKPDKDTLMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLP APIEKTI STKTGQPREPVYTLPPCREEMTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTTPMLDSDGSSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 26) EVQLLESGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKGL WVSSISGGSTYYADSRKGRTFTISRDNSENTLYLQMNSLRAEDTA CARDPGVAGWFGQYGMWDVWQGTLVTVTSSGGGGGGGGGGGG SQSVLTQPPSASGTPGQRVTISCTGSSNI GAGYDVHWYQQLPGTA PKLLIYRSNQRPGVPDRFSGSKSGTSASLAISGLRSEDEADYYCSSY AGNYNLVFGGGTKLTVLGGGGGGGGGGGGGGGGVCECPCCPAPPVA GPSVFLFPKPDKDTLMI SRTPEVTCVVVDVSHEDPEVQFNWYVDGVE VHNAKTKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLP APIEKTI STKTGQPREPVYTLPPCREEMTKNQVSLSCAVKGFYPSDI AVEWESNGQPENNYKTTPMLDSDGSSFFLYSKLTVDKSRWQQGNV FSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 27)	
DGL272	EVQLLESGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKGL WVSAISGGGSTYYADSVKGRTFTISRDNSKNTLYLQMNSLRAEDTA YYCARDFDYWGQGTLVTVTSSGGGGGGGGGGGGGGGGGGGGGG SASGTPGQRVTISCSGSSSNIGSNVYWWYQQLPGTAPKLLIYGNINRP SGVPDFRSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNDRV GGTKLTVDKTHTCPCCPAPAEAGAPSVFLFPPKPDKDTLMI SRTPEV CVVVVDVSHEDPEVFKFNWYVDGVEVHNAKTKPREEQYNSTYRV TVLHQDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPVYTLPP CRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPV L	

TABLE 2-continued

<u>Bispecific antibodies to ALK1 and BMPRII constructs</u>		
Antibody Designation	Amino acid sequence	
	SDGSFFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GEPEA (SEQ ID NO: 28) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMWVRQAPGKGL EWVSSISSSSYIYYADSVKGRFTISRDNISKNTLYLQMNSLRAEDTAV YYCARAVAAGGMFWGLDWQGQTLVTVTSSGGGGGGGGGGGGGG GSQSVLTQPPSASGTPGQRVTISCSGSRSNIGNSNVHNYQQLPGTA PKLLIYGNNSRPSGVPDFRSGSKSGTSASLAISGLRSEDEADYYCQS YDSSLNDHVVFGGGTKLTVLDKTHTCPPCPAPEAAGAPSFLFPPKPK KDTLMISRTPETVCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPVCTLPPSDELTKNQVSLSCAVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGWHPQFEK (SEQ ID NO: 29)	
DGL273	EVQLLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKGLE WVSAISGSGGTTYYADSVKGRFTISRDNISKNTLYLQMNSLRAEDTAV YYCARDFDYWQGQTLVTVTSSGGGGGGGGGGGGGGQSVLTQPP SASGTPGQRVTISCSGSSSNIGSNYVWYQQLPGTAPKLLIYGNINRP SGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFG GGTKLTLPAPCPAPEAAGAPSFLFPPKPKDTLMISRTPETVCVVVD VSHEDEPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVLTVLHQ DWLNKEYKCKVSNKALPAPIEKTISKAKGQPREPVYVTLPPCRDEL TKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 30) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMWVRQAPGKGL EWVSSISSSSYIYYADSVKGRFTISRDNISKNTLYLQMNSLRAEDTAV YYCARAVAAGGMFWGLDWQGQTLVTVTSSGGGGGGGGGGGG GSQSVLTQPPSASGTPGQRVTISCSGSRSNIGNSNVHNYQQLPGTA PKLLIYGNNSRPSGVPDFRSGSKSGTSASLAISGLRSEDEADYYCQS YDSSLNDHVVFGGGTKLTVLPAPCPAPEAAGAPSFLFPPKPKDTLM ISRTPETVCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNST YRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVCTLPPSDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKT TPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGWHPQFEK (SEQ ID NO: 31)	
DGL274	EVQLLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKLE WVSAISGSGGTTYYADSVKGRFTISRDNISKNTLYLQMNSLRAEDTAV YYCARDFDYWQGQTLVTVTSSGGGGGGGGGGGGGGQSVLTQPP SASGTPGQRVTISCSGSSSNIGSNYVWYQQLPGTAPKLLIYGNINRP SGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFG GGTKLTLPAPCPAPEAAGAPSFLFPPKPKDTLMISRTPETVC VVVDVSHEDEPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVSVL TQLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPVYVTLPP RDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG EPEA (SEQ ID NO: 32) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMWVRQAPGKGL EWVSSISSSSYIYYADSVKGRFTISRDNISKNTLYLQMNSLRAEDTAV YYCARAVAAGGMFWGLDWQGQTLVTVTSSGGGGGGGGGGGG GSQSVLTQPPSASGTPGQRVTISCSGSRSNIGNSNVHNYQQLPGTA PKLLIYGNNSRPSGVPDFRSGSKSGTSASLAISGLRSEDEADYYCQS YDSSLNDHVVFGGGTKLTVLPAPCPAPEAAGAPSFLFPPKPK DTLMISRTPETVCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREE QYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG QPREPVCTLPPSDELTKNQVSLSCAVKGFYPSDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALH NHYTQKSLSLSPGWHPQFEK (SEQ ID NO: 33)	
DGL275	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYYAMSWVRQAPGKLE WVANINQDGSEKNYVDSMGRFTISRDNISKNTLYLQMNSLRAEDTA VYYCAREFDYWQGQTLVTVTSSGGGGGGGGGGGGQSVLAQP PSASGTPGQRVTISCSGSSSNIGSNYVWYQQLPGTAPKLLIYGNNK RPSGVPDFRSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRV FGGGTKLTVLDKTHTCPPCPAPEAAGAPSFLFPPKPKDTLMISRTP ETVCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVS TQLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPVYTL	

TABLE 2-continued

<u>Bispecific antibodies to ALK1 and BMPRII constructs</u>		
Antibody Designation	Amino acid sequence	
	PCRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL PGEPEA (SEQ ID NO: 34) EVQLLESGGLVQPGGSLRLSCAASGFTPSDYYMTWIRQAPGKGLE WVSSISGGSTYYADSRKGRTFISRDNSKNTLYLQMNSLRAEDTAVYY CARDFGVAGWFGQYGMDWVGQGTLLTVSSGGGGSGGGGGCGGG SQSVLTQPPSASGTPGQRTVITISCTGSSSNIGAGYDVHNVQQLPGTA PKLLIYRSNQRPGVPDRFSGSKSGTSASLAISGLRSEDEADYYCSSY AGNYNLVFGGGTAKLTVLDTHTCPCPAPEAAGAPSFLFPPPKD LMISRTPEVTCVVVDVSHEDEPKFNWYVDGVEVHNAAKTKPREEQY NSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ REPQVCTLPPSRDELTKNQVSLSCAVKGFPYPSDIAVEWESNGOPEN NYKTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGWHPQFEK (SEQ ID NO: 35)	
DGL276	EVQLLESGGLVQPGGSLRLSCAASGFTPSDYYMTWIRQAPGKGLE WVANINQDGSEKNVYDSMRGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREFDYWGQGTLLTVTSSGGGGSGGGGSQVLAQPM PSASGTPGQRTVITCSGSSSNIGSNVYVYQQLPGTAPKLLIYGN RPSGVDPDRFSGSKSGTSASLAISGLRSEDEADYYCAANDDSLNG RGFFGGTAKLTVLCPCCPAPEAAGAPSFLFPPPKD TLMISRTPEVTCVV VDVSHEDEPKFNWYVDGVEVHNAAKTKPREEQYNTYRVSVLTV HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPPCRD ELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGE EA (SEQ ID NO: 36) EVQLLESGGLVQPGGSLRLSCAASGFTPSDYYMTWIRQAPGKGLE WVSSISGGSTYYADSRKGRTFISRDNSKNTLYLQMNSLRAEDTAVYY CARDFGVAGWFGQYGMDWVGQGTLLTVSSGGGGSGGGGGCGGG SQSVLTQPPSASGTPGQRTVITISCTGSSSNIGAGYDVHNVQQLPGTA PKLLIYRSNQRPGVPDRFSGSKSGTSASLAISGLRSEDEADYYCSSY AGNYNLVFGGGTAKLTVLCPCCPAPEAAGAPSFLFPPPKD TLMISRTPEVTCVV VDVSHEDEPKFNWYVDGVEVHNAAKTKPREEQYNTYRVSV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVC TLPPSRDELTKNQVSLSCAVKGFPYPSDIAVEWESNGQPENNYKTPP VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL LSPGWHPQFEK (SEQ ID NO: 37)	
DGL277	EVQLLESGGLVQPGGSLRLSCAASGFTPSDYYMTWIRQAPGKGLE WVANINQDGSEKNVYDSMRGRFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREFDYWGQGTLLTVTSSGGGGSGGGGSQVLAQPM PSASGTPGQRTVITCSGSSSNIGSNVYVYQQLPGTAPKLLIYGN RPSGVDPDRFSGSKSGTSASLAISGLRSEDEADYYCAANDDSLNG RGFFGGTAKLTVLPLAPCPCCPAPEAAGAPSFLFPPPKD TLMISRTPEVTCVV VDVSHEDEPKFNWYVDGVEVHNAAKTKPREEQYNTYRVSV LTIVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVTLPP CRDELTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD SDGSFFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GEPEA (SEQ ID NO: 38) EVQLLESGGLVQPGGSLRLSCAASGFTPSDYYMTWIRQAPGKGLE WVSSISGGSTYYADSRKGRTFISRDNSKNTLYLQMNSLRAEDTAVYY CARDFGVAGWFGQYGMDWVGQGTLLTVSSGGGGGGGGGGGG SQSVLTQPPSASGTPGQRTVITISCTGSSSNIGAGYDVHNVQQLPGTA PKLLIYRSNQRPGVPDRFSGSKSGTSASLAISGLRSEDEADYYCSSY AGNYNLVFGGGTAKLTVLPLAPCPCCPAPEAAGAPSFLFPPPKD TLMISRTPEVTCVV VDVSHEDEPKFNWYVDGVEVHNAAKTKPREEQYNTYRVSV NSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE PQVCTLPPSRDELTKNQVSLSCAVKGFPYPSDIAVEWESNGQPENNY KTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYT QKSLSLSPGWHPQFEK (SEQ ID NO: 39)	
DGL278	EVQLLESGGLVQPGGSLRLSCAASGFTPSIYAMSWVRQAPGKGLE WVSAISGGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARDFDYWGQGTLLTVTSSASTKGPSVPLAPSSKSTSGGTAAL GCLVKDVFPEPVTVWSNSGALTSGVHTFPAVLQSSGLYSLSSVVTVP SSSLGTQTYICNVNHHPSNTKVDKKVEPKSCDKTHTCPCCPAPEAAG APSFLFPPPKD TLMISRTPEVTCVV VDVSHEDEPKFNWYVDGVE HNAAKTKPREEQYNTYRVSVLTVLHQDWLNGKEYKCKVSNKALP	

TABLE 2-continued

<u>Bispecific antibodies to ALK1 and BMPRII constructs</u>		
Antibody Designation	Amino acid sequence	
	<pre> APIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTTTPVPLDSGSFFLYSKLTVDKSFWQQGNVF SCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 40) QSVLQTQPPSASGTPQRVTISCSGSSSNIGSNVYVWYQQLPGTAPKL LIYGNINRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCAAWDD SLNDRVFGGGTQLTVLGQPKAAPSVTLPFPSSSEELQANKATLVLCLSD FYPGAVTVAWKADSSPVKAQGVETTPSKQSNNKYAASSYSLTPEQ WKSRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 41) EVQLLESGGLVQPGGSRLSCAASGFTFSNAWMWVRQAPGKLE WVAISGSGGTYYADSVKGRFTISRDNSKNTLYLQMNLSRAEDTAV YCYCARDFDYWGQGTLTVTSSGGGSGGGGSGGGGSQSVLTQPP SASGTPGQRVTISCSGSSSNIGSNVYVWYQQLPGTAPKLIIYGNINRP SGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNDRVFG GGTKLTVLDKHTCPCPAPAEAGAPSVELFPFPKPKDTLMISRTPEV CVVVDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTIISKAKGQPREPQVCTLPP SRDELTKNQVSLSCAVKGYPSPDIAVEWESNGQPENNYKTTPPVLD DGSFFLVSKLTVDKSRWQQGNVFSCVMHEALHNHYTQKSLSLSPG KWSHPQFEK (SEQ ID NO: 42) </pre>	
DGL279	<pre> EVQLLESGGLVQPGGSRLSCAASGFTFSNAWMWVRQAPGKGL EWVSSISSSSYIYYADSVKGRFTISRDNSKNTLYLQMNLSRAEDTAV YYCARAVAAGGMFWGLDQWQGTLTVTSSASTKGPSVFLAPSS KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVTPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSCDKTHTC PPCPAPAEAGAPSVELFPFPKPKDTLMISRTPEVTCVVVDVSHEDPEV KFNWYVGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTIISKAKGQPREPQVYTLPPCRDELTKNQVSL CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 43) QSVLQTQPPSASGTPGQRVTISCSGSRSNIGSNVSHWYQQLPGTAPKL LIYGNINRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCQSYDS SLNDHVFVGGGTQLTVLGQPKAAPSVTLPFPSSSEELQANKATLVLCLIS DFYPGAVTVAWKADSSPVKAQGVETTPSKQSNNKYAASSYSLTPEQ WKSRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 44) EVQLLESGGLVQPGGSRLSCAASGFTFSNAWMWVRQAPGKGL EWVSSISSSSYIYYADSVKGRFTISRDNSKNTLYLQMNLSRAEDTAV YYCARAVAAGGMFWGLDQWQGTLTVTSSGGGSGGGGGGGGG GSQSVLQTQPPSASGTPGQRVTISCSGSRSNIGSNVSHWYQQLPGTA PKLLYIGNSNRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCQS YDSSLNDHVVFGGGTQLTVLDKHTCPCPAPAEAGAPSVFLFPKP KDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIISKAG QPREPQVCTLPPSDELTKNQVSLSCAVKGYPSPDIAVEWESNGQP ENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCVMHEALH NHYTQKSLSLSPGKWSHPQFEK (SEQ ID NO: 45) </pre>	
DGL280	<pre> EVQLLESGGLVQPGGSRLSCAASGFTFSYAMSWSVRQAPGKLE WVANINQDGSEKNYVDSMRGFTISRDNSKNTLYLQMNLSRAEDTA VYYCAREFDYWGQGTLTVTSSASTKGPSVFLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVP SSSLGTQTYICNVNHHKPSNTKVDKKVEPKSCDKTHTCPCPAPAEAG APSFLFPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVGVE VHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP APIEKTIISKAKGQPREPQVYTLPPCRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSFWQQGNVF SCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 46) QSVLQTQPPSASGTPGQRVTISCSGSSSNIGSNVYVWYQQLPGTAPKL LIYGNNKRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCAAWDD SLNDRVFGGGTQLTVLGQPKAAPSVTLPFPSSSEELQANKATLVLCLSD FYPGAVTVAWKADSSPVKAQGVETTPSKQSNNKYAASSYSLTPEQ WKSRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 47) EVQLLESGGLVQPGGSRLSCAASGFTFSYAMSWSVRQAPGKLE WVANINQDGSEKNYVDSMRGFTISRDNSKNTLYLQMNLSRAEDTA VYYCAREFDYWGQGTLTVTSSGGGSGGGGGGGGSQSVLAQP PSASGTPGQRVTISCSGSSSNIGSNVYVWYQQLPGTAPKLIIYGNNK RPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNDRV FGGGTQLTVLDKHTCPCPAPAEAGAPSVFLFPKPDTLMISRTP VTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVV VLTBLHQDWLNGKEYKCKVSNKALPAPIEKTIISKAKGQPREPQVCLP PSRDELTKNQVSLSCAVKGYPSPDIAVEWESNGQPENNYKTTPPVLD </pre>	

TABLE 2-continued

<u>Bispecific antibodies to ALK1 and BMPRII constructs</u>		
Antibody Designation	Amino acid sequence	
	SDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GKWSHPQFEK (SEQ ID NO: 48)	
DGL281	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYDYYMTWIRQAPGKGLE WVSSISGGSTYYADSRKGRTFISRDNSENTLYLQMNSLRAEDTAVYY CARDFGVAGWFGQYGMWDVWQGTLTVSSASTKGPSVFLAPSSK STSGGTAALGCLVKDYFPEPVTVWSNGALTSGVHTFPVALQSSGLY SLSSVVTVPSSLGTQTYIICNVNHHKPSNTKVDKKVEPKSCDKTHTCP PCPAPEAAAGAPSFLFPPPKDLMISRTPEVTCVVVDVSHEDPEVKF NWYVGDVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLWCL VKGFYPSDIAVEWESENQOPENNYKTTPPVLDSDGSFFLYSKLTVDKS RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 49) QSVLQTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAP KLLIYRSNQRPSGVDRFGSKSGTSASLAIISGLRSEDEADYYCSSY GNYNLVFGGGTKLTVLGQPKAAPSFLFPPSSEELQANKATLVCCLISD FYPGAVTVAWKADSSPVKAGVETTTPSKQSQNNKYAASSYLSLTPEQ WKSHRSYSQCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 50) EVQLLESGGGLVQPGGSLRLSCAASGFTFSYDYYMTWIRQAPGKGLE WVSSISGGSTYYADSRKGRTFISRDNSENTLYLQMNSLRAEDTAVYY CARDFGVAGWFGQYGMWDVWQGTLTVSSGGGGGGGGGGGGGG SQSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAP PKLLIYRSNQRPSGVDRFGSKSGTSASLAIISGLRSEDEADYYCSSY AGNYNLVFGGGTKLTVLGQPKAAPSFLFPPPKDLMISRTPEVTCVVVDVSHEDPEVKE LNMSRTPEVTCVVVDVSHEDPEVKEENWYVGDVEVHNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQ REPQVCTLPPSRDELTKNQVSLSCAVKGFPYPSDIAVEWESENQOPEN NYKTTPPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNH YTQKSLSLSPGKWSHPQFEK (SEQ ID NO: 51)	
DGL282	EVQLLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKGLE WVSAISGGGTYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV YYCARDFDYWGQGTLTVTSSASVAAPSVFIFPPSDEQLKSGTASVV CLNNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFRGECDKTHTCPVCPAP EAAGAPSFLFPPPKDLMISRTPEVTCVVVDVSHEDPEVKFNWYV DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKG PSDIAVEWESENQOPENNYKTTPPVLDSDGSFFLVSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGWSPQFEK (SEQ ID NO: 52) QSVLQTQPPSASGTPGQRVTISCGSSSNIGSNVYWWYQQLPGTAPKL LIYGNINRPSGVDRFGSKSGTSASLAIISGLRSEDEADYYCAAWDD SLNDRVFGGGTKLTVLSSASTKGPSVFLAPSSKSTSGGTAALGCLV KDYFPEPVTVWSNGALTSGVHTFPVALQSSGLYSLSSVTVPSSL GTQTYICNVNHHKPSNTKVDKVEPKSC (SEQ ID NO: 53) EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMNWVRQAPGKGL EWVSSISSSSSYIYYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAV YYCARAVAAGGMFWGLDQWGQGTLTVTSSASTKGPSVFLAPSS KSTSGGTAALGCLVKDYFPEPVTVWSNGALTSGVHTFPVALQSSGL YSLSSVTVTPSSSLGTQTYICNVNHHKPSNTKVDKVEPKSCDKTHTC PPC PAPEAAAGAPSFLFPPPKDLMISRTPEVTCVVVDVSHEDPEV KFNWYVGDVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEY KCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDELTKNQVSLW CLVKGFYPSDIAVEWESENQOPENNYKTTPPVLDSDGSFFLYSKLTV KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 54) QSVLQTQPPSASGTPGQRVTISCGSRSNIIGNSNSVHWYQQLPGTAPKL LIYGNINRPSGVDRFGSKSGTSASLAIISGLRSEDEADYYCQSYDS SLNDHVFGGGTKLTVLGQPKAAPSFLFPPSSEELQANKATLVCCLIS DFYPGAVTVAWKADSSPVKAGVETTTPSKQSQNNKYAASSYLSLTPEQ WKSHRSYSQCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 55)	
DGL283	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMS WVRQAPGKGLE WVANINQDSEKNYVDSMRGRTFISRDN SKNTLYLQMNSLRAEDTA VYCAREFDYWGQGTLTVTSSASVAAPSVFIFPPSDEQLKSGTASV VCLNNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSST TLSKADYEKHKVYACEVTHQGLSSPVTKSFRGECDKTHTCPVCPA PEAAGAPSFLFPPPKDLMISRTPEVTCVVVDVSHEDPEVKFNWY DGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKV KALPAPIEKTISKAKGQPREPQVCTLPPSRDELTKNQVSLSCAVKG	

TABLE 2-continued

<u>Bispecific antibodies to ALK1 and BMPRII constructs</u>		
Antibody Designation	Amino acid sequence	
	YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFPLVSKLTVDKSRWQ QGNVFSCVMHEALHNHYTQKSLSLSPGWHPQFEK (SEQ ID NO: 56) QSVLAQPPSASGTPGQRVTISCGSSSNIGSNYVWYQQLPGTAPKL LIYGMNKRPSPGVPDFSGSKSGTSASLAISGLRSEDEADYYCAAWDD SLNGRVFGGGTKLTVLSSASTKGPSVFLAPSSKSTSGGTAALGCLV KDYPFPEPVTVWNNGALTSGVHTFPAVLQSSGLYSLSVVTVPSSL GTQTYICNVNHHKPSNTKVDKVEPKSC (SEQ ID NO: 57) EVQLESQGGGLVQPGGSLRLSCAASGFTPSDYYMTWIRQAPGKLE WVSSISGGSTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYY CARDFGVAGWFQGYGMDVWQGTLTVTSSASTKGPSVFLAPSSK STSGGTAALGCLVKDYPFPEPVTVWNNGALTSGVHTFPAVLQSSGLY LSSSVTVPSSSLGTQTYICNVNHHKPSNTKVDKVEPKSCDKTHTCP PCPAPEAAGAPSFLFPPPKPDTLMSRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYK CKVSNKALPAPIEKTISKAKGQPREPVYTLPPCRDELTKNQVSLWCL VKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKS RKWQGQNVFSCVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 58) QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAP KLLIYRSNQRPSPGVPDFSGSKSGTSASLAISGLRSEDEADYYCSSYA GNYNLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISD FYPGAVTVAWKADSSPVKAGVETTTPSKQSQNNKYAASSYLSLPEQ WKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 59)	
DGL285	EVQLESQGGGLVQPGGSLRLSCAASGFTPSIYAMSWVRQAPGKLE WVSAISGSGGTTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARDFDYWQGQTLTVTVTSSGGGGSGGGGSGQSVLTQPP SASGTPGQRVTISCGSSNIGSNVWYQQLPGTAPKLLIYGNINRPP SGVPDFRGSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFG GGTKLTVLDKGPSVFLAPEPKSSEVQLESQGGLVQPGGSLRLSCA ASGFTFSNAWMNWRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCARAVAAGGMFWGLDQWQGG TLTVTVTSSGGGGSGGGGGSGGGGSQSVLTQPPSASGTPGQRVTISCS GSRSNIGNSNVWYQQLPGTAPKLLIYGNINRPSGVPDFRGSGKSG TSASLAISGLRSEDEADYYCQSYDSSLNDHVVFGGGTKLTVLDKTH CPPCPAPEAAGAPSFLFPPPKPDTLMSRTPEVTCVVVDVSHEDPE VKFNWYVDGVEVHNAAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQGQNVFSCVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 60)	
DGL286	EVQLESQGGGLVQPGGSLRLSCAASGFTPSNAWMNWRQAPGKGL EWVSSISSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARAVAAGGMFWGLDQWQGQTLTVTVTSSGGGGSGGGGSGGG QSQSVLTQPPSASGTPGQRVTISCGSGRSRNIGSNSVHWYQQLPGTA PKLLIYGNINRPSGVPDFRGSGSKSGTSASLAISGLRSEDEADYYCQ YDSSLNDHVVFGGGTKLTVLDKGPSVFLAPEPKSSEVQLESQGG VQPGGSLRLSCAASGFTPSIYAMSWVRQAPGKGLEWVSAISGSGS VYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDFDYW GQGTLTVTVTSSGGGGSGGGGGSGGGGSQSVLTQPPSASGTPGQRVT ISCGSSSNIGSNYVWYQQLPGTAPKLLIYGNINRPSGVPDFRGSGK SGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFGGGTKLTVLDKTH TCPPCPAPEAAGAPSFLFPPPKPDTLMSRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK YKCKVSNKALPAPIEKTISKAKGQPREPVYTLPPSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD DKSRWQGQNVFSCVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 61)	
DGL287	EVQLESQGGGLVQPGGSLRLSCAASGFTFSYYAMSWVRQAPGKLE WVANINQDGSEKNYVDSMRGRFTISRDNSKNTLYLQMNSLRAEDTA VYVYCAREFDYWQGQTLTVTVTSSGGGGSGGGGGSGGGGSQSVLAQP PSASGTPGQRVTISCGSSSNIGSNYVWYQQLPGTAPKLLIYGNINR RPSGVPDFRGSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRV FGGGTKLTVLDKGPSVFLAPEPKSSEVQLESQGGLVQPGGSLRLS CAASGFTFSYYMTWIRQAPGKGLEWVSSISGGSTYYADSRKGRFTI SRDNSENTLYLQMNSLRAEDTAVYYCARDFGVAGWFQGYGMDVWG QGTLTVTVSSGGGGSGGGGGSGGGGSQSVLTQPPSASGTPGQRVTIS CTGSSSNIGAGYDVHWYQQLPGTAPKLLIYRSNQRPSPGVPDFRGSG KSGTSASLAISGLRSEDEADYYCQSYAGNYNLVFGGGTKLTVLDKTH TCPPCPAPEAAGAPSFLFPPPKPDTLMSRTPEVTCVVVDVSHEDP EVKFNWYVDGVEVHNAAKTKPREEQYNSTYRVVSVLTVLHQDWLNGK	

TABLE 2-continued

<u>Bispecific antibodies to ALK1 and BMPRII constructs</u>		
Antibody Designation	Amino acid sequence	
	EYKCKVSNKALPAPIEKTIASKAKGQPREPVYTLPSSRDELTKNQVSL TCLVKGFYPSDIAVEWESNGQPENNYKTPVLDSDGSFFLYSKLT DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 62)	
DGL288	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYDYYMTWIRQAPGKLE WVSSISGGSTYYADSRKGRTIISRDNSENTLYLQMNSLRAEDTAVYY CARDFGVAGWFQYGMDDWVGQGTLLTVTSSGGGGSGGGGGGGGG SQSVLTQPPSASGTPGQRVTISCTGSSNIAGAGYDVHNYQQLPGTA PKLLIYRSNQRPSPGVDRFSGSKSGTSASLAISGLRSEDEADYYCSSL AGNYNLVFGGGTKLTVLDKGPSPVFLAPEPKSSEVQLLIESGGGLVQP GGSLRLSCAASGFTFSYAMSWVRQAPGKLEWVANINQDGSEKN YVDNSMRGRFTIISRDNSKNTLYLQMNSLRAEDTAVYYCAREFDYWGQ GTLTVTTSGGGGSGGGGGSGGGQSVLAQPPSASGTPGQRVTIS CSGSSSNIGSNYVWYQQLPGTAPKLLIYQNNKRPSGVDRFSGSKS GTSASLAISGLRSEDEADYYCAAWDDSLNGRVFPGGGTKLTVLDKHT CPPCPAPEAAAGAPSFLFPPKPKDTLMSRTPEVTCVVVDVSHDPE VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTIASKAKGQPREPVYTLPSSRDELTKNQVSLT CLVKGFYPSDIAVEWESNGQPENNYKTPVLDSDGSFFLYSKLT DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 63)	
PRO003	EVQLLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKLE WVSSISGGSTYYADSVKGRTIISRDNSKNTLYLQMNSLRAEDTAV YYCARDFDYWGQGTLLTVTSSGGGGSGGGGGSGGGQSVLQPP SASGTPGQRVTISCSGSSNIIGSNYVWYQQLPGTAPKLLIYQNNR SGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFG GGTKLTVDKTHTCPCCPAPEAAAGAPSFLFPPKPKDTLMSRTPEV CVVVDVSHDPEVFKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSL TTLHQDWLNGKEYKCKVSNKALPAPIEKTIASKAKGQPREPVYTLP SRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPVLD DGSFLYSLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG GGGGSGGGSEVQLLIESGGGLVQPGGSLRLSCAASGFTFSNAWMN WVRQAPGKLEWVSSISSSSYIYADSVKGRTIISRDNSKNTLYLQ MNSLRAEDTAVYYCARAVAAGGMFWGLDWQGQGTLLTVTSSGG GSGGGGGGGGSQSVLTQPPSASGTPGQRVTISCSGSRSNIGNSV HWYQQLPGTAPKLLIYGNNSRPGVPDRFSGSKSGTSASLAISGLRS EDEADYYCQSYDSSLNDHVVFGGGTKLTVL (SEQ ID NO: 64)	
PRO004	EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMNWVRQAPGKGL EWVSSISSSSYIYADSVKGRTIISRDNSKNTLYLQMNSLRAEDTAV YYCARAVAAGGMFWGLDWQGQGTLLTVTSSGGGGSGGGGGGGGG GSQSVLTQPPSASGTPGQRVTISCSGSRSNIGNSNVHWYQQLPGTA PKLLIYGNNSRPGVPDRFSGSKSGTSASLAISGLRSEDEADYYCQ YDSSLNDHVFFGGGTKLTVLDKTHTCPCCPAPEAAAGAPSFLFPPK KDTLMISRTPEVTCVVVDVSHDPEVFKFNWYVDGVEVHNAKTKPREE QYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIASKAG QPREPVYTLPSSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHN HYTQKSLSLSPGGGGGGGGSEVQLLIESGGGLVQPGGSLRLSCA ASGFTFSIYAMSWVRQAPGKLEWVSAISGSGGSTYYADSVKGRTI SRDN SKNTLYLQMNSLRAEDTAVYYCARDFDYWGQGTLLTVTSSGG GSGGGGGGGGSQSVLTQPPSASGTPGQRVTISCSGSSNIIGNSV WVYQQLPGTAPKLLIYGNINRPGVPDRFSGSKSGTSASLAISGLRS EDEADYYCAAWDDSLNGRVFPGGGTKLTVL (SEQ ID NO: 65)	
PRO005	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKLE WVANINQDGSEKNYVDSMRGRFTIISRDNSKNTLYLQMNSLRAEDTA VYVYCAREFDYWGQGTLLTVTSSGGGGSGGGGGSGGGQSVLQAP PSASGTPGQRVTISCSGSSNIIGSNYVWYQQLPGTAPKLLIYQNNK RPSGVDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRV FGGGTKLTVLDKTHTCPCCPAPEAAAGAPSFLFPPKPKDTLMSRTPE VTCVVVDVSHDPEVFKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTBLHQDWLNGKEYKCKVSNKALPAPIEKTIASKAKGQPREPVYTLP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPVLD DGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSP GGGGGGGGSEVQLLIESGGGLVQPGGSLRLSCAASGFTFSYDYM TWIRQAPGKLEWVSSISGGSTYYADSRKGRTIISRDNSENTLYLQM NSLRAEDTAVYYCARDFGVAGWFQYGMDDWVGQGTLLTVTSSGG GSGGGGGGGGSQSVLTQPPSASGTPGQRVTISCTGSSNIAGAGYD WVYQQLPGTAPKLLIYRSNQRPSPGVDRFSGSKSGTSASLAISGLR EDEADYYCSSLQYAGNNLVFGGGTKLTVL (SEQ ID NO: 66)	

TABLE 2-continued

Bispecific antibodies to ALK1 and BMPRII constructs		
Antibody Designation	Amino acid sequence	
PRO006		
EVQLLESGGGLVQPGGSLRLSCAASGFTPSDYYMTWIRQAPGKGLE WVSSISGGSTYYADSRKGRTFISRDNSENTLYLQMNSLRAEDTAVYY CARDFGVAGWFQYGMDVWGQTLTVTSSGGGSGGGGSGGG SQSVLTQPPSASGTPGQRVTISCTGSSNIAGAGYDVHWYQQLPGTA PKLLIYRSNQRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCSSY AGNYNLVFGGGTKLTVLDKTHTCPCCPAPEAAGAPSVFLFPPPKDT LMISRTPEVTCVVVDVSHEDPEVKENWYVGVEVHNNAKTKPREEQY NSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVTLPSSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTPPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEALHNHY TQKSSLSPGGGGSGGGSEVQLESGGGLVQPGGSLRLSCAAS GFTFSSYAMSWRQAPGKGLEWVANINQDGSEKNYVDSMRGRFTIS RDNSKNTLYLQMNSLRAEDTAVYYCAREFDYWQQGTLVTVTSSGG GSGGGGGSGGGGSQSVLAQPPSASGTPGQRVTISCGSSNIGSNYV YWWQQLPGTAPKLLIYGNKRPSGVPDFSGSKSGTSASLAISGLRS EDEADYYCAAWDDSLNNGRVFGGGTKLTVL (SEQ ID NO: 67)		
DGL289		
EVQLLESGGGLVQPGGSLRLSCAASGFTPSIYAMSWVRQAPGKGLE WVSAISGGGSTYYADSVKGRTFISRDNSKNTLYLQMNSLRAEDTAV YYCARDFDYWGQGTIVLTVTSSPAPNLLGGPEVQLLESGGGLVQPGG SLRLSCAASGFTFSNAWMNWVRQAPGKGLEWVSSISSSSYIYAD SVKGRTFISRDN SKNTLYLQMNSLRAEDTAVYYCARAVAAGGMFWG LDQWGQGTIVLTVTSSASTKGPSVFLAPSSKSTSGGTAALGCLVKDY FPEPVTVWSNGALTSVHFTPAVLQSSGLYSLSVVTPVSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPCCPAPEAAGAPSVLF PPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEA LHNHYTQKSSLSPG (SEQ ID NO: 68) QSVLQPPSASGTPGQRVTISCGSSNI GSNYVWYQQLPGTAPKL LIYGNINRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCAAWDD SLNNGRVFGGGTKLTVLPAPNLLGGPQSVLTQPPSASGTPGQRVTISC SGSRSNIGNSNSVHWYQQLPGTAPKLLIYGNINRPSGVPDFSGSKS GTSASLAISGLRSEDEADYYCQSYDSLNDHVVFGGGKLTBLQPK AAPSVTLFPPSSEELQANKATLVCISDVFYPGAVTVANKADSSPVKAG VETTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEK TVAPTECS (SEQ ID NO: 69)		
DGL290		
EVQLLESGGGLVQPGGSLRLSCAASGFTPSNAWMNWVRQAPGKGL EWVSSISSSSYIYADSVKGRTFISRDN SKNTLYLQMNSLRAEDTAV YYCARAVAAGGMFWGLDQWGQGTIVLTVTSSPAPNLLGGPEVQLLE SGGGLVQPGGSLRLSCAASGFTPSIYAMSWVRQAPGKGLEWVSAIS GSGGSTYYADSVKGRTFISRDN SKNTLYLQMNSLRAEDTAVYYCARD FDYWGQGTIVLTVTSSASTKGPSVFLAPSSKSTSGGTAALGCLVKDY FPEPVTVWSNGALTSVHFTPAVLQSSGLYSLSVVTPVSSSLGTQ TYICNVNHKPSNTKVDKKVEPKSCDKTHTCPCCPAPEAAGAPSVLF PPKPKDTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNNAKTK PREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK AKGQPREPQVYTLPPSSRDELTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCVMHEA LHNHYTQKSSLSPG (SEQ ID NO: 70) QSVLQPPSASGTPGQRVTISCGSRNSNIGNSNSVHWYQQLPGTAPKL LIYGNINRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCQSYDS SLNDHVVFGGGKLTBLVLPAPNLLGGPQSVLTQPPSASGTPGQRVTIS CGSSSNIGNSNYVWYQQLPGTAPKLIIYGNINRPSGVPDFSGSKS GTSASLAISGLRSEDEADYYCAAWDDSLNNGRVFGGGKLTBLQPK AAPSVTLFPPSSEELQANKATLVCISDVFYPGAVTVANKADSSPVKAG VETTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEK TVAPTECS (SEQ ID NO: 71)		

TABLE 2-continued

<u>Bispecific antibodies to ALK1 and BMPRII constructs</u>		
Antibody Designation	Amino acid sequence	
DGL291	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLE WVANINQDGSEKNYVDMSMRGFTISRDNSKNTLYLQMNSLRAEDTA VYYCAREFDYWGQGTIVTVTSSPAPNLLGGPEVOLLESGGGLVQPG GSLRLSCAASGFTSDYMTWIRQAPGKGLEWVSIISGGSTYYADS RKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDFGVAGWFQY GMDVWGQGTIVTVSASTKGPSVFLAPSSKSTSGGTAALGCLVKD YFPEPVTVSNWSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGT QTYICNVNHPNSNTKVDKVEPKSCDKTHTCPPCPAPEAAAGAPSVFL FPPPKDTLMISRTPETCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI KAKGQPREPVYTLPPSRDELTKNQVSLSCLVKGFYPSDIAVEWESN GQPEMNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNFSCSVMHE ALHNHYTQKSLSLSPG (SEQ ID NO: 72) QSVLAQPPSASGTPGQRTVTISCGSSSNIGSNVYVYQQLPGTAPKL LIYGNNKRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCAAWDD SLNDRVFGGGTKLTVLPAPNLLGGPQSVLTQPPSASGTGQRTVITSC TGSSSNIGAGYDVWYQQLPGTAPKLLIYRSNQPSGVPDFSGSK SGTSASLAISGLRSEDEADYYCSSYAGNNYLNVPGGTKLTVLGQPKA APSVTLFPPSSEELQANKATLVCILSDFYPGAVTVAWKADSSPVKAGV ETTPSKQSNKKAASSYSLTPEQWKSHRSYSQCQVTHEGSTVEKT VAPTECS (SEQ ID NO: 73)	
DGL292	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYMTWIRQAPGKGLE WVSSISGGSTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYY CARDFGVAGWFQYGMWDVGQGTIVTVSSPAPNLLGGPEVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVANIN QDGSEKNYVDMSMRGFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR EFDYWGQGTIVTVSASTKGPSVFLAPSSKSTSGGTAALGCLVKD YFPEPVTVSNWSGALTSGVHTFPAVLQSSGLYSLSVVTVPSSSLGT QTYICNVNHPNSNTKVDKVEPKSCDKTHTCPPCPAPEAAAGAPSVFL FPPPKDTLMISRTPETCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI KAKGQPREPVYTLPPSRDELTKNQVSLSCLVKGFYPSDIAVEWESN GQPEMNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNFSCSVMHE ALHNHYTQKSLSLSPG (SEQ ID NO: 74) QSVLQOPPSASGTPGQRTVTISCTGSSSNIGAGYDVWYQQLPGTAP KLLIYRSNQPSGVPDFRGSGSKSGTSASLAISGLRSEDEADYYCSSY GNYNLVFGGGTKLTVLPAPNLLGGPQSVLAQPSASGTGQRTVITSC SGSSSNIGSNVYVYQQLPGTAPKLLIYGNKNRPSGVPDFSGSKS GTSASLAISGLRSEDEADYYCAAWDDSLNDRVFGGGTKLTVLGQPK AAPSVTFLFPPSSEELQANKATLVCILSDFYPGAVTVAWKADSSPVKAG VETTPSKQSNKKAASSYSLTPEQWKSHRSYSQCQVTHEGSTVEKT VAPTECS (SEQ ID NO: 75)	

Example 2. Screen for Agonistic Activity

[0377] The bispecific antibodies were screened for agonist activity. PathHunter U2Os ALK-1/BMPR-2 dimerization assay was obtained from DiscoverX Corporation (93-096203). These cells use Enzyme Fragment Complementation (EFC) technology using β -galactosidase fragments to evaluate protein-protein interactions. Reporter cells were revived and cultured according to supplier's recommendations. Bispecific antibodies were compared to the natural ligands, BMP9 and BMP10.

[0378] To perform the assay, cells were detached and removed from the flask with cell detachment reagent (DiscoverX, 92-0009). Cells were spun at 300 g for four minutes and resuspended at a density of 250K/ml in assay plating media (DiscoverX 93-0563R22A). 20 μ l of the suspension were plated/well of a 384 well plate and incubated at 37° C. for 24 hours. Bispecifics were made at 5 \times the final concentration. 12-point titrations using a 1:10 dilution were done to generate curves. 5 μ l of the bispecific was added to the 384 well plate and incubated for three hours. 25 μ l of flash

detection reagent (DiscoverX, 93-0247) was added/well and the plates were read on a Verilux Skan at 60 minutes. Data was analyzed using PRISM.

TABLE 3

Agonist activity of the bispecific antibody constructs			
	EC50 (nM)	EMAX (RLU)	% Emax BMP9
BMP9	0.02	2639991	100
BMP10	0.1	2570138	97
DGL266	2.0	1040871	39
DGL267	0.9	1225023	46
DGL268	0.1	35238	1
DGL269	ND	-8297	0
DGL270	ND	9205	0
DGL271	ND	55926	2
DGL273	4.2	1223399	46
DGL274	1.7	1251235	47
DGL275	0.9	1279811	48
DGL276	1.2	1143824	43
DGL277	1.0	1345570	51

TABLE 3-continued

Agonist activity of the bispecific antibody constructs			
	EC50 (nM)	EMAX (RLU)	% Emax BMP9
DGL278	14	683855	26
DGL279	ND	ND	ND
DGL281	330	1105548	42
DGL282	170	954074	36
DGL283	28	879452	33
DGL284	1.0	1302185	49
DGL285	0.08	1470045	56
DGL286	0.2	1800963	68
DGL287	0.04	1255425	48
DGL288	0.07	1997935	76
DGL289	2.4	1800109	68
DGL290	5.3	1818708	69
DGL291	0.2	951876	36
DGL292	0.09	1957874	74
PRO003	0.1	1247113	47
PRO004	0.5	1214568	46
PRO005	0.075	931154	35
PRO006	0.1	929009	35

[0379] It was observed that the bispecific antibodies in the tetravalent form (i.e., two binding domains for ALK1 and two binding domains for BMPRII) elicited stronger agonism than bispecific antibodies in a divalent form (i.e., one binding domain for ALK1 and one binding domain for BMPRII). The divalent bispecific antibodies are DGL266-DGL271, which had 0-46% of the activity of BMP9, while the tetravalent bispecific antibodies, such as DGL285-DGL292 consistently yielded higher values. It was unexpectedly discovered that tetravalent bispecific antibodies having, from N-terminus to C-terminus, the BMPRII binding domain then the ALK1 binding domain, had substantially higher agonism relative to tetravalent bispecific antibodies having, from N-terminus to C-terminus, the ALK1 binding domain then the BMPRII binding domain. The data above is recapitulated below to compare bispecific antibodies with the two different orientations.

ID	ALK1 binder	BMPRII binder	Orientation (N-terminus to C-terminus)	% BMP9
DGL285	scFv1	scFv8	ALK1/BMPRII	56
DGL286	scFv1	scFv8	BMPRII/ALK1	68
DGL287	scFv29	scFv36	ALK1/BMPRII	48
DGL288	scFv29	scFv36	BMPRII/ALK1	76
DGL289	scFv1	scFv8	ALK1/BMPRII	68
DGL290	scFv1	scFv8	BMPRII/ALK1	69
DGL291	scFv29	scFv36	ALK1/BMPRII	36
DGL292	scFv29	scFv36	BMPRII/ALK1	74

[0380] The effect was observed in a dual scFv tetravalent format and a DVD-Ig format. Bispecific antibodies DGL285-288 are in the dual scFv tetravalent format, and DGL289-292 are in the DVD-Ig format.

[0381] The dual scFv tetravalent format comprises two polypeptide chains, each chain, from N-terminus to C-terminus, comprising a first scFv against a first target of either ALK1 or BMPRII, a second scFv against a second target of either ALK1 or BMPRII, and a Fc domain. The first target and second target are different, such that if the first target is BMPRII, the second target is ALK1. A linker, such as the modified hinge described herein, may be used to link the first scFv to the second scFv.

[0382] The DVD-Ig format comprises four polypeptide chains. The first and second polypeptide chains each comprise, from N-terminus to C-terminus, a first VH (VH1), a second VH (VH2), and an Fc domain. The third and fourth polypeptide chains each comprise, from N-terminus to C-terminus, a first VL (VL1) and a second VL (VL2). VH1 and VL1 form a first binding domain against a first target of either ALK1 or BMPRII, and VH2 and VL2 form a second binding domain against a second target of either ALK1 or BMPRII. The first target and second target are different, such that if the first target is BMPRII, the second target is ALK1. A linker, such as the modified hinge described herein, may be used to link the VH1 to the VH2 and/or the VL1 to the VL2.

Example 3: Measurement of pSMAD in HUVEC Cells

[0383] HUVEC cells from ATCC (CRL-1730) were plated at 15K cells per well of a 96 well plate in 100 μ l of complete HUVEC media overnight (F12K (Corning, 10-025-CV), 10% FBS (Gibco, A31605-02), ECGS (30 μ g/ml, Corning, 356006), 0.1 mg/ml Heparin (Sigma, H3393), 1×Pen/Strep (Gibco, 15140-122). The following morning, cells were starved for 4 hours by replacing media with 50 μ l serum free/ECGS free F12K media. Cells were then treated with 50 μ l of serum free/ECGS free media containing 2× concentration dose curve of the bispecifics or BMP ligands. At various time points (5, 15, 30, 60 min) media was removed from cells and 50 μ l lysis buffer (Abcam ELISA kit, AB186037) was added per well. After lysis, buffer from four wells were pooled for a single 200 μ l lysed sample per condition, which was frozen and later run on ELISAs measuring either total SMAD1 (Abcam, AB186037) or pSMAD1 (Abcam, AB186036). As a negative control, an anti-HEL antibody with LALA-PG mutations (BioXCell, CP149) was used.

TABLE 4

Phosphorylation of SMAD1 following treatment with bispecific antibodies.			
	Concentration of ligand or antibody (nM)	RLU 15 minutes	RLU 60 minutes
BMP9	1	105.7	81.8
BMP9	0.2	102.2	83.2
BMP9	0.04	101.4	81.8
BMP9	0	4.9	6.1
DGL286	10	4.9	10.6
DGL286	2	4.7	9.3
DGL286	0.4	4.4	7.0
DGL286	0	4.6	4.5
DGL288	10	6.7	22.7
DGL288	2	6.5	26.9
DGL288	0.4	4.9	35.0
DGL288	0	4.5	4.5
DGL289	10	4.7	6.9
DGL289	2	4.4	5.2
DGL289	0.4	4.4	5.0
DGL289	0	4.6	4.4
DGL292	10	6.7	33.9
DGL292	2	5.7	32.3
DGL292	0.4	4.6	23.7

TABLE 4-continued

Phosphorylation of SMAD1 following treatment with bispecific antibodies.			
	Concentration of ligand or antibody (nM)	RLU 15 minutes	RLU 60 minutes
DGL292	0	4.6	4.4
Control	10	4.7	4.5
Control	2	4.8	4.6
Control	0.4	4.5	4.5
Control	0	4.7	4.5

Example 4: Measurement of in Vivo Activity

[0384] Antibodies were measured for agonistic activity in a mouse model of HHT wherein circulating BMP9/BMP10 were neutralized by anti-BMP9/10 antibodies (Ruiz S, et al, Scientific Reports, 2016 Nov. 22: 5:37366). These mice develop vascular defects in the postnatal retina. Three animals were dosed with either DGL288 or a negative control antibody (Anti-HEL, LALA-PG, BioXCell, CP149) for two days, P3 and P4, at 15 mg/kg/day. BMP9/10 antibodies were dosed on the same days. Analysis was completed on P6. Retinas were dissected and whole-mount prepared, then stained with both isolectin B4 and SMA to label retinal

vasculature and detect arteriovenous malformations (AVMs). Results are in FIG. 3A. Mice dosed with DGL288 showed no formation of AVMs, whereas the negative control showed an average of 4.8 AVMs/retina.

[0385] For the second set of experiments, all animals were dosed with BMP9/10 antibodies on P3 and P4. DGL288, DGL292 or PBS control were dosed at 1 mg/kg/day on P4 and P5. Analysis was completed on P6 for DGL288 and the littermate negative control animals, or P7 for DGL292 and littermates dosed with the PBS control. Retinas were dissected and whole-mount prepared, then stained with both isolectin B4 and SMA to detect AVMs. Mice dosed with DGL292 did not form AVMs, compared with an average of 5.7/retina for the controls (FIG. 3B). Mice dosed with DGL288 did not form AVMs, compared with an average of 4.5/retina for the controls (FIG. 30). No differences in body weight were observed, suggesting that the agonists are well tolerated.

Example 5: Additional Engineering of Binders

[0386] Based on structural modeling of the receptor/antibody complex, the binders were engineered to further optimize the complementary regions of the binding to the antigen. Both ALK1 and BMPRII variants were designed for improved potency and/or stability.

TABLE 5

Optimized ALK1 and BMPRII binders.

Alk1_platform_1	EVQLLESGGGLVQPGGSRLSCAASGFTFSYAMSWVRQAPGKLEW VSAISGSGGVYYADSVKGRTFISRDNISKNTLYLQMNSLRAEDTAVY YCAREFDWWGQGTIVTVTSGGGGSGGGGSQQSVLTQPPSASG TPGQRVTISCSSSNIGSNVYVWQQLPGTAPKLLIYGNINRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNNGRVFGGGTK LTVLDKTHTCPPCPAPEAAAGAPSVPFLFPKPKDITLMISRTPEVTCVV VDVSHEDPVKFNWYVGVEVHNAKTPREEQYNSTYRVVSVLTVLH QDWLNKEYCKCVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMEHALHNHYTQKSLSSLSPGEPEA (SEQ ID NO: 76)
Alk1_platform_2	EVQLLESGGGLVQPGGSRLSCAASGFTFSYAMSWVRQAPGKLEW VSAISGSGGVYYADSVKGRTFISRDNISKNTLYLQMNSLRAEDTAVY YCAREFDWWGQGTIVTVTSGGGGSGGGGGGGGSQQSVLTQPPSASG TPGQRVTISCSSSNIGSNVYVWQQLPGTAPKLLIYGNINRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNNGRVFGGGTK LTVLDKTHTCPPCPAPEAAAGAPSVPFLFPKPKDITLMISRTPEVTCVV VDVSHEDPVKFNWYVGVEVHNAKTPREEQYNSTYRVVSVLTVLH QDWLNKEYCKCVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMEHALHNHYTQKSLSSLSPGEPEA (SEQ ID NO: 77)
Alk1_platform_3	EVQLLESGGGLVQPGGSRLSCAASGFTFSYAMSWVRQAPGKLEW VSAISGSGGVYYADSVKGRTFISRDNISKNTLYLQMNSLRAEDTAVY YCAREFDWWGQGTIVTVTSGGGGSGGGGGGGGSQQSVLTQPPSASG TPGQRVTISCSSSNIGSNVYVWQQLPGTAPKLLIYGNINRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNNGRVFGGGTK LTVLDKTHTCPPCPAPEAAAGAPSVPFLFPKPKDITLMISRTPEVTCVV VDVSHEDPVKFNWYVGVEVHNAKTPREEQYNSTYRVVSVLTVLH QDWLNKEYCKCVSNKALPAPIEKTISKAKGQPREPQVYTLPPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMEHALHNHYTQKSLSSLSPGEPEA (SEQ ID NO: 78)
Alk1_platform_4	EVQLLESGGGLVQPGGSRLSCAASGFTFSYAMSWVRQAPGKLEW VANINQDGSEKNYVDSMRGRTFISRDNISKNTLYLQMNSLRAEDTAVY YCAREFDWWGQGTIVTVTSGGGGSGGGGGGGGSQQSVLAQPPSASG TPGQRVTISCSSSNIGSNVYVWQQLPGTAPKLLIYGNINRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNNGRVFGGGTK

TABLE 5-continued

Optimized ALK1 and BMPRII binders.

LTVLDKTHTCPCPAPEAAGAPSFLFPPPKDTLMSIRTPETCVV
 VDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVSVS^LTVL^H
 QDWLN^GKEYCKC^VS^NK^LP^AI^EK^TI^SKAKGQPREQPVYTL^LPCRDE
 LTKNQVSLWCLVKGFYPSDIAVEWE^SNQ^PENNYKT^TTPV^LSDGSF
 FLYSKLTVDKSRWQOGNVFSCVMHEALHNHYTQKSLSLSPGEPEA
 (SEQ ID NO: 79)

Alk1_platform_5

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMS^WVRQAPGKGLEW
 VANINQDGSEK^NYVDSMGRFTI^SRDN^SKNTLYLQMNSLRAE^DTAVY
 YCARDY^WVGQ^GTLVT^TSSGGGGSGGGSGGGSQ^SVLAQ^QPPSASG
 TPGQRVTI^SCGSSSNIGSNVY^WYQ^LPGTAP^KL^IIYGN^NKRPSGV
 PDRFSGSKSGTSASLAI^SGLRSEDEADYYCAAWDD^SLNGR^FGGGT^K
 LTVL^DKTHTC^PCPAPEAAGAPSFLFPPPKDTLMSIRTPETCVV
 VDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVSV^STVL^H
 QDWLN^GKEYCKC^VS^NK^LP^AI^EK^TI^SKAKGQPREQPVYTL^LPCRDE
 LTKNQVSLWCLVKGFYPSDIAVEWE^SNQ^PENNYKT^TTPV^LSDGSF
 FLYSKLTVDKSRWQOGNVFSCVMHEALHNHYTQKSLSLSPGEPEA
 (SEQ ID NO: 80)

Alk1_platform_6

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMS^WVRQAPGKGLEW
 VANINQDGSEK^NYVDSMGRFTI^SRDN^SKNTLYLQMNSLRAE^DTAVY
 YCAREYQ^WVGQ^GTLVT^TSSGGGGSGGGSGGGSQ^SVLAQ^QPPSASG
 TPGQRVTI^SCGSSSNIGSNVY^WYQ^LPGTAP^KL^IIYGN^NKRPSGV
 PDRFSGSKSGTSASLAI^SGLRSEDEADYYCAAWDD^SLNGR^FGGGT^K
 LTVL^DKTHTC^PCPAPEAAGAPSFLFPPPKDTLMSIRTPETCVV
 VDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVSV^STVL^H
 QDWLN^GKEYCKC^VS^NK^LP^AI^EK^TI^SKAKGQPREQPVYTL^LPCRDE
 LTKNQVSLWCLVKGFYPSDIAVEWE^SNQ^PENNYKT^TTPV^LSDGSF
 FLYSKLTVDKSRWQOGNVFSCVMHEALHNHYTQKSLSLSPGEPEA
 (SEQ ID NO: 81)

Alk1_platform_7

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMS^WVRQAPGKGLEW
 VANINQDGSEK^NYVDSMGRFTI^SRDN^SKNTLYLQMNSLRAE^DTAVY
 YCAREYQ^WVGQ^GTLVT^TSSGGGGSGGGSGGGSQ^SVLAQ^QPPSASG
 TPGQRVTI^SCGSSSNIGSNVY^WYQ^LPGTAP^KL^IIYGN^NKRPSGV
 PDRFSGSKSGTSASLAI^SGLRSEDEADYYCAAWDD^SLNGR^FGGGT^K
 LTVL^DKTHTC^PCPAPEAAGAPSFLFPPPKDTLMSIRTPETCVV
 VDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVSV^STVL^H
 QDWLN^GKEYCKC^VS^NK^LP^AI^EK^TI^SKAKGQPREQPVYTL^LPCRDE
 LTKNQVSLWCLVKGFYPSDIAVEWE^SNQ^PENNYKT^TTPV^LSDGSF
 FLYSKLTVDKSRWQOGNVFSCVMHEALHNHYTQKSLSLSPGEPEA
 (SEQ ID NO: 82)

Alk1_platform_8

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMS^WVRQAPGKGLEW
 VANINQDGSEK^NYVDSMGRFTI^SRDN^SKNTLYLQMNSLRAE^DTAVY
 YCARNYQ^WVGQ^GTLVT^TSSGGGGSGGGSGGGSQ^SVLAQ^QPPSASG
 TPGQRVTI^SCGSSSNIGSNVY^WYQ^LPGTAP^KL^IIYGN^NKRPSGV
 PDRFSGSKSGTSASLAI^SGLRSEDEADYYCAAWDD^SLNGR^FGGGT^K
 LTVL^DKTHTC^PCPAPEAAGAPSFLFPPPKDTLMSIRTPETCVV
 VDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVSV^STVL^H
 QDWLN^GKEYCKC^VS^NK^LP^AI^EK^TI^SKAKGQPREQPVYTL^LPCRDE
 LTKNQVSLWCLVKGFYPSDIAVEWE^SNQ^PENNYKT^TTPV^LSDGSF
 FLYSKLTVDKSRWQOGNVFSCVMHEALHNHYTQKSLSLSPGEPEA
 (SEQ ID NO: 83)

Alk1_platform_9

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMS^WVRQAPGKGLEW
 VANINQDGSEK^NYVDSMGRFTI^SRDN^SKNTLYLQMNSLRAE^DTAVY
 YCARNYQ^WVGQ^GTLVT^TSSGGGGSGGGSGGGSQ^SVLAQ^QPPSASG
 TPGQRVTI^SCGSSSNIGSNVY^WYQ^LPGTAP^KL^IIYGN^NKRPSGV
 PDRFSGSKSGTSASLAI^SGLRSEDEADYYCAAWDD^SLNGR^FGGGT^K
 LTVL^DKTHTC^PCPAPEAAGAPSFLFPPPKDTLMSIRTPETCVV
 VDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVSV^STVL^H
 QDWLN^GKEYCKC^VS^NK^LP^AI^EK^TI^SKAKGQPREQPVYTL^LPCRDE
 LTKNQVSLWCLVKGFYPSDIAVEWE^SNQ^PENNYKT^TTPV^LSDGSF
 FLYSKLTVDKSRWQOGNVFSCVMHEALHNHYTQKSLSLSPGEPEA
 (SEQ ID NO: 84)

Alk1_platform_10

EVQLLESGGGLVQPGGSLRLSCAASGFTFSIYAMS^WVRQAPGKGLEW
 VSAISGG^STYYADSVKGRFTI^SRDN^SKNTLYLQMNSLRAE^DTAVY
 YCARDGLY^WVGQ^GTLVT^TSSGGGGSGGGSGGGSQ^SVLTQ^QPPSASG
 TPGQRVTI^SCGSSSNIGSNVY^WYQ^LPGTAP^KL^IIYGN^NKRPSGV
 PDRFSGSKSGTSASLAI^SGLRSEDEADYYCAAWDD^SLNGR^FGGGT^K
 LTVL^DKTHTC^PCPAPEAAGAPSFLFPPPKDTLMSIRTPETCVV
 VDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVSV^STVL^H
 QDWLN^GKEYCKC^VS^NK^LP^AI^EK^TI^SKAKGQPREQPVYTL^LPCRDE

TABLE 5-continued

Optimized ALK1 and BMPRII binders.

	LTKNQVSLWCLVKGFYPSDIAVEWESNGOPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 85)
Alk1_platform_11	EVQLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARNGLYWQGTLTVTSSGGGGGGGGGGGGGGSQSVLTQPPSASG TPGQRTVTCSCGSSSNIGSNYVWYQQLPGTAPKLLIYGNINRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFGGGTK LTVIDKTHTCPCPAPEAACAPSFLFPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISAKGQPREPQVYTLPPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESNGOPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 86)
Alk1_platform_12	EVQLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARNGLYWQGTLTVTSSGGGGGGGGGGGGGGGGSQSVLTQPPSASG TPGQRTVTCSCGSSSNIGSNYVWYQQLPGTAPKLLIYGNINRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFGGGTK LTVIDKTHTCPCPAPEAACAPSFLFPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISAKGQPREPQVYTLPPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESNGOPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 87)
Alk1_platform_13	EVQLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARNGLDFWQGTLTVTSSGGGGGGGGGGGGGGGGSQSVLTQPPSASG TPGQRTVTCSCGSSSNIGSNYVWYQQLPGTAPKLLIYGNINRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFGGGTK LTVIDKTHTCPCPAPEAACAPSFLFPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISAKGQPREPQVYTLPPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESNGOPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 88)
Alk1_platform_14	EVQLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKLEW VSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARDYLYWQGTLTVTSSGGGGGGGGGGGGGGGGSQSVLTQPPSASG TPGQRTVTCSCGSSSNIGSNYVWYQQLPGTAPKLLIYGNINRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFGGGTK LTVIDKTHTCPCPAPEAACAPSFLFPKPKDTLMISRTPEVTCVV VDVSHEDPEVKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISAKGQPREPQVYTLPPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESNGOPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 89)
Alk1_platform_15	EVQLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKLEW VANIKQDGSEKNYVDSMRGFTISRDNSKNTLYLQMNSLRAEDTAVY YCAREYDYWQGTLTVTSSGGGGGGGGGGGGGGGGSQSVLAQPPSASGT PGQRTVTCSCGSSSNIGSNYVWYQQLPGTAPKLLIYGNNKRPSGV DRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFGGGTKL TVLDKTHTCPCPAPEAACAPSFLFPKPKDTLMISRTPEVTCVV DVSHEDEPVFKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISAKGQPREPQVYTLPPCRDEL TKNQVSLWCLVKGFYPSDIAVEWESNGOPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 90)
Alk1_platform_16	EVQLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKLEW VANINQDGSEKYYVDSMRGFTISRDNSKNTLYLQMNSLRAEDTAVY YCAREYDYWQGTLTVTSSGGGGGGGGGGGGGGSQSVLAQPPSASGT PGQRTVTCSCGSSSNIGSNYVWYQQLPGTAPKLLIYGNNKRPSGV DRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFGGGTKL TVLDKTHTCPCPAPEAACAPSFLFPKPKDTLMISRTPEVTCVV DVSHEDEPVFKFNWYVDGVEVHNATKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISAKGQPREPQVYTLPPCRDEL TKNQVSLWCLVKGFYPSDIAVEWESNGOPENNYKTTPPVLDSDGSFF LYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 91)

TABLE 5-continued

 Optimized ALK1 and BMPRII binders.

ALK1_platform_17	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYMSWVRQAPGKLEW VANIKQDGSEKNYVDSMRGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCAREFDPWGQGTIVTWTSGGGGGGGGSQSVLAQPPSASGT PGQRVTISCSGSSSNIGSNVYVYQQLPGTAPKLIIYGNKNKRPSGV DRFSGSKSGTSASLAIISGLRSEDEADYYCAAWDDSLNGRVFGGGTLK TVLVDKTHTCPPCAPEAAAGAPSVLFPFPKPDKTLMISRTPEVTCVV DVSHEDPEVKFNWYVTDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYCKVSNKALPAPIEKTISAKGQPREPVYTLPPCRDEL TKNQVSLWLKVGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 92)
ALK1_platform_18	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYMSWVRQAPGKLEW VANINQDGSEKNYVDSMRGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCAREFDWWGQGTIVTWTSGGGGGGGGGGGGGGSQSVLAQPPSASG TPGQRVTISCSGSSSNIGSNVYVYQQLPGTAPKLIIYGNKNKRPSGV PDRFSGSKSGTSASLAIISGLRSEDEADYYCAAWDDSLNGRVFGGGTLK TVLVDKTHTCPPCAPEAAAGAPSVLFPFPKPDKTLMISRTPEVTCVV DVSHEDPEVKFNWYVTDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGWCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 93)
ALK1_platform_19	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYMSWVRQAPGKLEW VANINQDGSEKNYVDSMRGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCAREFDWWGQGTIVTWTSGGGGGGGGGGGGGGSQSVLAQPPSASG TPGQRVTISCSGSSSNIGSNVYVYQQLPGTAPKLIIYGNKNKRPSGV PDRFSGSKSGTSASLAIISGLRSEDEADYYCAAWDDSLNGRVFGGGTLK TVLVDKTHTCPPCAPEAAAGAPSVLFPFPKPDKTLMISRTPEVTCVV DVSHEDPEVKFNWYVTDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYCKVSNKALPAPIEKTISAKGQPREPVYTLPPCRDEL TKNQVSLWLKVGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 94)
BMPRII_platform_1	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKLEW VSSISGGSTTYADSRKGRTISRDNSENTLYLQMNSLRAEDTAVYYC ARDFGVAGWFGQYGMWDVGQGTIVTWTSGGGGGGGGGGGGSQSVL TQPSASGTPGQRVTISCTGSSSNIGAGYDVHNVYQQLPGTAPKLIIY RSNQRPSCGPDRFSGSKSGTSASLAIISGLRSEDEADYYCSSLQAGYN LVFGGGTQLTVLDKTHTCPPCAPEAAAGAPSVLFPFPKPDKTLMISR TPEVTCVVVDVSHEDPEVKFNWYVTDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISAKGQPREPVQC TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPP VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGWSHPQFEK (SEQ ID NO: 95)
BMPRII_platform_2	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKLEW VSSISGGSTTYADSRKGRTISRDNSENTLYLQMNSLRAEDTAVYYC ARWETSSGGFGSGGLSHWGQGTIVTWTSGGGGGGGGGGGGSQSVL TQPSASGTPGQRVTISCTGSSSNIGAGYDVHNVYQQLPGTAPKLIIY RSNQRPSCGPDRFSGSKSGTSASLAIISGLRSEDEADYYCSSLQAGYN LVFGGGTQLTVLDKTHTCPPCAPEAAAGAPSVLFPFPKPDKTLMISR TPEVTCVVVDVSHEDPEVKFNWYVTDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISAKGQPREPVQC TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPP VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGWSHPQFEK (SEQ ID NO: 96)
BMPRII_platform_3	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKLEW VSSISGGSTTYADSRKGRTISRDNSENTLYLQMNSLRAEDTAVYYC ARLTVDGGGYGSGGLDLWQGQGTIVTWTSGGGGGGGGGGGGSQSVL TQPSASGTPGQRVTISCTGSSSNIGAGYDVHNVYQQLPGTAPKLIIY RSNQRPSCGPDRFSGSKSGTSASLAIISGLRSEDEADYYCSSLQAGYN LVFGGGTQLTVLDKTHTCPPCAPEAAAGAPSVLFPFPKPDKTLMISR TPEVTCVVVDVSHEDPEVKFNWYVTDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYCKVSNKALPAPIEKTISAKGQPREPVQC TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPP VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGWSHPQFEK (SEQ ID NO: 97)
BMPRII_platform_4	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKLEW VSSISGGSTTYADSRKGRTISRDNSENTLYLQMNSLRAEDTAVYYC ARNEVSGGGYGEFGLSLWQGQGTIVTWTSGGGGGGGGGGSQSVL

TABLE 5-continued

Optimized ALK1 and BMPRII binders.

TABLE 5-continued

 Optimized ALK1 and BMPRII binders.

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SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIASKGQPREPQ
VCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGWSHPQFEK (SEQ ID NO: 104)

BMPRII_platform_11 EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMNWVRQAPGKGLEW
VSSISSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY
YCARAVAGTSMWYGLDQWGQGTIVTWTSSGGGGGGGGGGGGQSV
LTQPPSASGTPGQRVTISCSGSRSNIGNSNSVHWYQQLPGTAPKLLIY
GNSNRPSPGVDPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSLN
DHVPGGGTKLTVLDKTHTCPCCPAPEAAGAPSFLFPFPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIASKGQPREPQ
VCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGWSHPQFEK (SEQ ID NO: 105)

BMPRII_platform_12 EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMNWVRQAPGKGLEW
VSSISSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY
YCARAVAGGFWGLDQWGQGTIVTWTSSGGGGGGGGGGGGQSV
LTQPPSASGTPGQRVTISCSGSRSNIGNSNSVHWYQQLPGTAPKLLIY
GNSNRPSPGVDPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSLN
DHVPGGGTKLTVLDKTHTCPCCPAPEAAGAPSFLFPFPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIASKGQPREPQ
VCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGWSHPQFEK (SEQ ID NO: 106)

BMPRII_platform_13 EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMNWVRQAPGKGLEW
VSSISSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY
YCARAVAAGGFWGLDQWGQGTIVTWTSSGGGGGGGGGGGGQSV
LTQPPSASGTPGQRVTISCSGSRSNIGNSNSVHWYQQLPGTAPKLLIY
GNSNRPSPGVDPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSLN
DHVPGGGTKLTVLDKTHTCPCCPAPEAAGAPSFLFPFPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIASKGQPREPQ
VCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGWSHPQFEK (SEQ ID NO: 107)

BMPRII_platform_14 EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMNWVRQAPGKGLEW
VSSISSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY
YCARAVAAGGFWGLDQWGQGTIVTWTSSGGGGGGGGGGGGQSV
LTQPPSASGTPGQRVTISCSGSRSNIGNSNSVHWYQQLPGTAPKLLIY
GNSNRPSPGVDPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSLN
DHVPGGGTKLTVLDKTHTCPCCPAPEAAGAPSFLFPFPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIASKGQPREPQ
VCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGWSHPQFEK (SEQ ID NO: 108)

BMPRII_platform_15 EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMNWVRQAPGKGLEW
VSSISSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY
YCARAVAAGGMFWGLDQWGQGTIVTWTSSGGGGGGGGGGGGQSV
LTQPPSASGTPGQRVTISCSGSRSNIGNSNSVHWYQQLPGTAPKLLIY
GNSNRPSPGVDPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSLN
DHVPGGGTKLTVLDKTHTCPCCPAPEAAGAPSFLFPFPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIASKGQPREPQ
VCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTT
PPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGWSHPQFEK (SEQ ID NO: 109)

BMPRII_platform_16 EVQLLESGGGLVQPGGSLRLSCAASGFTFSNAWMNWVRQAPGKGLEW
VSSISSSSYIYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY
YCARAVAAGGFWGLDQWGQGTIVTWTSSGGGGGGGGGGGGQSV
LTQPPSASGTPGQRVTISCSGSRSNIGNSNSVHWYQQLPGTAPKLLIY
GNSNRPSPGVDPDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSLN
DHVPGGGTKLTVLDKTHTCPCCPAPEAAGAPSFLFPFPKPKDTLMI
SRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTY
RVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIASKGQPREPQ
VCTLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTT
  
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TABLE 5-continued

 Optimized ALK1 and BMPRII binders.

PVVLSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL
SLSPGWHPQFEK (SEQ ID NO: 110)

BMPRII_platform_17 EVQLLESGGGLVQPGGSLRLSCAASGFTFSYDYYMNWIRQAPGKGLEW
VSSISGGSTTYADSVKGRFTISRDNSENTLYLQMNSLRAEDTAVYYC
ARDFGVAGWFGQYGMDEVWGQGTLTVTSSGGGGGGGGGGGGGSQSVL
TQPPSASGTPGQRVTISCTGSSNIAGAGYDVHWYQQLPGTAPKLLIY
RSNQRPSPGVDRFSGSKSGTSASLAISGLRSEDEAQYCSSYAGNN
LVFGGGTKLTVDKLTHTCPCCPAPEAAGAPSFLFPPPKDKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVGVEVHNNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVC
TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPPP
VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGWHPQFEK (SEQ ID NO: 111)

BMPRII_platform_18 EVQLLESGGGLVQPGGSLRLSCAASGFTFSYDYYMNWIRQAPGKGLEW
VSSISGGSTTYADSVKGRFTISRDNSENTLYLQMNSLRAEDTAVYYC
ARDFGVAGWFGQYGMDEVWGQGTLTVTSSGGGGGGGGGGGGGSQSVL
TQPPSASGTPGQRVTISCTGSSNIAGAGYDVHWYQQLPGTAPKLLIY
RSNQRPSPGVDRFSGSKSGTSASLAISGLRSEDEAQYCSSYAGNN
LVFGGGTKLTVDKLTHTCPCCPAPEAAGAPSFLFPPPKDKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVGVEVHNNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVC
TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPPP
VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGWHPQFEK (SEQ ID NO: 112)

BMPRII_platform_19 EVQLLESGGGLVQPGGSLRLSCAASGFTFSYDYYMTWIRQAPGKGLEW
VSSISGGSTTYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYC
ARDFGVAGWFGQYGMDEVWGQGTLTVTSSGGGGGGGGGGGGGSQSVL
TQPPSASGTPGQRVTISCTGSSNIAGAGYDVHWYQQLPGTAPKLLIY
RSNQRPSPGVDRFSGSKSGTSASLAISGLRSEDEAQYCSSYAGNN
LVFGGGTKLTVDKLTHTCPCCPAPEAAGAPSFLFPPPKDKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVGVEVHNNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVC
TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPPP
VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGWHPQFEK (SEQ ID NO: 113)

BMPRII_platform_20 EVQLLESGGGLVQPGGSLRLSCAASGFTFSYDYYMTWIRQAPGKGLEW
VSSISGGSTTYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYC
ARDFGVAGWFGQYGMDEVWGQGTLTVTSSGGGGGGGGGGGGGSQSVL
TQPPSASGTPGQRVTISCTGSSNIAGAGYDVHWYQQLPGTAPKLLIY
RSNQRPSPGVDRFSGSKSGTSASLAISGLRSEDEAQYCSSYAGNN
LVFGGGTKLTVDKLTHTCPCCPAPEAAGAPSFLFPPPKDKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVGVEVHNNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVC
TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPPP
VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGWHPQFEK (SEQ ID NO: 114)

BMPRII_platform_21 EVQLLESGGGLVQPGGSLRLSCAASGFTFSYDYYMTWIRQAPGKGLEW
VSSISGGSTTYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYC
ARDFGVAGWFGQYGMDEVWGQGTLTVTSSGGGGGGGGGGGGGSQSVL
TQPPSASGTPGQRVTISCTGSSNIAGAGYDVHWYQQLPGTAPKLLIY
RSNQRPSPGVDRFSGSKSGTSASLAISGLRSEDEAQYCSSYAGNN
LVFGGGTKLTVDKLTHTCPCCPAPEAAGAPSFLFPPPKDKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVGVEVHNNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVC
TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPPP
VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGWHPQFEK (SEQ ID NO: 115)

BMPRII_platform_22 EVQLLESGGGLVQPGGSLRLSCAASGFTFSYDYYMTWIRQAPGKGLEW
VSSISGGSTTYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYC
ARDFGVAGWFGQYGMDEVWGQGTLTVTSSGGGGGGGGGGGGGSQSVL
TQPPSASGTPGQRVTISCTGSSNIAGAGYDVHWYQQLPGTAPKLLIY
RSNQRPSPGVDRFSGSKSGTSASLAISGLRSEDEAQYCSSYAGNN
LVFGGGTKLTVDKLTHTCPCCPAPEAAGAPSFLFPPPKDKDTLMISR
TPEVTCVVVDVSHEDPEVKFNWYVGVEVHNNAKTKPREEQYNSTYRV
VSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVC
TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPPP
VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
SPGWHPQFEK (SEQ ID NO: 116)

TABLE 5-continued

 Optimized ALK1 and BMPRII binders.

BMPRII_platform_23	EVQLESGGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKGLEW VSSISGGTTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYC ARDGVAGWFGQYGMDEVWGQGTLLTVTSSGGGGSGGGGSQSVL TQPPSASGTPQRTISCTGSSNIAGYDHWYQQLPGTAPKLIIY RSNQRPSPGVDRFSGSKSGTSASLAISGLRSEDEADYYCSSLQYAGN LVFGGGTKLTVDKHTCPCPAPEAAGAPSFLFPKPDKTLMISR TPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVC TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPP VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SPGWHPQFEK (SEQ ID NO: 117)
BMPRII_platform_24	EVQLESGGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKGLEW VSSISGGTTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYC ARDGVAGWFGQYGMDEVWGQGTLLTVTSSGGGGSGGGGSQSVL TQPPSASGTPQRTISCTGSSNIAGYDHWYQQLPGTAPKLIIY RSNQRPSPGVDRFSGSKSGTSASLAISGLRSEDEADYYCSSLQYAGN LVFGGGTKLTVDKHTCPCPAPEAAGAPSFLFPKPDKTLMISR TPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVC TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPP VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SPGWHPQFEK (SEQ ID NO: 118)
BMPRII_platform_25	EVQLESGGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKGLEW VSSISGGTTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYC ARDGVAGWFGQYGMDEVWGQGTLLTVTSSGGGGSGGGGSQSVL TQPPSASGTPQRTISCTGSSNIAGYDHWYQQLPGTAPKLIIY RSNQRPSPGVDRFSGSKSGTSASLAISGLRSEDEADYYCSSLQYAGN LVFGGGTKLTVDKHTCPCPAPEAAGAPSFLFPKPDKTLMISR TPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVC TLPSSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPP VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SPGWHPQFEK (SEQ ID NO: 119)
scFv_1	EVQLESGGGLVQPGGSLRLSCAASGFTFSIYAMSWVRQAPGKGLEW VSAISGGTTYYADSRKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARDFDYWQGTLLTVTSSGGGGSGGGSGGGGSQSVLQPPSASG TPGQRTVTCSSGSSNIIGSNVYVYQQLPGTAPKLIIYGNINRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFGG GTK LTVDKHTCPCPAPEAAGAPSFLFPKPDKTLMISRTPEVTCVV VDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVSVLVLH QDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVYTLPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 120)
scFv_8	EVQLESGGGLVQPGGSLRLSCAASGFTFSNAWMNWVRQAPGKGLEW VSSISSSSYYADSRKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARAVAAGGMFWGLDQWGQGTLLTVTSSGGGGSGGGSGGGGSQSV LTQPPSASGTPQRTVTCSSGSRNISGNSNVHWWQQLPGTAPKLIIY GNSNRPSPGVDRFSGSKSGTSASLAISGLRSEDEADYYCQSYDSSLN DHVPGGGTKLTVDKHTCPCPAPEAAGAPSFLFPKPDKTLMI SRTPEVTCVVVDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTY RVSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQ VCTLPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTT PPVLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL SLSPGWHPQFEK (SEQ ID NO: 121)
scFv_29	EVQLESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKGLEW VANINQDGSEKNNVDSMRGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCAREFDYWQGTLLTVTSSGGGGSGGGSGGGGSQSVLAQPPSASG TPGQRTVTCSSGSSNIIGSNVYVYQQLPGTAPKLIIYGNINRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNGRVFGG GTK LTVDKHTCPCPAPEAAGAPSFLFPKPDKTLMISRTPEVTCVV VDVSHEDPEVKFNWYVGVEVHNAKTKPREEQYNSTYRVSVLVLH QDWLNKEYKCKVSNKALPAPIEKTISSAKGQPREPQVYTLPCRDE LTKNQVSLWCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 122)
scFv_36	EVQLESGGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKGLEW VSSISGGSTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYC ARDGVAGWFGQYGMDEVWGQGTLLTVTSSGGGGSGGGSGGGGSQSVL

TABLE 5-continued

Optimized ALK1 and BMPRII binders.

TQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIY
 RSNQRPSGVPDFSGSKSGTSASLAISSLRSEDEADYYCSSLAGYN
 LVFGGGTKLTVLDEHTHTCPCCPAPEAAGAPSVFLFPPPKPDKTLMISR
 TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV
 VSVLTVLHQDWLNKEYKCKVSNSKALPAPIEKTIASKAKQPREPQVC
 TLPPSRDELTKNQVSLSCAVKGFYPSDIAVEWESNGQPENNYKTPP
 VLDSDGSFFLVSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL
 SPGWSHPQFEK (SEQ ID NO: 123)

TABLE 6

Optimized ALK1 and BMPRII bispecific antibodies.

Name	Chain 1	Chain 2
DGL621	Alk1_platform_1	scFv_8
DGL622	Alk1_platform_2	scFv_8
DGL623	Alk1_platform_3	scFv_8
DGL624	Alk1_platform_4	scFv_8
DGL625	Alk1_platform_5	scFv_36
DGL626	Alk1_platform_6	scFv_36
DGL627	Alk1_platform_7	scFv_36
DGL628	Alk1_platform_8	scFv_36
DGL629	Alk1_platform_9	scFv_36
DGL630	Alk1_platform_10	scFv_8
DGL631	Alk1_platform_11	scFv_8
DGL632	Alk1_platform_12	scFv_8
DGL633	Alk1_platform_13	scFv_8
DGL634	Alk1_platform_14	scFv_8
DGL635	BMPRII_platform_1	scFv_29
DGL636	BMPRII_platform_2	scFv_29
DGL637	BMPRII_platform_3	scFv_29
DGL638	BMPRII_platform_4	scFv_29
DGL639	BMPRII_platform_5	scFv_29
DGL640	BMPRII_platform_6	scFv_29
DGL641	BMPRII_platform_7	scFv_1
DGL642	BMPRII_platform_8	scFv_1
DGL643	BMPRII_platform_9	scFv_1
DGL644	BMPRII_platform_10	scFv_1
DGL645	BMPRII_platform_11	scFv_1
DGL646	BMPRII_platform_12	scFv_1
DGL647	BMPRII_platform_13	scFv_1
DGL648	BMPRII_platform_14	scFv_1
DGL649	BMPRII_platform_15	scFv_1
DGL650	BMPRII_platform_16	scFv_1
DGL651	Alk1_platform_15	scFv_36
DGL652	Alk1_platform_16	scFv_36
DGL653	Alk1_platform_17	scFv_36
DGL654	BMPRII_platform_17	scFv_29
DGL655	BMPRII_platform_18	scFv_29
DGL656	BMPRII_platform_19	scFv_29
DGL730	BMPRII_platform_20	scFv_29
DGL731	BMPRII_platform_21	scFv_29
DGL732	BMPRII_platform_22	scFv_29
DGL733	BMPRII_platform_23	scFv_29
DGL734	BMPRII_platform_24	scFv_29
DGL735	BMPRII_platform_25	scFv_29
DGL736	Alk1_platform_18	scFv_36
DGL737	Alk1_platform_19	scFv_36
DGL860	ALK1_platform_15	BMPRII_Platform_17
DGL861	ALK1_platform_16	BMPRII_Platform_17
DGL862	ALK1_platform_17	BMPRII_Platform_17
DGL863	ALK1_platform_15	BMPRII_Platform_18
DGL864	ALK1_platform_16	BMPRII_Platform_18
DGL865	ALK1_platform_17	BMPRII_Platform_18
DGL866	ALK1_platform_15	BMPRII_Platform_19
DGL867	ALK1_platform_16	BMPRII_Platform_19
DGL868	ALK1_platform_17	BMPRII_Platform_19

TABLE 6-continued

Optimized ALK1 and BMPRII bispecific antibodies.

Name	Chain 1	Chain 2
DGL869	scFv29_L1_H3	scFv36
DGL870	scFv29_L2_H3	scFv36
DGL871	scFv29_L3_H3	scFv36
DGL872	scFv29_L4_H3	scFv36
DGL873	scFv29_L1	scFv36
DGL874	scFv29_L2	scFv36
DGL875	scFv29_L3	scFv36
DGL876	scFv29_L4	scFv36
DGL877	scFv29	scFv36_L1
DGL878	scFv29	scFv36_L2
DGL879	scFv29	scFv36_L3
DGL880	scFv29	scFv36_L4
DGL893	Alk_platform_15	BMPRII_platform_21
DGL894	Alk_platform_15	BMPRII_platform_22
DGL895	Alk_platform_15	BMPRII_platform_23
DGL896	Alk_platform_15	BMPRII_platform_25
DGL897	Alk1_platform_16	BMPRII_platform_21
DGL898	Alk1_platform_16	BMPRII_platform_22
DGL899	Alk1_platform_16	BMPRII_platform_23
DGL900	Alk1_platform_16	BMPRII_platform_25
DGL901	Alk1_platform_17	BMPRII_platform_21
DGL902	Alk1_platform_17	BMPRII_platform_22
DGL903	Alk1_platform_17	BMPRII_platform_23
DGL904	Alk1_platform_17	BMPRII_platform_25
DGL905	Alk1_platform_18	BMPRII_platform_17
DGL906	Alk1_platform_18	BMPRII_platform_18
DGL907	Alk1_platform_18	BMPRII_platform_19
DGL908	Alk1_platform_18	BMPRII_platform_21
DGL909	Alk1_platform_18	BMPRII_platform_22
DGL910	Alk1_platform_18	BMPRII_platform_23
DGL911	Alk1_platform_18	BMPRII_platform_25
DGL912	Alk1_platform_19	BMPRII_platform_17
DGL913	Alk1_platform_19	BMPRII_platform_18
DGL914	Alk1_platform_19	BMPRII_platform_19
DGL915	Alk1_platform_19	BMPRII_platform_21
DGL916	Alk1_platform_19	BMPRII_platform_22
DGL917	Alk1_platform_19	BMPRII_platform_23
DGL918	Alk1_platform_19	BMPRII_platform_25

TABLE 7

Additional engineered variants.

ID	Sequence
CH969 (ScFv29_L1_H3_CH)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKG LEWVANINQSGSEKNEYVDSMRGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCAREFDWQGQTLTVVSSGGGGSGGGGSQSV LAQPPSASGTPGQRTVTISCGSASNIGSNYVYQQLPGTAPKL LIYGNKRPSGVDPDFSGSKSGTSASLAIISGLRSEDEADYYCAA WDDSLNGRVFGGGTQLTVLDKTHTCPPCPAPEAGAPSFLFPP PKDITLMISRTPETVCTVVVDVSHEDPEVKFNWYDGVEVHNAKT KPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISAKGQPREPVYTLPPCRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 124)
CH970 (scFv29_L2_H3_CH)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKG LEWVANINQSGSEKNEYVDSMRGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCAREFDWQGQTLTVVSSGGGGSGGGGSQSV LAQPPSASGTPGQRTVTISCGSASSNIGSNYVYQQLPGTAPKL LIYGNKRPSGVDPDFSGSKSGTSASLAIISGLRSEDEADYYCAA WDDSLNGRVFGGGTQLTVLDKTHTCPPCPAPEAGAPSFLFPP PKDITLMISRTPETVCTVVVDVSHEDPEVKFNWYDGVEVHNAKT KPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISAKGQPREPVYTLPPCRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 125)
CH971 (scFv29_L3_H3_CH)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKG LEWVANINQSGSEKNEYVDSMRGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCAREFDWQGQTLTVVSSGGGGSGGGGSQSV AQPPSASGTPGQRTVTISCGSASSNIGSNYVYQQLPGTAPKL IYGNKRPSGVDPDFSGSKSGTSASLAIISGLRSEDEADYYCAA DDSLSGRVFGGGTQLTVLDKTHTCPPCPAPEAGAPSFLFPP PKDITLMISRTPETVCTVVVDVSHEDPEVKFNWYDGVEVHNAKT PREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISAKGQPREPVYTLPPCRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN FSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 126)
CH972 (scFv29_L4_H3_CH)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKG LEWVANINQSGSEKNEYVDSMRGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCAREFDWQGQTLTVVSSGGGGSGGGGSQSV LAQPPSASGTPGQRTVTISCGSASNIGSNYVYQQLPGTAPKL LIYGNKRPSGVDPDFSGSKSGTSASLAIISGLRSEDEADYYCAA WDDSLSGRVFGGGTQLTVLDKTHTCPPCPAPEAGAPSFLFPP PKDITLMISRTPETVCTVVVDVSHEDPEVKFNWYDGVEVHNAKT KPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISAKGQPREPVYTLPPCRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 127)
CH973 (scFv29_L1_CH)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKG LEWVANINQDGSEKNEYVDSMRGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCAREFDWQGQTLTVVSSGGGGSGGGSGGGGSQSV LAQPPSASGTPGQRTVTISCGSASNIGSNYVYQQLPGTAPKL LIYGNKRPSGVDPDFSGSKSGTSASLAIISGLRSEDEADYYCAA WDDSLNGRVFGGGTQLTVLDKTHTCPPCPAPEAGAPSFLFPP PKDITLMISRTPETVCTVVVDVSHEDPEVKFNWYDGVEVHNAKT KPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISAKGQPREPVYTLPPCRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 128)
CH974 (scFv29_L2_CH)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSYAMSWVRQAPGKG LEWVANINQDGSEKNEYVDSMRGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCAREFDWQGQTLTVVSSGGGGSGGGSGGGGSQSV LAQPPSASGTPGQRTVTISCGSASSNIGSNYVYQQLPGTAPKL LIYGNKRPSGVDPDFSGSKSGTSASLAIISGLRSEDEADYYCAA WDDSLNGRVFGGGTQLTVLDKTHTCPPCPAPEAGAPSFLFPP PKDITLMISRTPETVCTVVVDVSHEDPEVKFNWYDGVEVHNAKT KPREEQYNSTYRVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE

TABLE 7-continued

Additional engineered variants.	
ID	Sequence
	<p>KTISAKGQPREPVYTLPPCRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 129)</p>
CH975 (scFv29_L3_CH)	<p>EVLQLESGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKG LEWVANINQDGSEKNYVDMSMRGRTFISRDN SKNTLYLQMNSLRA EDTAVYYCAREFDYWQGQTLVTVSSGGGGSGGGGSQSV LAQPPSASGTPGQRVTISCGSSSNIGSNYVWYQQLPGTAPKL LIYGNNKRPMSGVPDRFSGSKSGTSASLAI SGLRSEDEADYYCAA WDDSLSGRVFGGGTKLTVLDKTHTCPPCPAPEAAGAPSFLFPP KPKDTLMISRTPEVTCVVVDVSHDPEVKFNWYVGVEVHNAKT KPRREQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISAKGQPREPVYTLPPCRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 130)</p>
CH976 (scFv29_L4_CH)	<p>EVLQLESGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKG LEWVANINQDGSEKNYVDMSMRGRTFISRDN SKNTLYLQMNSLRA EDTAVYYCAREFDYWQGQTLVTVSSGGGGSGGGGSQSV LAQPPSASGTPGQRVTISCGSSSNIGSNYVWYQQLPGTAPKL LIYGNNKRPMSGVPDRFSGSKSGTSASLAI SGLRSEDEADYYCAA WDDSLSGRVFGGGTKLTVLDKTHTCPPCPAPEAAGAPSFLFPP KPKDTLMISRTPEVTCVVVDVSHDPEVKFNWYVGVEVHNAKT KPRREQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE KTISAKGQPREPVYTLPPCRDELTKNQVSLWCLVKGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGN VFSCSVMHEALHNHYTQKSLSLSPGEPEA (SEQ ID NO: 131)</p>
CH977 (scFv36_L1_CH)	<p>EVLQLESGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKG LEWSSISGGSTYYADSRKGRFTISRDN SENTLYLQMNSLRAED TAVYYCARDFGVAGWFQYGMWDWQGQTLVTVSSGGGGSGGGGS GGGGSQSVLTQPPSASGTPGQRVTISCTGSASNI GAGYDVHWYQ QLPGTAPKLLIYRSNQRPMSGVPDRFSGSKSGTSASLAI SGLRSE DEADYYCSSYAGNYNLVFGGGTKLTVLDKTHTCPPCPAPEAAGA PSVFLFPPPKDTLMISRTPEVTCVVVDVSHDPEVKFNWYVG VEVHNAKT KPRREQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTI SKAKGQPREPVQCTLPPSRDELTKNQVSLSCAV KGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLVS KLTV KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGWHPQFEK (SEQ ID NO: 132)</p>
CH978 (scFv36_L2_CH)	<p>EVLQLESGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKG LEWSSISGGSTYYADSRKGRFTISRDN SENTLYLQMNSLRAED TAVYYCARDFGVAGWFQYGMWDWQGQTLVTVSSGGGGSGGGGS GGGGSQSVLTQPPSASGTPGQRVTISCTGSASNI GAGYDVHWYQ QLPGTAPKLLIYRSNQRPMSGVPDRFSGSKSGTSASLAI SGLRSE DEADYYCSSYAGNYNLVFGGGTKLTVLDKTHTCPPCPAPEAAGA PSVFLFPPPKDTLMISRTPEVTCVVVDVSHDPEVKFNWYVG VEVHNAKT KPRREQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTI SKAKGQPREPVQCTLPPSRDELTKNQVSLSCAV KGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLVS KLTV KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGWHPQFEK (SEQ ID NO: 133)</p>
CH979 (scFv36_L3_CH)	<p>EVLQLESGGLVQPGGSLRLSCAASGFTFSYMTWIRQAPGKG LEWSSISGGSTYYADSRKGRFTISRDN SENTLYLQMNSLRAED TAVYYCARDFGVAGWFQYGMWDWQGQTLVTVSSGGGGSGGGGS GGGGSQSVLTQPPSASGTPGQRVTISCTGSASNI GAGYDVHWYQ QLPGTAPKLLIYRSNQRPMSGVPDRFSGSKSGTSASLAI SGLRSE DEADYYCSSYAGNYNLVFGGGTKLTVLDKTHTCPPCPAPEAAGA PSVFLFPPPKDTLMISRTPEVTCVVVDVSHDPEVKFNWYVG VEVHNAKT KPRREQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN KALPAPIEKTI SKAKGQPREPVQCTLPPSRDELTKNQVSLSCAV KGFYPSDI AVEWESNGQPENNYKTPPVLDSDGSFFLVS KLTV KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGWHPQFEK (SEQ ID NO: 134)</p>

TABLE 7-continued

Additional engineered variants.

ID	Sequence
CH980 (scFv36_L4_CH)	EVQLESGGGLVQPGSSLRLSCAASGFTPSDYYMTWIRQAPGKG LEWVSSISGGSTYYADSRKGRFTISRDNSENTLYLQMNSLRAED TAVYYCARDFGVAGWFQGYMDVWQGQTLTVSSGGGGGGGG GGGGSQSVLTQPPSASGTPQQRVTISCTGSASNIGAGYDVHWC QLPGTAPKLLIYRSNQRPAGVPDRFSGSKSGTSASLAI SGLRSE DEADYVCSSYAGLYNLVFGGGTKLTVLKDTHTCPCPAPEAAGA PSVFLFPPPDKDTLMISRTPETCVVVDVSHEDPEVKFNWYVDG VEVHNAKTKPREEQVNSTRVVSVLTVLHQDWLNKEYCKVSN KALPAPIEKTIASKAKGQPREPQVCTLPPSRDELTKNQVSLSCAV KGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLVSKLTV KSRWQQGNVFSCVMHEALHNHYTQKSLSLSPGWSHPQFEK (SEQ ID NO: 135)

[0387] These binders were then tested using an ELISA assay. High binding plates (Corning, 9018) were coated with either 2 µg/ml of human BMPRII protein (Sino Biological, #10551-H08H) or 2 µg/ml of human ALK1 protein (Sino Biological, #10066-H08H) overnight at 40. The plates were then washed three times with wash buffer (R&D Systems, WA126). The plates were blocked with 1% BSA in PBS for one hour at room temperature, then blocked with 1% BSA and 2 µg/ml of goat anti-human IgG (Jackson ImmunoResearch, 109-005-190) in PBS for another hour at room temperature. The plates were then washed three times with wash buffer and DGL antibodies or controls, which were

diluted with PBS and 0.1% BSA. The antibodies were incubated for one hour at room temperature and then the plates were washed three times with wash buffer. The plates were then incubated with mouse anti-human IgG Fc secondary—HRP (diluted with PBS/0.1% BSA); 100 ul per well at 2 µg/ml and incubated at room temperature for one hour. The plate was washed three times in wash buffer and then 100 ul TMB (R&D Systems, DY9998B, substrate reagent pack). After the wells turn blue, 50 ul of stop solution (R&D Systems, DY994) was added to each well and the absorbance of the plate was read at 450 nm. results can be found in Table 8.

TABLE 8

Name	Binding of optimized ALK1 and BMPRII bispecific antibodies.					
	Abs450 100 nM (ALK1)	Abs450 10 nM (ALK1)	Abs450 1 nM (ALK1)	Abs450 100 nM (BMPRII)	Abs450 10 nM (BMPRII)	Abs450 1 nM (BMPRII)
	ELISA	ELISA	ELISA	ELISA	ELISA	ELISA
DGL621	1.58	0.95	0.17	0.33	0.22	0.21
DGL622	1.58	0.75	0.15	0.50	0.36	0.37
DGL623	1.43	0.61	0.14	0.31	0.20	0.18
DGL624	1.54	1.21	0.25	0.93	0.24	0.16
DGL625	0.11	0.07	0.07	1.21	0.35	0.17
DGL626	0.06	0.07	0.06	0.71	0.25	0.17
DGL627	0.07	0.07	0.05	0.66	0.22	0.15
DGL628	0.52	0.12	0.05	0.80	0.27	0.17
DGL629	0.08	0.08	0.08	0.90	0.29	0.18
DGL630	0.08	0.07	0.07	0.53	0.31	0.30
DGL631	0.70	0.19	0.07	0.97	0.65	0.61
DGL632	0.06	0.05	0.06	0.88	0.46	0.46
DGL633	1.42	0.78	0.15	0.37	0.14	0.12
DGL634	0.10	0.06	0.05	0.40	0.19	0.12
DGL635	1.17	0.29	0.09	1.17	0.33	0.15
DGL636	1.45	0.56	0.11	0.20	0.16	0.14
DGL637	1.48	0.77	0.16	0.27	0.17	0.17
DGL638	1.02	0.22	0.05	0.23	0.22	0.17
DGL639	1.39	0.46	0.09	0.49	0.35	0.34
DGL640	1.40	0.47	0.09	0.43	0.30	0.30
DGL641	0.83	0.15	0.07	0.90	0.43	0.33
DGL642	0.50	0.09	0.08	0.51	0.55	0.53
DGL643	0.71	0.13	0.04	0.26	0.23	0.3
DGL644	0.54	0.10	0.06	0.17	0.20	0.23
DGL645	0.59	0.13	0.07	0.16	0.21	0.23
DGL646	0.80	0.15	0.06	0.34	0.22	0.25
DGL647	0.84	0.16	0.07	1.90	0.51	0.25
DGL648	0.80	0.17	0.08	0.77	0.33	0.24
DGL649	0.81	0.18	0.07	0.76	0.32	0.30
DGL650	0.65	0.15	0.08	0.79	0.49	0.54

Example 6. DiscoverX Data for Variants

[0388] The bispecific antibodies were screened for agonist activity as described in Example 2. Data reported (RLU) is

the average of two replicates at the highest concentration tested. Antibodies were compared to the natural ligand, BMP9 on every plate.

TABLE 9

Agonist activity of exemplary bispecific antibodies			
DGL	Description	Emax (RLU)	% Emax BMP9
DGL621	ALK1_platform_1_B_8	1091500	30
DGL622	ALK1_platform_2_B_8	936000	25
DGL623	ALK1_platform_3_B_8	1108500	30
DGL624	ALK1_platform_4_B_36	1550500	42
DGL625	ALK1_platform_5_B_36	615000	17
DGL626	ALK1_platform_6_B_36	258000	7
DGL627	ALK1_platform_7_B_36	502500	14
DGL628	ALK1_platform_8_B_36	883500	24
DGL629	ALK1_platform_9_B_36	424500	12
DGL630	ALK1_platform_10_B_8	168000	5
DGL631	ALK1_platform_11_B_8	470000	13
DGL632	ALK1_platform_12_B_8	130000	4
DGL633	ALK1_platform_13_B_8	585800	32
DGL634	ALK1_platform_14_B_8	288300	16
DGL635	BMPRII_platform_1_B29	2614800	141
DGL636	BMPRII_platform_2_B29	361800	20
DGL637	BMPRII_platform_3_B29	382300	21
DGL638	BMPRII_platform_4_B29	1474800	80
DGL639	BMPRII_platform_5_B29	752300	41
DGL640	BMPRII_platform_6_B29	1532800	83
DGL641	BMPRII_platform_7_B1	1407800	76
DGL642	BMPRII_platform_8_B1	255300	14
DGL643	BMPRII_platform_9_B1	246300	13
DGL644	BMPRII_platform_10_B1	153400	8
DGL645	BMPRII_platform_11_B1	352650	19
DGL646	BMPRII_platform_12_B1	332700	18
DGL647	BMPRII_platform_13_B1	1455250	79
DGL648	BMPRII_platform_14v2_B1	1448250	78
DGL649	BMPRII_platform_15_B1	648250	35
DGL650	BMPRII_platform_16_B1	801250	43
DGL651	ALK1_platform_15_B_36	17617667	72
DGL652	ALK1_platform_16_B_36	1484266.667	60
DGL653	ALK1_platform_17_B_36	1433766.667	58
DGL654	BMPRII_platform_17_B29	1871266.667	76
DGL655	BMPRII_platform_18_B29	437266.667	18
DGL656	BMPRII_platform_19_B29	1355266.667	55
DGL730	BMPRII_platform_20_B36_- Alk1_scFv29_BsAb	342493.75	22
DGL731	BMPRII_platform_21_B36_- Alk1_scFv29_BsAb	1559493.75	100
DGL732	BMPRII_platform_22_B36_- Alk1_scFv29_BsAb	844993.75	54
DGL733	BMPRII_platform_23_B36_- Alk1_scFv29_BsAb	1654493.75	106
DGL734	BMPRII_platform_24 B36_Alk1_scFv29_BsAb	216993.75	14
DGL735	BMPRII_platform_25_B36_- Alk1_scFv29_BsAb	1062493.75	68
DGL736	ALK1_platform_18_B29_- BMPRII_scFv36_BsAb	1131493.75	73
DGL737	ALK1_platform_19_B29_- BMPRII_scFv36_BsAb	1200493.75	77
DGL860	ALK1_platform_15_BMPRII_Platform_17	2011075	79
DGL861	ALK1_platform_16_BMPRII_Platform_17	2084075	81
DGL862	ALK1_platform_17_BMPRII_Platform_17	2131075	83
DGL863	ALK1_platform_15_BMPRII_Platform_18	603575	24
DGL864	ALK1_platform_16_BMPRII_Platform_18	553075	22
DGL865	ALK1_platform_17_BMPRII_Platform_18	755075	30
DGL866	ALK1_platform_15_BMPRII_Platform_19	1147575	45
DGL867	ALK1_platform_16_BMPRII_Platform_19	1479075	58
DGL868	ALK1_platform_17_BMPRII_Platform_19	1707075	67

TABLE 10

Agonist activity of exemplary bispecific antibodies			
DGL	Description	Emax (RLU)	% Emax BMP9
DGL869	scFv29_L1_H3_CH	1436575	56
DGL870	scFv29_L2_H3_CH	1423575	56
DGL871	scFv29_L3_H3_CH	1593075	62
DGL872	scFv29_I4_H3_CH	1456075	57
DGL873	scFv29_L1_CH	1545575	60
DGL874	scFv29_L2_CH	1558075	61
DGL875	scFv29_L3_CH	1656575	65
DGL876	scFv29_I4_CH	1568575	61
DGL877	scFv36_L1_CH	1950075	76
DGL878	scFv36_L2_CH	1880075	73
DGL879	scFv36_L3_CH	1806575	71
DGL880	scFv36_I4_CH	1682575	66

TABLE 11

Agonist activity of exemplary bispecific antibodies			
DGL	Description	Emax (RLU)	% Emax BMP9
DGL893	Alk_platform_15_BMPRII_platform_21	551775	20
DGL894	Alk_platform_15_BMPRII_platform_22	383225	14
DGL895	Alk_platform_15_BMPRII_platform_23	715275	26
DGL896	Alk_platform_15_BMPRII_platform_25	281725	10
DGL897	Alk1_platform_16_BMPRII_platform_21	700775	26
DGL898	Alk1_platform_16_BMPRII_platform_22	509125	19
DGL899	Alk1_platform_16_BMPRII_platform_23	812275	30
DGL900	Alk1_platform_16_BMPRII_platform_25	332675	12
DGL901	Alk1_platform_17_BMPRII_platform_21	799775	29
DGL902	Alk1_platform_17_BMPRII_platform_22	528925	19
DGL903	Alk1_platform_17_BMPRII_platform_23	917775	34
DGL904	Alk1_platform_17_BMPRII_platform_25	474575	17
DGL905	Alk1_platform_18_BMPRII_platform_17	972275	36
DGL906	Alk1_platform_18_BMPRII_platform_18	-41075	-2
DGL907	Alk1_platform_18_BMPRII_platform_19	320825	12
DGL908	Alk1_platform_18_BMPRII_platform_21	1234775	45
DGL909	Alk1_platform_18_BMPRII_platform_22	663275	24
DGL910	Alk1_platform_18_BMPRII_platform_23	1328775	49
DGL911	Alk1_platform_18_BMPRII_platform_25	520775	19
DGL912	Alk1_platform_19_BMPRII_platform_17	909775	33
DGL913	Alk1_platform_19_BMPRII_platform_18	8425	0
DGL914	Alk1_platform_19_BMPRII_platform_19	556775	20
DGL915	Alk1_platform_19_BMPRII_platform_21	123975	5
DGL916	Alk1_platform_19_BMPRII_platform_22	1114275	41
DGL917	Alk1_platform_19_BMPRII_platform_23	469475	17
DGL918	Alk1_platform_19_BMPRII_platform_25	1243275	46

Example 7. Engineering of scFv Containing Bispecific Agonist Antibodies with Optimized Hinges

[0389] Agonist activity of heteromeric antibodies with modified hinges identified by the DIAGONAL platform was also tested. A variant of DGL288, DGL809, was designed with hinge 1. DGL809 was designed, expressed, and purified as described above. Heteromeric antibodies were tested using the DiscoverX assay. DGL809 outperformed the parental DGL288, as seen in Table 12 (average values across two different experiment is shown), which shows the activity level relative to BMP9 at 100 nM antibody concentration.

TABLE 12

Agonist activity of exemplary bispecific antibodies		
DGL	Hinge	% Emax BMP9
DGL288	Hinge 6	72
DGL809	Hinge 1	79

Example 8. Engineering Bispecific Agonist Antibodies with Optimized Linkers in DVD-Ig Format

[0390] An alternative way to rigidify agonist antibodies is to optimize the linkers between IgG and additional variable domains in the DVD-Ig format. To pursue this route, the agonist activity of heteromeric antibodies with modified VH

to IgG hinge linkers identified by the DIAGONAL platform was tested. Variants of DGL292, DGL810, DGL811, and DGL812, were designed, expressed, and purified as described above. Heteromeric antibodies were tested using the DiscoverX assay where variants outperformed the parental DGL292, as seen in Table 14 (average values across two different experiments is shown).

TABLE 13

Linkers used in DVD-Ig format		
DGL	VH1-VH2 linker	VL1-VL2 linker
DGL292	PAPNLLGGP (SEQ ID NO: 157)	PAPNLLGGP (SEQ ID NO: 157)
DGL810	PLAP (SEQ ID NO: 2)	PLAP (SEQ ID NO: 2)
DGL811	PLAP (SEQ ID NO: 2)	PAPNLLGGP (SEQ ID NO: 157)

TABLE 13 - continued

Linkers used in DVD-Ig format		
DGL	VH1-VH2 linker	VL1-VL2 linker
DGL812	PAPNLLGGP (SEQ ID NO: 157)	PLAP (SEQ ID NO: 2)

TABLE 14

Agonist activity in DVD-Ig format		
DGL	% Emax	BMP9
DGL292	57	
DGL810	76	
DGL811	73	
DGL812	62	

TABLE 15

Sequences	
ID	Sequence
DGL288	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWVS SISGGSTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDF GVAGWFQYGMMDVWGQGTIVTVSSGGGGSGGGSGGGSQSVLTQPPSA SGTPQGRVTISCTGSSNNIGAGYDVHYWQQLPGTAPKLLIYRSNQRPSG VPDRFSGSKSGTSASLAISGLRSEDEADYYC5SYAGQNYNLVFGGGTKLT VLDKGPSVFPLAPEPKSSEVQLESGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVANINQDGSEKNYVDSMRGRFTISRDNSENTLY LQMNSLRAEDTAVYYCAREFDYWQGTIVTVSSGGGGSGGGSGGGGS QSVLAQPPSASGFTPGQRTVTCGSSNNIGSNVYVWYQQLPGTAPKLLI YGNKKRPSGPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLNG RVFGGGTKLTVLDKHTCPCPCAPEAGAPSFLFPKPDKTLMIIRTPEVTCV VVVDVSHEDPEVKFNWYWDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTIASKGQPREPQVYTLPPSRDELTKN NQVSLTCLVKGFYPSDIAVEWESNGQOPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 147)
DGL809	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWVS SISGGSTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDF GVAGWFQYGMMDVWGQGTIVTVSSGGGGSGGGSGGGSQSVLTQPPSA SLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVANINQDGSEKNYVDSMR GRFTISRDNSENTLYLQMNSLRAEDTAVYYCAREFDYWQGTIVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYLFPPEPVTVWSNGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHHKPSNTKVDKVK EPKSCDKTHTCPPCPAPEAGAPSFLFPKPDKTLMIIRTPEVTCVV DVSHEDPEVKFNWYWDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ LNGKEYKCKVSNKALPAPIEKTIASKGQPREPQVYTLPPSRDELTKN VSLTCLVKGFYPSDIAVEWESNGQOPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 148)
DGL292_HC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMTWIRQAPGKGLEWVS SISGGSTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDF GVAGWFQYGMMDVWGQGTIVTVSSGGGGSGGGSGGGSQSVLTQPPSA SLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVANINQDGSEKNYVDSMR GRFTISRDNSENTLYLQMNSLRAEDTAVYYCAREFDYWQGTIVTVSS ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYLFPPEPVTVWSNGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHHKPSNTKVDKVK EPKSCDKTHTCPPCPAPEAGAPSFLFPKPDKTLMIIRTPEVTCVV DVSHEDPEVKFNWYWDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ LNGKEYKCKVSNKALPAPIEKTIASKGQPREPQVYTLPPSRDELTKN VSLTCLVKGFYPSDIAVEWESNGQOPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG (SEQ ID NO: 149)

TABLE 15-continued

Sequences	
ID	Sequence
DGL292_LC	QSVLTQPPSASGTPGQRVTISCTGSSNIAGAGYDHWYQQLPGTAPKLL IYRSNQRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCSSLNIGSNY LVFGGGTKLTLPAPNLLGGPQSVLAQPPSASGTPGQRVTISCTGSSNN IGSNYVYQQLPGTAKLIIYGNNKRPSPGVPDFSGSKSGTSASLAIS GLRSEDEADYYCAAWDDSLNGRVFGGGTKLTVLGQPKAAPSVTLFPPSS EELQANKATLVCILISDFYPGAVTVAWDSSPVKAGVETTPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 150)
DGL810_HC	EVQLLESGGGLVQPGGSRLSCAASGFTFSDDYMTWIRQAPGKLEWVS SISSGGSTYYADSRKGRFTISRDNSENTLYLQMNLSRAEDTAVYYCARDF GVAGWFGQYGMMDVWGQGTLVTVSSPLAPEVQLLESGGGLVQPGGSRLS CAASGFTFSSYAMSWVRQAPGKLEWVANINQDGSEKNYVDSMRGRFTI SRDNSKNTLYLQMNLSRAEDTAVYYCAREFDYWGQGTLVTVTSSASTKG PSVFLAPSSKSTSGGTAALGCLVKDYFPEPVTVWSNSGALTSGVHTFP AVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGAPSFLFPPPKDTLMISRTPEVTCVVVDVSH DPEVKFNWYVGVEVHNAKTPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTIISKAKGQPREFQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFCSVHEALHNHYTQKSLSLSPG (SEQ ID NO: 151)
DGL810_LC	QSVLTQPPSASGTPGQRVTISCTGSSNIAGAGYDHWYQQLPGTAPKLL IYRSNQRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCSSLNIGSNY LVFGGGTKLTLPAPNLLGGPQSVLAQPPSASGTPGQRVTISCTGSSNN IGSNYVYQQLPGTAKLIIYGNNKRPSPGVPDFSGSKSGTSASLAIS GLRSEDEADYYCAAWDDSLNGRVFGGGTKLTVLGQPKAAPSVTLFPPSS EELQANKATLVCILISDFYPGAVTVAWDSSPVKAGVETTPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 152)
DGL811_HC	EVQLLESGGGLVQPGGSRLSCAASGFTFSDDYMTWIRQAPGKLEWVS SISSGGSTYYADSRKGRFTISRDNSENTLYLQMNLSRAEDTAVYYCARDF GVAGWFGQYGMMDVWGQGTLVTVSSPLAPEVQLLESGGGLVQPGGSRLS CAASGFTFSSYAMSWVRQAPGKLEWVANINQDGSEKNYVDSMRGRFTI SRDNSKNTLYLQMNLSRAEDTAVYYCAREFDYWGQGTLVTVTSSASTKG PSVFLAPSSKSTSGGTAALGCLVKDYFPEPVTVWSNSGALTSGVHTFP AVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHHKPSNTKVDKKVEPKSC DKTHTCPPCPAPEAAGAPSFLFPPPKDTLMISRTPEVTCVVVDVSH DPEVKFNWYVGVEVHNAKTPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTIISKAKGQPREFQVYTLPPSRDELTKNQVSLTC LVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFCSVHEALHNHYTQKSLSLSPG (SEQ ID NO: 153)
DGL811_LC	QSVLTQPPSASGTPGQRVTISCTGSSNIAGAGYDHWYQQLPGTAPKLL IYRSNQRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCSSLNIGSNY LVFGGGTKLTLPAPNLLGGPQSVLAQPPSASGTPGQRVTISCTGSSNN IGSNYVYQQLPGTAKLIIYGNNKRPSPGVPDFSGSKSGTSASLAIS GLRSEDEADYYCAAWDDSLNGRVFGGGTKLTVLGQPKAAPSVTLFPPSS EELQANKATLVCILISDFYPGAVTVAWDSSPVKAGVETTPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 154)
DGL812_HC	EVQLLESGGGLVQPGGSRLSCAASGFTFSDDYMTWIRQAPGKLEWVS SISSGGSTYYADSRKGRFTISRDNSENTLYLQMNLSRAEDTAVYYCARDF GVAGWFGQYGMMDVWGQGTLVTVSSPAPNLLGGPEVQLLESGGGLVQPGG SLRLSCAASGFTFSSYAMSWVRQAPGKLEWVANINQDGSEKNYVDSMR GRFTISRDNSKNTLYLQMNLSRAEDTAVYYCAREFDYWGQGTLVTVSS ASTKGPSVFLAPSSKSTSGGTAALGCLVKDYFPEPVTVWSNSGALTSG VHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHHKPSNTKVDKKV EPKSCDKTHTCPPCPAPEAAGAPSFLFPPPKDTLMISRTPEVTCVV DVSCHEDPEVKFNWYVGVEVHNAKTPREEQYNSTYRVVSVLTVLHQDW LNKEYKCKVSNKALPAPIEKTIISKAKGQPREFQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFCSVHEALHNHYTQKSLSLSPG (SEQ ID NO: 155)
DGL812_LC	QSVLTQPPSASGTPGQRVTISCTGSSNIAGAGYDHWYQQLPGTAPKLL IYRSNQRPSGVPDFSGSKSGTSASLAISGLRSEDEADYYCSSLNIGSNY LVFGGGTKLTLPAPNLLGGPQSVLAQPPSASGTPGQRVTISCTGSSNN IGSNYVYQQLPGTAKLIIYGNNKRPSPGVPDFSGSKSGTSASLAIS GLRSEDEADYYCAAWDDSLNGRVFGGGTKLTVLGQPKAAPSVTLFPPSS EELQANKATLVCILISDFYPGAVTVAWDSSPVKAGVETTPSKQSNNK YAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 156)

TABLE 15-continued

Sequences	
ID	Sequence
	NKATLVLCLISDFYPGAVTVAWKADSSPVKAGVETTPSKQSNNKYAASS YLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS (SEQ ID NO: 156)

TABLE 16

Sequences	
ID	Sequence
CH1118_HC	EVQLLESGGGLVQPGGSRLSCAASGFTFSDDYYMTWIRQAPGKLEWVSS SGGSTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDFGVAG WFGQYGMWDVGQGTLTVTSSPAPNLLGGPEVQLESGGGLVQPGGSRLSC AASGFTFSSYAMSWRQRQPKGLEWVANINQDGSEKNVDSMRGRFTISRDN NSKNTLYLQMNSLRAEDTAVYYCAREFDYWGGQTLTVSSASTKGPSVFPL APSSKSTSGGTAALGCLVKDYLFFPEPVTVWSNSGALTSGVHTFPAPLQSSGL YSLSSVTPSSSLGTQTYICNVNHPKSNTKVDKKVEPKSCDKTHTCP APEAAGAPSFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVG VEVHNAKTKPREEQYNTSYRVSLSVTLHQDWLNKEYKCKVSNKALPAPI EKTISAKQPREQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI NGQFENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEHALHN HYTQKSLSLSPG (SEQ ID NO: 136)
CH1119_HC (DGL945 HC)	EVQLLESGGGLVQPGGSRLSCAASGFTFSDDYYMTWIRQAPGKLEWVSS SGGSTYYADSRKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDFGVAG WFGQYGMWDVGQGTLTVTSSPAPNLLGGPEVQLESGGGLVQPGGSRLSCAASGF TFSSYAMSWRQRQPKGLEWVANINQDGSEKNVDSMRGRFTISRDN NSKNTLYLQMNSLRAEDTAVYYCAREFDYWGGQTLTVSSASTKGPSVFPL STSGGTAALGCLVKDYLFFPEPVTVWSNSGALTSGVHTFPAPLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHPKSNTKVDKKVEPKSCDKTHTCP GAPSFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVG AKTKPREEQYNTSYRVSLSVTLHQDWLNKEYKCKVSNKALPAPI EKTISAKQPREQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI NNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEHALHN HYTQKSLSLSPG (SEQ ID NO: 137)
CH1120_HC (DGL946 HC)	EVQLLESGGGLVQPGGSRLSCAASGFTFSDDYYMNWIRQAPGKLEWVSS SGGSTYYADSVKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDFGVAG WFGQYGMWDVGQGTLTVTSSPAPNLLGGPEVQLESGGGLVQPGGSRLSCAASGF TFSSYAMSWRQRQPKGLEWVANINQDGSEKNVDSMRGRFTISRDN NSKNTLYLQMNSLRAEDTAVYYCAREFDYWGGQTLTVSSASTKGPSVFPL STSGGTAALGCLVKDYLFFPEPVTVWSNSGALTSGVHTFPAPLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHPKSNTKVDKKVEPKSCDKTHTCP GAPSFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVG AKTKPREEQYNTSYRVSLSVTLHQDWLNKEYKCKVSNKALPAPI EKTISAKQPREQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI NNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEHALHN HYTQKSLSLSPG (SEQ ID NO: 138)
CH1121_HC (DGL947 HC)	EVQLLESGGGLVQPGGSRLSCAASGFTFSDDYYMNWIRQAPGKLEWVSS SGGSTYYADSVKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDFGVAG WFGQYGMWDVGQGTLTVTSSPAPNLLGGPEVQLESGGGLVQPGGSRLSCAASGF TFSSYAMSWRQRQPKGLEWVANINQDGSEKNVDSMRGRFTISRDN NSKNTLYLQMNSLRAEDTAVYYCAREFDYWGGQTLTVSSASTKGPSVFPL STSGGTAALGCLVKDYLFFPEPVTVWSNSGALTSGVHTFPAPLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHPKSNTKVDKKVEPKSCDKTHTCP GAPSFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVG AKTKPREEQYNTSYRVSLSVTLHQDWLNKEYKCKVSNKALPAPI EKTISAKQPREQVYTLPPSRDELTKNQVSLTCLVKGFYPSDI NNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMEHALHN HYTQKSLSLSPG (SEQ ID NO: 139)
CH1122_HC (DGL948 HC)	EVQLLESGGGLVQPGGSRLSCAASGFTFSDDYYMNWIRQAPGKLEWVSS SGGSTYYADSVKGRFTISRDNSENTLYLQMNSLRAEDTAVYYCARDFGVAG WFGQYGMWDVGQGTLTVTSSPAPNLLGGPEVQLESGGGLVQPGGSRLSCAASGF TFSSYAMSWRQRQPKGLEWVANINQDGSEKNVDSMRGRFTISRDN NSKNTLYLQMNSLRAEDTAVYYCAREFDYWGGQTLTVSSASTKGPSVFPL STSGGTAALGCLVKDYLFFPEPVTVWSNSGALTSGVHTFPAPLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHPKSNTKVDKKVEPKSCDKTHTCP GAPSFLFPPKPKDTLYITREPEVTCVVVDVSHEDPEVKFNWYVG HYTQKSLSLSPG (SEQ ID NO: 140)

TABLE 16 -continued

Sequences	
ID	Sequence
	AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI KAKGQPREFQVYTLPPSDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQK SLSLSPG (SEQ ID NO: 140)
CH1123_HC (DGL949 HC)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDDYYMNTWIRQAPGKGLEWVSS SGGSTYYADSVKGRTISRDNSENTLYLQMNSLRAEDTAVYYCARDFGVAG WFGQYGMWDVGQGTLTVTSSPLAPEVQLLESGGGLVQPGGSLRLSCAASGF TFSSYWMWSWRQAPGKGLEWVANI KQDGSEKNYVDSMRGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCAREFDFWGQGTLTVSSASTKGPSVFP LAPSSK STSGGTAALGCLVKDYFPEPVTVWSWNSGALTSGVHTFPAAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHPKSNTKVDKKVEPKSCDKTHTCPPCPAPEAA GAPSVFLFPPPKPKDTLYITREPEVTCVVVDVSHEDPEVFKFNWYVGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI KAKGQPREFQVYTLPPSDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFYSKLTVDKSRWQQGNVFSCSVMEALHNHYTQK SLSLSPG (SEQ ID NO: 141)
CH1247 (DGL1146 HC)	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDDYYMNTWIRQAPGKGLEWVSS SGGSTYYADSVKGRTISRDNSENTLYLQMNSLRAEDTAVYYCARDFGVAG WFGQYGMWDVGQGTLTVTSSPLAPEVQLLESGGGLVQPGGSLRLSCAASGF TFSSYAMSWSWRQAPGKGLEWVANI NQDGSEKNYVDSMRGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCAREFDFWGQGTLTVSSASTKGPSVFP LAPSSK STSGGTAALGCLVKDYFPEPVTVWSWNSGALTSGVHTFPAAVLQSSGLYSLSS VVTVPSSSLGTQTYICNVNHPKSNTKVDKKVEPKSCDKTHTCPPCPAPEAA GAPSVFLFPPPKPKDTLYITREPEVTCVVVDVSHEDPEVFKFNWYVGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTI KAKGQPREFQVYTLPPSDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFYSKLTVDKSRWQQGNVFSCSVLHEALHSHYTQK SLSLSPG (SEQ ID NO: 142)
CH385_LC	QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIY RSNQRPSGVPDFSGSKSGTSASLAI SGLRSEDEADYYCSSLAGNYNLVFG GGTKLTVLPAPNLGGPQSVLAQPPSASGTPGQRVTISCGSSSNIGSNYV WYQQLPGTAPKLLIYGNNNKRPSGVPDFSGSKSGTSASLAI SGLRSEDEA DYYCAAWDDSLNDRVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATL VCLISDFYGAVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPE QWKSHRSYSQVTHEGSTVEKTVAPTECS (SEQ ID NO: 143)
CH1126_LC	QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIY RSNQRPSGVPDFSGSKSGTSASLAI SGLRSEDEADYYCSSLAGNYNLVFG GGTKLTVLPAPQSVLAQPPSASGTPGQRVTISCGSSSNIGSNYVWYQQ LPGTAPKLLIYGNNNKRPSGVPDFSGSKSGTSASLAI SGLRSEDEADYYCA AWDDSLNDRVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATL VCLIS DFYGAVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSH RSYSQVTHEGSTVEKTVAPTECS (SEQ ID NO: 144)
CH1127_LC	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDDYYMNTWIRQAPGKGLEWVSS SGGSTYYADSVKGRTISRDNSENTLYLQMNSLRAEDTAVYYCARDFGVAG WFGQYGMWDVGQGTLTVTSSPLAPEVQLLESGGGLVQPGGSLRLSCAASGF NIQSNYVWYQQLPGTAPKLLIYGNNNKRPSGVPDFSGSKSGTSASLAI SGL RSEDEADYYCAAWDDSLNDRVFGGGTKLTVLGQPKAAPSVTLFPPSSEEL QANKATL VCLISDFYGAVTVAWKADSSPVKAGVETTPSKQSNNKYAASS YLSLTPEQWKSHRSYSQVTHEGSTVEKTVAPTECS (SEQ ID NO: 145)
CH943_LC (DGL945 LC, DGL946 LC, DGL947 LC, DGL948 LC, DGL949 LC, DGL1146 LC)	QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIY RSNQRPSGVPDFSGSKSGTSASLAI SGLRSEDEADYYCSSLAGNYNLVFG GGTKLTVLPAPQSVLAQPPSASGTPGQRVTISCGSSSNIGSNYVWYQQ LPGTAPKLLIYGNNNKRPSGVPDFSGSKSGTSASLAI SGLRSEDEADYYCA AWDDSLNDRVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATL VCLIS DFYGAVTVAWKADSSPVKAGVETTPSKQSNNKYAASSYLSLTPEQWKSH RSYSQVTHEGSTVEKTVAPTECS (SEQ ID NO: 146)

TABLE 17

Sequences - CDRs	
ID	Sequence
DGL945/DGL1146 ALK1 HCDR1	SYAMS (SEQ ID NO: 158)
DGL945/DGL1146 ALK1 HCDR2	NINQDGSEKNYVDSMRG (SEQ ID NO: 159)
DGL945/DGL1146 ALK1 HCDR3	EFDY (SEQ ID NO: 160)
DGL945/DGL1146 BMPRII HCDR1	DYYMT (SEQ ID NO: 169)
DGL945/DGL 1146 BMPRII HCDR2	SISGGSTYYADSRKG (SEQ ID NO: 170)
DGL945/DGL1146 BMPRII HCDR3	DFGVAGWFGQYGM DV (SEQ ID NO: 171)
DGL947 ALK1 HCDR1	SYWMS (SEQ ID NO: 164)
DGL947 ALK1 HCDR2	NINQDGSEKYVDSMRG (SEQ ID NO: 165)
DGL947 ALK1 HCDR3	EYDY (SEQ ID NO: 166)
DGL947 BMPRII HCDR1	DYYMN (SEQ ID NO: 175)
DGL947 BMPRII HCDR2	SISGGSTYYADSVKG (SEQ ID NO: 176)

TABLE 17-continued

Sequences - CDRs	
ID	Sequence
DGL947 BMPRII HCDR3	DFGVAGWFGQYGM DV (SEQ ID NO: 177)
DGL949 ALK1 HCDR1	SYWMS (SEQ ID NO: 164)
DGL949 ALK1 HCDR2	NIKQDGSEKNYVDSMRG (SEQ ID NO: 167)
DGL949 ALK1 HCDR3	EFDF (SEQ ID NO: 168)
DGL949 BMPRII HCDR1	DYYMN (SEQ ID NO: 175)
DGL949 BMPRII HCDR2	SISGGSTYYADSVKG (SEQ ID NO: 176)
DGL949 BMPRII HCDR3	DFGVAGWFGYGM DV (SEQ ID NO: 179)
CH943 ALK1 LCDR1	SGSSSNIGSNYVY (SEQ ID NO: 161)
CH943 ALK1 LCDR2	GNNKRPS (SEQ ID NO: 162)
CH943 ALK1 LCDR3	AAWDDSLNGRV (SEQ ID NO: 163)
CH943 BMPRII LCDR1	TGSSSNIGAGYDVH (SEQ ID NO: 172)
CH943 BMPRII LCDR2	RSNQRPS (SEQ ID NO: 173)
CH943 BMPRII LCDR3	SSYAGNNLV (SEQ ID NO: 174)

TABLE 17

Sequences - VH/VL	
ID	Sequence
DGL945/DGL1146 ALK1 VH	EVQLLESGGGLVQPQGGSLRLSCAASGFTFSSYAMSVRQAPGKG LEWVANINQDGSEKNYVDSMRGFTISRDN SKNTLYLQMNSLRA EDTAVYYCAREFDYWGQQGTLTVSS (SEQ ID NO: 180)
DGL945/DGL1146 ALK1 VL	QSVLAQPPSASGTPGQRTVITCSGSSNIGSNYVYWYQQLPGTA PKLLIYGNNKRPSGPDRFSGSKSGTSASL AISGLRSEDEADYY CAAWDDSLNGRVFGGGTKLTVL (SEQ ID NO: 181)
DGL945/DGL1146 BMPRII VH	EVQLLESGGGLVQPQGGSLRLSCAASGFTFSDDYYTWIRQAPGKG LEWVSSISGGSTYYADSRKGFTISRDN SENTLYLQMNSLRAED TAVYYCARDFGVAGWFGQYGM DVWGQGTLTVSS (SEQ ID NO: 184)
DGL945/DGL1146 BMPRII VL	QSVLTQPPSASGTPGQRTVITCSGSSNIGAGYDVH WYQQLPGT APKLLIYRSNQRPSPGPDRFSGSKSGTSASL AISGLRSEDEADYY YCSSYAGNNLVFGGGTKLTVL (SEQ ID NO: 185)
DGL947 ALK1 VH	EVQLLESGGGLVQPQGGSLRLSCAASGFTFSSYMSVRQAPGKG LEWVANINQDGSEKYYVDSMRGFTISRDN SKNTLYLQMNSLRA EDTAVYYCAREDYWGQQGTLTVSS (SEQ ID NO: 182)
DGL947 ALK1 VL	QSVLAQPPSASGTPGQRTVITCSGSSNIGSNYVYWYQQLPGTA PKLLIYGNNKRPSGPDRFSGSKSGTSASL AISGLRSEDEADYY CAAWDDSLNGRVFGGGTKLTVL (SEQ ID NO: 181)
DGL947 BMPRII VH	EVQLLESGGGLVQPQGGSLRLSCAASGFTFSDDYYMNWIRQAPGKG LEWVSSISGGSTYYADSVKGRFTISRDN SENTLYLQMNSLRAED TAVYYCARDFGVAGWFGQYGM DVWGQGTLTVSS (SEQ ID NO: 186)

TABLE 17-continued

Sequences - VH/VL	
ID	Sequence
DGL947 BMPRII VL	QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVWVYQQLPGT APKLLIYRSNQRPSGVPDFSGSKSGTSASLAISGLRSEDEADYY YCSSYAGNYNLVFGGGTKLTVL (SEQ ID NO: 185)
DGL949 ALK1 VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYWMWSVRQAPGKG LEWVANIKQDGSEKNNYVDSMGRFTISRDNKNTLYLQMNSLRAED EDTAVYYCAREPDFFWGQGTLTVSS (SEQ ID NO: 183)
DGL949 ALK1 VL	QSVLAQPPSASGTPGQRVTISCTGSSSNIGSNYVWYQQLPGTA PKLLIYGNNKRPSPGVPDFSGSKSGTSASLAISGLRSEDEADYY CAAWDDSLNGRVFGGGTKLTVL (SEQ ID NO: 181)
DGL949 BMPRII VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSDYYMNWIRQAPGKG LEWVSSISGGSTYYADSVKGRFTISRDNSENTLYLQMNSLRAED TAVYYCARDFGVAGWFGYYGMDVWGQGTLTVSS (SEQ ID NO: 187)
DGL949 BMPRII VL	QSVLTQPPSASGTPGQRVTISCTGSSSNIGAGYDVWVYQQLPGT APKLLIYRSNQRPSGVPDFSGSKSGTSASLAISGLRSEDEADYY YCSSYAGNYNLVFGGGTKLTVL (SEQ ID NO: 185)

Example 9. Screen for Agonistic Activity

[0391] The bispecific antibodies were screened for agonist activity. PathHunter U2Os ALK-1/BMPR-2 dimerization assay was obtained from DiscoverX Corporation (93-0962C3). These cells use Enzyme Fragment Complementation (EFC) technology using β -galactosidase fragments to evaluate protein-protein interactions. Reporter cells were revived and cultured according to supplier's recommendations. Bispecific antibodies were compared to the natural ligands, BMP9 and BMP10.

[0392] To perform the assay, cells were detached and removed from the flask with cell detachment reagent (DiscoverX, 92-0009). Cells were spun at 300 g for four minutes and resuspended at a density of 250K/ml in assay plating media (DiscoverX 93-0563R22A). 20 μ l of the suspension were plated/well of a384 well plate and incubated at 37° C. for 24 hours. Bispecifics were made at 5x the final concentration. 12-point titrations using a 1:10 dilution were done to generate curves. 5 μ l of the bispecific was added to the 384 well plate and incubated for three hours. 25 μ l of flash detection reagent (DiscoverX, 93-0247) was added/well and the plates were read on a Verilux Skan at 60 minutes. Data was analyzed using PRISM. The results are represented below in Table 17. The data demonstrates that each of the tested bispecific antibodies had robust agonist activity.

TABLE 17

Agonist activity in DiscoverX assay	
DGL	% E _{max} BMP9
DGL292	60
DGL945	78
DGL947	47
DGL949	42
DGL1146	78

Example 10. Measurement of Agonistic Activity in Endothelial Cells

[0393] HMEC-1 cells were plated at 30K cell/well in 96 well plate in 200 μ l complete 10% MCDB growth media and

incubated overnight. Approximately 16 hrs later, complete media was replaced with 50 μ l serum free MCDB media. Cells were incubated for 4 hrs in serum free media before the addition of 2xDGL tools in 50 μ l of serum free MCDB media. After 45 minutes, media was removed and cells were washed once with PBS before addition of lysis buffer from the ELISA kit. Lysates were then analyzed via ELISA following the manufacturer's instructions (Abcam pSMAD1 ELISA AB186036). 12-point titrations using a 1:10 dilution were done to generate curves. As a negative control, an anti-HEL antibody with LALA-PG mutations (BioXCell, CP149) was used. Data was analyzed using PRISM. Data reported is the average of two experiments. The results are represented below in Table 18. The data demonstrates that each of the tested bispecific antibodies had robust agonist activity, as measured through pSMAD1 levels.

TABLE 18

Agonist activity in endothelial cells	
DGL	% Emax BMP9
DGL292	69
DGL945	77
DGL947	55
DGL949	35
DGL1146	79

Example 11. Measurement of in Vivo Activity

[0394] Antibodies were measured for agonistic activity in a mouse model of HHT wherein circulating BMP9/BMP10 were neutralized by anti-BMP9/10 antibodies (Ruiz S, et al, Scientific Reports, 2016 Nov. 22: 5:37366). These mice develop vascular defects in the postnatal retina. Three animals were dosed with DGL292, DGL945, DGL947 or a negative control antibody (Anti-HEL, LALA-PG, BioXCell, CP149) for two days, P3 and P4, at 1 mg/kg/day. BMP9/10 antibodies were dosed on the same days. Analysis was

completed on P6. Retinas were dissected and whole-mount prepared, then stained with both isolectin B4 and SMA to label retinal vasculature and detect arteriovenous malformations (AVMs). Results are shown in FIG. 4. Mice dosed with any ALK1-BMPRII agonist showed a significant reduction in the formation of AVMs, whereas the negative control showed an average of 4.5 AVMs/retina.

Example 12. Analysis of Thermal Stability

[0395] Differential scanning calorimetry (DSC) is a thermo-analytical technique used to characterize the thermal stability of protein samples and assess conformational differences between them. Measurements were performed on MicroCal PEAQ DSC (Malvern) for thermal transition midpoint (T_m) and onset of unfolding (TONset) testing. Samples were diluted to 1 mg/mL with the reference buffer (20 mM Histidine, 8% (w/v) sucrose, 0.02% (w/v) PS80, pH 6.0. 400 μ L of respective reference buffers were added into the odd-numbered wells of a 96-well plate and 400 μ L of samples were added into the even-numbered wells of the same plate. Experimental parameters were set such that the scan temperature ramped from 10 to 95° C. at a scan rate of 200° C./h. Data analysis was performed in MicroCal PEAQ-DSC automated data analysis software. Melting temperature data is depicted below in Table 19. Surprisingly, it was discovered that DGL947 and DGL949 possessed increased stability, as demonstrated by an increase in both the onset temperature of thermal unfolding (Tonset) and the first unfolding event (T_m) relative to DGL945 and DGL1146. The variable domains of DGL947 and DGL949 differ from DGL945 and DGL1146 only within the CDRs.

TABLE 19

Molecule	Melting temperatures			
	T_{Onset} (° C.)	T_{m1} (° C.)	T_{m2} (° C.)	T_{m3} (° C.)
DGL945	47.1	61.7	86.7	NA
DGL947	59.0	71.2	87.3	NA
DGL949	57.1	65.9	82.1	87.4
DGL1146	48.4	61.6	69.0	82.0

Example 13. Gene Expression Analysis of HMEC-1 Cells

[0396] HMEC-1 cells from ATCC were plated at 30K cells/well of 96 well plate in 100 μ L complete growth media (MCDB base, +10% FBS, Pen/Strep, L-glutamine, and hydrocortisone, EGF) overnight. After overnight incubation media was removed and replaced with 50 μ L reduced serum media (same as growth but 1% FBS). Cells were allowed to incubate for approximately 4 hours while standard curves of agonists were made in reduced serum media at 2x final concentration. After 4 hours, 50 μ L of the antibody or BMP9 was added to cells and allowed to incubate overnight. After overnight incubation, media was removed and RNA lysis buffer from ZYMO was added. RNA was isolated from the cell lysates using a ZYMO 96 RNA isolation kit and RT reaction was performed using Quanta Biosciences kit. qPCR was performed on cDNA using Thermo designed Taqman assays for ID1, Serpine1 and GAPDH as a housekeeping control. Fold change was calculated as DD ct. The results of the gene expression analysis, as shown in Table 20-22, demonstrate that the bispecific antibodies stimulate gene expression of an ALK1 target (ID1) using GAPDH as a housekeeping gene. Table 23-25 is a second experiment, using RPL36AL as the housekeeping gene.

TABLE 20

On target ID1 fold change over no treatment						
BMP9	DGL945	DGL947	DGL292	DGL1146	DGL949	
1 nM	5.5	36.4	7.9	8.6	8.7	3.7
100 pM	7.8	31.8	6.9	9.0	14.8	4.0
10 pM	1.2	11.0	3.6	2.1	5.5	3.8
1 pM	2.3	9.9	3.6	3.3	2.6	3.2

TABLE 21

Off target Serpine1 fold change over no treatment						
BMP9	DGL945	DGL947	DGL292	DGL1146	DGL949	
1 nM	1.4	2.6	1.2	1.1	1.1	1.3
100 pM	1.5	3.4	1.5	1.3	1.4	1.6
10 pM	1.0	3.4	1.6	1.0	1.3	1.5
1 pM	1.9	4.0	2.1	1.8	0.9	1.5

TABLE 22

On target/off target effect						
BMP9	DGL945	DGL947	DGL292	DGL1146	DGL949	
1 nM	4.0	14.0	6.7	8.0	8.1	2.8
100 pM	5.2	9.4	4.6	6.9	10.7	2.6

TABLE 22-continued

On target/off target effect						
	BMP9	DGL945	DGL947	DGL292	DGL1146	DGL949
10 pM	1.2	3.2	2.3	2.1	4.2	2.5
1 pM	1.2	2.5	1.7	1.9	2.8	2.1

TABLE 23

On target ID1 fold change over no treatment						
	BMP9	DGL945	DGL947	DGL292	DGL1146	DGL949
1 nM	9.1	2.3	1.0	2.5	1.9	0.6
100 pM	3.5	3.2	0.3	2.1	0.7	0.6
10 pM	1.0	0.4	0.3	1.7	0.4	0.2
1 pM	0.7	0.3	0.1	0.4	0.5	0.2

TABLE 24

Off target Serpine1 fold change over no treatment						
	BMP9	DGL945	DGL947	DGL292	DGL1146	DGL949
1 nM	1.2	0.3	0.3	0.4	0.2	0.2
100 pM	0.7	0.6	0.1	0.6	0.1	0.3
10 pM	0.8	0.2	0.2	1.7	0.2	0.2
1 pM	0.4	0.2	0.1	0.2	0.3	0.1

TABLE 25

On target/off target effect						
	BMP9	DGL945	DGL947	DGL292	DGL1146	DGL949
1 nM	7.8	7.7	3.9	6.2	9.5	3.4
100 pM	4.7	5.7	2.0	3.6	5.3	2.0
10 pM	1.3	2.1	1.2	1.0	2.1	1.3
1 pM	1.8	1.3	1.1	1.7	1.5	1.3

[0397] A separate cell line, the TIME cell line, as also used in gene expression analysis. TIME cells (ATCC), which are hTERT-immortalized cells exhibiting endothelial-like morphology, were plated at 30K cells/well of 96 well plate in 100 μ l complete growth media (Vascular cell basal media plus microvascular endothelial cell growth kit-VEGF) overnight. After overnight incubation, media was removed and replaced with 50 μ l reduced serum media (Growth media diluted 1:10 with Vascular cell basal media). Cells were allowed to incubate for approximately 4 hours while standard curves of agonists were made in reduced serum media

at 2 \times final concentration. After 4 hours, 50 μ l of agonist was added to cells and allowed to incubate overnight. After overnight incubation, media was removed and RNA lysis buffer from ZYMO was added. RNA was isolated from the cell lysates using a ZYMO 96 RNA isolation kit and RT reaction was performed using Quanta Biosciences kit. qPCR was performed on CDNA using Thermo designed Taqman assays for ID1, Serpinel and GAPDH or RPL36AL as a housekeeping control. Fold change was calculated as DD ct. Table 26-27 shows the results using RPL36AL as the housekeeping control.

TABLE 26

On target ID1 fold change over no treatment						
	BMP9	DGL945	DGL947	DGL292	DGL1146	DGL949
1 nM	6.4	7.0	4.5	12.3	n.d.	n.d.
100 pM	1.5	4.6	0.6	4.7	n.d.	n.d.
10 pM	0.3	1.0	0.4	0.3	n.d.	n.d.
1 pM	0.6	0.3	0.3	0.3	n.d.	n.d.

TABLE 27

Off target Serpine1 fold change over no treatment					
	BMP9	DGL945	DGL947	DGL292	DGL1146
1 nM	0.6	0.5	0.4	1.9	n.d.
100 pM	0.7	0.5	0.2	1.5	n.d.
10 pM	0.2	0.3	0.2	0.2	n.d.
1 pM	0.7	0.2	0.2	0.3	n.d.

TABLE 28

On target/off target effect					
	BMP9	DGL945	DGL947	DGL292	DGL1146
1 nM	11.3	14.9	11.5	6.6	n.d.
100 pM	2.1	9.4	4.0	3.1	n.d.
10 pM	1.8	2.8	1.7	1.0	n.d.
1 pM	0.9	1.5	1.9	1.2	n.d.

n.d.—not determined

Example 14. Stabilization of the ALK1 Receptor on the Surface of Cells

[0398] The bispecific antibodies of the disclosure may stabilize the ALK1 receptor complexed with any one of BMPRII, ActRIIA, and ActRIIB on the surface of a cell. Through stabilization of the receptor, signaling may be sustained for longer durations.

[0399] To assess ALK1 receptor complex stabilization on the surface of cells, staining may be performed against ALK1 and one or BMPRII, ActRIIA, and ActRIIB. An exemplary protocol is described below, however one of skill in the art will readily recognize alternative approaches for detecting a protein on the surface of a cell. Moreover, the specific parameters outlined in the exemplary protocol (e.g., buffer choice, buffer component concentrations, cell line choice, total cells, antibody concentration, time, temperature, and others) may be adjusted as need to optimize the assay.

Staining for ALK1 and BMPRII in MS1 Cells:

[0400] Autoclaved coverslips are placed in cell culture 24-well plate, and MS1 cells are seeded onto the coverslips in complete medium, allowing them to adhere overnight. Subsequently, the cells are starved for about 3 hours and then treated with a bispecific antibody disclosed herein (such as DGL288) or an IgG control at a concentration of about 1

μg/mL for 2 hrs. Following treatment, the coverslips are rinsed twice with PBS for about 5 minutes each and fixed in 4% paraformaldehyde for about 10 minutes, followed by another PBS wash.

[0401] Next, the cells are permeabilized for about 15 minutes using 0.25% Triton X-100 in PBS and blocked for about 1 hour with a solution containing 5% normal goat serum (Sigma-Aldrich, #G9023-10ML) and 0.25% Triton X-100 in PBS. Primary antibodies, including ALK1 (dilution 1:100, Santacruz #sc-101556), BMPRII (dilution 1:100, Invitrogen #MA5-15827), and CD31-AF667 (dilution 1:50, Miltenyi #130-128-736), diluted in a solution of 1% NGS and 0.25% Triton X-100 in PBS, are then applied and allowed to incubate overnight at 4° C. The following day, the coverslips are washed twice with PBS for 5 minutes each and then incubated with secondary antibodies diluted in a solution of 1% NGS and 0.25% Triton X-100 in PBS at a dilution of 1:1000 (Goat anti-rat IgG H+L AF568, Thermo Fisher Scientific, #A-11077; Goat anti-mouse IgG1 AF488, Thermo Fisher Scientific #A-21121). After an additional 3 washes with PBS, the cells are stained with DAPI (BD Biosciences, #564907), followed by 3 more PBS washes. Finally, the coverslips are mounted on glass slides using ProLong™ Diamond Antifade Mountant (Thermo Fisher #P36965). Cell imaging was performed using a confocal Zeiss LSM900 microscope at 63× magnification, and image analysis was conducted using Zenblue Zeiss software.

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DPEVQFNWYV DGVEVHNAKT KPREEQFNST FRVVSVLTVV HQDWLNGKEY KCKVSNKGLP 360
APIEKTIKST KQQPREPQVY TLPPCREEMT KNQVSLWCLV KGFYPSDIAV EWESNGQOPEN 420
NYKTTPPMLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPG 477

SEQ ID NO: 19      moltype = AA length = 485
FEATURE           Location/Qualifiers
source            1..485
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 19
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWSS ISGGSTYYAD 60
SRKGRTTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMW VWGQGTLVT 120
SSGGGGSGG CGGGGGSQSV LTQPPSASGT PGQRVTISCT GSNSNIGAGY DVHWYQQLPG 180
TAPKLLIYGN NQRPSGVPDF FSGSKSGTS SLAISGLRSE DEADYYCQSY AGNYNLVFGG 240
GTKLTIVLGGG CGGGGGGGG GSVECPCCP APPVAGPSVF LFPPPKPD TLMISRTPEVTC 300
VVVVDVSHEDP EVQFNWYVVG VEVHNAKT KPREEQFNSTFR VVSVLTVHQ DWLNGKEYKC 360
KVSNKGLPAP IFEKTIKSTKG QPREPQVCTL PPSREEMTKN QVSLSCAVKG FYPSDIAVEW 420
ESNGQOPENNY KTTPPMLDSD GSFFLVS KTVDKSRWQQG QVFCSCSVMHEA LHNHYTQKSL 480
SLSLSPG          485

SEQ ID NO: 20      moltype = AA length = 477
FEATURE           Location/Qualifiers
source            1..477
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 20
EVQLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGGGSTYY 60
ADSVKGRTTI SRDNSKNTLY LQMNSLRAED TAVYYCARDF DYWGQGTLVT VTSSGGGGSG 120
GGGSGGGGSG QVLTQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG 180
NINRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTIVLG 240
GGGSGGGGSG GGGSGVECPP CPAPPVAGPS VFLFPPPKPD TLMISRTPEV TCVVVDVSHE 300
DPEVQFNWYV DGVEVHNAKT KPREEQFNST FRVVSVLTVV HQDWLNGKEY KCKVSNKGLP 360
APIEKTIKST KQQPREPQVY TLPPCREEMT KNQVSLWCLV KGFYPSDIAV EWESNGQOPEN 420
NYKTTPPMLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPG 477

SEQ ID NO: 21      moltype = AA length = 477
FEATURE           Location/Qualifiers
source            1..477
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 21
EVQLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGGGSTYY 60
ADSVKGRTTI SRDNSKNTLY LQMNSLRAED TAVYYCARDF DYWGQGTLVT VTSSGGGGSG 120
GGGSGGGGSG QVLTQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG 180
NINRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTIVLG 240
GGGSGGGGSG GGGSGVECPP CPAPPVAGPS VFLFPPPKPD TLMISRTPEV TCVVVDVSHE 300
DPEVQFNWYV DGVEVHNAKT KPREEQFNST FRVVSVLTVV HQDWLNGKEY KCKVSNKGLP 360
APIEKTIKST KQQPREPQVY TLPPSREEMT KNQVSLSCAV KGFYPSDIAV EWESNGQOPEN 420
NYKTTPPMLD SDGSFFLVS KTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPG 477

SEQ ID NO: 22      moltype = AA length = 487

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FEATURE	Location/Qualifiers
source	1..487 mol_type = protein organism = synthetic construct
SEQUENCE: 22	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNNWRQQA PGKGLEWVSS ISSSSSYIYY 60	
ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARAV AAGGMFWGLD QWGQGTLVT 120	
TSSGGGGGGG CGGGGGGSQS VLTOPPSASG TPQQRVTISC SGSRNSNIGSN SVHWWYQQLPG 180	
TAPKLLIYGN SNRPSGVPDF FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLNDHVV 240	
GGGTKLTVLG CGGSGGGGGG GGGSGVECPP CPAPPVAGPS VFLFPKPKD TLMSRTPEV 300	
TCVVVDVSHE DPEVQFNWYV DGVEVHNAKT KPREEQFNST FRVSVLT 360	
KCKVSNKGLP APIEKTSKT KGQPREPQVC TLPPSREEMT KNQVSLWCLV KGFYPSDI 420	
EWESNGQOPEN NYKTTPPMLD SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK 480	
SLSLSPG	487
SEQ ID NO: 23	moltype = AA length = 487
FEATURE	Location/Qualifiers
source	1..487 mol_type = protein organism = synthetic construct
SEQUENCE: 23	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNNWRQQA PGKGLEWVSS ISSSSSYIYY 60	
ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARAV AAGGMFWGLD QWGQGTLVT 120	
TSSGGGGGGG CGGGGGGSQS VLTOPPSASG TPQQRVTISC SGSRNSNIGSN SVHWWYQQLPG 180	
TAPKLLIYGN SNRPSGVPDF FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLNDHVV 240	
GGGTKLTVLG CGGSGGGGGG GGGSGVECPP CPAPPVAGPS VFLFPKPKD TLMSRTPEV 300	
TCVVVDVSHE DPEVQFNWYV DGVEVHNAKT KPREEQFNST FRVSVLT 360	
KCKVSNKGLP APIEKTSKT KGQPREPQVC TLPPSREEMT KNQVSLWCLV KGFYPSDI 420	
EWESNGQOPEN NYKTTPPMLD SDGSFFLVSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK 480	
SLSLSPG	487
SEQ ID NO: 24	moltype = AA length = 477
FEATURE	Location/Qualifiers
source	1..477 mol_type = protein organism = synthetic construct
SEQUENCE: 24	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQQA PGKGLEWVAN INQDGSEKN 60	
VDSMRGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCAREF DYWGQGTLVT VTSSGGGGSG 120	
GGGGGGGGSQ SVLAQPPSAS GTPGQRVTIS CSGSSNIGS NYVYWWYQQLP GTAPKLLIYG 180	
NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLG 240	
GGGGGGGGGG CGGSGVECPP CPAPPVAGPS VFLFPKPKD TLMSRTPEV TCVVVDVSHE 300	
DPEVQFNWYV DGVEVHNAKT KPREEQFNST FRVSVLT 360	
APIEKTSKT KGQPREPQVC TLPPSREEMT KNQVSLWCLV KGFYPSDI 420	
NYKTTPPMLD SDGSFFLVSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPG	477
SEQ ID NO: 25	moltype = AA length = 477
FEATURE	Location/Qualifiers
source	1..477 mol_type = protein organism = synthetic construct
SEQUENCE: 25	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQQA PGKGLEWVAN INQDGSEKN 60	
VDSMRGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCAREF DYWGQGTLVT VTSSGGGGSG 120	
GGGGGGGGSQ SVLAQPPSAS GTPGQRVTIS CSGSSNIGS NYVYWWYQQLP GTAPKLLIYG 180	
NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLG 240	
GGGGGGGGGG CGGSGVECPP CPAPPVAGPS VFLFPKPKD TLMSRTPEV TCVVVDVSHE 300	
DPEVQFNWYV DGVEVHNAKT KPREEQFNST FRVSVLT 360	
APIEKTSKT KGQPREPQVC TLPPSREEMT KNQVSLWCLV KGFYPSDI 420	
NYKTTPPMLD SDGSFFLVSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPG	477
SEQ ID NO: 26	moltype = AA length = 485
FEATURE	Location/Qualifiers
source	1..485 mol_type = protein organism = synthetic construct
SEQUENCE: 26	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIRQA PGKGLEWVSS ISGGSTYYAD 60	
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVT 120	
SSGGGGGGGG GGGGGGGSQSV LTQPPSASGT PGQQRVTISC GSNNIGAGY DVHWWYQQLPG 180	
TAPKLLIYRS NQRPSGVPDF FSGSKSGTSA SLAISGLRSE DEADYYCSSL AGNYNLVFGG 240	
GKTLTVLGCGGGGGGGGG GSGVECPCC APPVAGPSVLF FPKPKDTL MISRTPEVTC 300	
VVVVDVSHEDP EVQFNWYVVG VEVHNAKTKE REEQFNSTR VVSVLTVHQ DWLNKEYKC 360	
KVSNKGLPAP IEKTIKTKG QPREPVYTL PPCREEMTKN QVSLWCLVKG FYPYPSDI 420	
ESNGQOPENNY KTTTPMLDSD GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL 480	
SLSPG	485

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SEQ ID NO: 27      moltype = AA  length = 485
FEATURE
source          Location/Qualifiers
1..485
mol_type = protein
organism = synthetic construct

SEQUENCE: 27
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIRQA PGKGLEWVSS ISGGSTYYAD 60
SRKGRTISR DNSENTLYLQ MNSLRAEDTA VYYCARDVFV AGWFGQYGMV VWGQGLTVT 120
SSGGGGSGGG GSGGGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHWHYQQLPG 180
TAPKLLIYRS NQRPSGPVDR FSGSKSGTSA SLAISGLRSE DEADYYCSSL AGNYNLLVFGG 240
GTKLTVLGGG GSgggggggg GSGVCECPGP APPVAGPSVF LFPPPKDNL MISRTPEVTC 300
VVVDVSHEDP EVQFNWYVDG VEVHNAKTTP REEQFNSTFR VVSVLTVHQ DWLNGKEYKC 360
KVSNKGLPAP IEKTISKTKG QPREPVQVCTL PPSREEMTKN QVSLSCAVKG FYPSDIAVEW 420
ESNGQPENNY KTTPPMLDSD GSFFFLVSKLT VDKSRWQGN VFSCSVMHEA LHNHYTQKSL 480
SLSPG                                     485

SEQ ID NO: 28      moltype = AA  length = 469
FEATURE
source          Location/Qualifiers
1..469
mol_type = protein
organism = synthetic construct

SEQUENCE: 28
EVOLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVSA ISGSGGSTYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDF DYWGQGLTVT VTSSGGGGSG 120
GGGGGGGGSQ SVLTQPPSAS GTPGQRVTIS CSGSSNIGGS NYVYWYQQLP GTAPKLLIYG 180
NINRPSGVFD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD 240
KTHTCPCCPA PEAAGPSVF LFPPPKDNL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG 300
VEVHNAKTTP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG 360
QPREPVYVTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 420
GSFFFLVSKLT VDKSRWQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA 469

SEQ ID NO: 29      moltype = AA  length = 483
FEATURE
source          Location/Qualifiers
1..483
mol_type = protein
organism = synthetic construct

SEQUENCE: 29
EVOLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSYYIYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARAV AAGGMMFWGLD QWGQGLTVT 120
TSSGGGGSGG GSgggggggg VLTQPPSASG TPQGRVTIS CSGRSNIGSN SVHWHYQQLPG 180
TAPKLLIYGN SNRPSGPVDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLNDHVVF 240
GGGTKLTVLD KTHTCPCCPA PEAAGPSVF LFPPPKDNL MISRTPEVTC VVVDVSHEDP 300
EVKFNWYVDG VEVHNAKTTP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP 360
IEKTISKAKG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPSDIAVEW ESNGQPENNY 420
KTTPPVLDSD GSFFFLVSKLT VDKSRWQGN VFSCSVMHEA LHNHYTQKSL SLSPGWHPQ 480
FEK                                     483

SEQ ID NO: 30      moltype = AA  length = 464
FEATURE
source          Location/Qualifiers
1..464
mol_type = protein
organism = synthetic construct

SEQUENCE: 30
EVOLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVSA ISGSGGSTYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDF DYWGQGLTVT VTSSGGGGSG 120
GGGGGGGGSQ SVLTQPPSAS GTPGQRVTIS CSGSSNIGGS NYVYWYQQLP GTAPKLLIYG 180
NINRPSGVFD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLC 240
PPCPAPEAAG APSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN 300
AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP 360
QVYTLPPCRD ELTKNQVSLW CLVKGFYPSD IAVEWESNGQ PENNYKTPP VLDSDGSFFL 420
YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG EPEA 464

SEQ ID NO: 31      moltype = AA  length = 478
FEATURE
source          Location/Qualifiers
1..478
mol_type = protein
organism = synthetic construct

SEQUENCE: 31
EVOLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSYYIYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARAV AAGGMMFWGLD QWGQGLTVT 120
TSSGGGGSGG GSgggggggg VLTQPPSASG TPQGRVTIS CSGRSNIGSN SVHWHYQQLPG 180
TAPKLLIYGN SNRPSGPVDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLNDHVVF 240
GGGTKLTVLC PPCPAPEAAG APSVFLFPPK PKDTLMISRT PEVTCVVVDV SHEDPEVKFN 300
WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI 360
SKAKGQPREP QVCTLPPSRD ELTKNQVSLW CAVKGFYPSD IAVEWESNGQ PENNYKTPP 420

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VLDSDGSFFL VS KLTV DKSR WQQGNVFSCS VMHEALHNH TQKSLSLSPG WSHPQFEK 478

SEQ ID NO: 32 moltype = AA length = 468
 FEATURE Location/Qualifiers
 source 1..468
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 32
 EVQLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGGGGSTYY 60
 ADSVKGRFTI SRD NSKNTLY LQMNSLRAED TAVYYCARDF DYWGQGTLVT VTSSGGGGSG 120
 GGGGGGGGSQ SVLAQPPSAS GTPGQRVTIS CSGSSNIGS NYVYWYQQLP GTAPKLLIYG 180
 NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTLP 240
 LAPCPCPAP EAAGAPS VFL FPPPKD TLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV 300
 EVHNAKTKPR EEQYNSTYRV VS VLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ 360
 PREPQVYTL P CRDELTKNQ VSLWCLVKG YPSDIAVEWE SNGQPENNYK TPPVLDSDG 420
 SFFLYSKLTV DKS RWQ QGNV FSC SVMHEAL HNHYTQKSL S LSPGEPEA 468

SEQ ID NO: 33 moltype = AA length = 482
 FEATURE Location/Qualifiers
 source 1..482
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 33
 EVQLLESGGG LVQPGGSLRL SCAASGFTFS NAMMNWVRQA PGKGLEWVSS ISSSSYYIYY 60
 ADSVKGRFTI SRD NSKNTLY LQMNSLRAED TAVYYCARAV AAGGMFWGLD QWGQGTLTV 120
 TSSGGGGGGG GS GGGGGGSQS VLTOPPSASG TPQQRVTISC SG SRSNIGSN SVHWYQQLPG 180
 TAPKLLIYGN SNRPSGVPD FSGSKSGTA SLAISGLRSE DEADYYCSY DSSLNDHVVF 240
 GGGTKLTLP LAPCPCPAP EAAGAPS VFL FPPPKD TLM ISRTPEVTCV VVDVSHEDPE 300
 VKFNWYVDGV EVHNAKTKPR EEQYNSTYRV VS VLTVLHQD WLNGKEYKCK VSNKALPAPI 360
 EKTISKAKGQ PREPQVCTLP PSRDELTKNQ VSLSCAVKG YPSDIAVEWE SNGQPENNYK 420
 TPPVLDSDG SFFLVSKLT DKS RWQ QGNV FSC SVMHEAL HNHYTQKSL S LSPGWHPQF 480
 EK 482

SEQ ID NO: 34 moltype = AA length = 469
 FEATURE Location/Qualifiers
 source 1..469
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 34
 EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY 60
 VDSMRGRFTI SRD NSKNTLY LQMNSLRAED TAVYYCAREF DYWGQGTLVT VTSSGGGGSG 120
 GGGGGGGGSQ SVLAQPPSAS GTPGQRVTIS CSGSSNIGS NYVYWYQQLP GTAPKLLIYG 180
 NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTLP 240
 KTHTCP CPCA PEAAGAPS VFL FPPPKD TLM MISRTPEVTCV VVDVSHEDPE EVKFNWYVDG 300
 VEVHNAKTKP REEQYNSTYR VVS VLTVLHQD WLNGKEYKCK VSNKALPAP IEKTISKAKG 360
 QPREPQVYTL PPCRDELTKN QVSLWCLVKG FYP S DIAVEW E SNGQPENNY K TPPVLDSDG 420
 SFFLYSKLTV DKS RWQ QGNV VFSC SVMHEA LHNHYTQKSL S LSPGEPEA 469

SEQ ID NO: 35 moltype = AA length = 481
 FEATURE Location/Qualifiers
 source 1..481
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 35
 EVQLLESGGG LVQPGGSLRL SCAASGFTFS DY YMTWIRQA PGKGLEWVSS ISGGSTYYAD 60
 SRKGRFTI SRD NTENSLYQL MNSLRAEDTA VYYCARD FGV AGWFGQYGM D VWGQGTLTV 120
 SSGGGGGGGG GS GGGGGGSQSV LTQPPSASGT PGQRVTISCT GS SNSNIGAGY DVHWYQQLPG 180
 TAPKLLIYRS NQRPSGV PDR FSGSKSGTA SLAISGLRSE DEADYYCSSY AGN YNLF VFGG 240
 GTKLTLPDKT HTC PCPAPAE AAGAPS VFL FPPPKD TLM SRTPEVTCV VDV SHEDPEV 300
 KFNWYVDGV VEVHNAKTKP REEQYNSTYRV SVLTVLHQD WLNGKEYKCK VSNKALPAPIE 360
 KTISKAKGQ QP REPV QV CTLPP SRDELTKNQ VSLSCAVKG YF PSDIAVEW E SNGQPENNY K TPPVLDSDG FFLVSKLT DKS RWQ QGNV FSC SVMHEAL HNHYTQKSL S LSPGWHPQF 480
 K 481

SEQ ID NO: 36 moltype = AA length = 464
 FEATURE Location/Qualifiers
 source 1..464
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 36
 EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY 60
 VDSMRGRFTI SRD NSKNTLY LQMNSLRAED TAVYYCAREF DYWGQGTLVT VTSSGGGGSG 120
 GGGGGGGGSQ SVLAQPPSAS GTPGQRVTIS CSGSSNIGS NYVYWYQQLP GTAPKLLIYG 180
 NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTLP 240
 PNCPA PAPAEAG APSVFL FPPPK PKDTLMISRT PEVTCVV DV SHEDPEV KFN WYV DGVEVHN 300
 AKTKPREEQY NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPA PIEKTI SKAKGQ PREP 360

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QVYTLPPCRD ELTKNQVSLW CLVKGFYP PSD IAVEWESNGQ PENNYKTPP VLSDGSFFL	420
YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG EPEA	464
SEQ ID NO: 37	moltype = AA length = 476
FEATURE	Location/Qualifiers
source	1..476
	mol_type = protein
	organism = synthetic construct
 SEQUENCE: 37	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD	60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLTV	120
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHNYQQLPG	180
TAPKLLIYRS NQRPSGV PDR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFGG	240
GTKLTVLCPP CPAPEAAAGAP SVFLPPPKPK DTLMIISRTPE VTCVVDVSH EDPEVKFNWY	300
VDGVEVHNK PTKREEQYNS TYRVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEK TISK	360
AKQOPREPQV CTLPPSRDEL TKNQVSLCSA VKGFYP PSDIA VEWESENQPE NNYKTPPV	420
DSDGSSFFLVS KLTVDKSRWQ QGNVFS CSVHEALHN HYTQKSLSLSPGWS HPQFEK	476
SEQ ID NO: 38	moltype = AA length = 468
FEATURE	Location/Qualifiers
source	1..468
	mol_type = protein
	organism = synthetic construct
 SEQUENCE: 38	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY	60
VDSMRGRFTI SRDMSKNTLY LQMNSLRAEDTA TAVYYCAREF DYWGQGTLVT VTSSGGGSG	120
GGGGGGGGGSQSV SVLAQPPSAS GTPGQRVTISCT CSGSSSNIGS NYVYVWYQQLP GTAPKLLIYG	180
NNKRPSGV PDR FSGSKSGTSA SLAISGLRSE EDEADYYCAA WDDSLNGRVF GGGTKLTVLP	240
LAPCPPCPAP EAAGAPS VFL FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV	300
EVNNAKTKP R EQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ	360
PREPQVYTL P CRDELTKNQV SVLCLVKG YPSDIAVEWE SNGQPENNYK TPPVLDSDG	420
SFLYSLKLT DKS RWQGNV FSCSVHEALHN HYTQKSLSLSPGEPEA	468
SEQ ID NO: 39	moltype = AA length = 480
FEATURE	Location/Qualifiers
source	1..480
	mol_type = protein
	organism = synthetic construct
 SEQUENCE: 39	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD	60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLTV	120
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHNYQQLPG	180
TAPKLLIYRS NQRPSGV PDR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFGG	240
GTKLTVPLA PCPPCPAPEA AGAPS VFL FPKPKDTLMIS RTPEVTCVV DVSHEDEPEVK	300
FNWYVDGVEV HNAKTKPREE QYNSTYRVVS VLTVLHQDWL NGKEYKCVS NKALPAPIEK	360
TISKAKGQPR EPQVCTLPPS RDELTKNQVS LSCAVKG YPSDIAVEWE SNGQPENNYKTT	420
PPVLDSDGSF FLVSKLTVDK SRWQGNV FSCSVHEALHN HYTQKSLSLSPGEPEA	480
SEQ ID NO: 40	moltype = AA length = 447
FEATURE	Location/Qualifiers
source	1..447
	mol_type = protein
	organism = synthetic construct
 SEQUENCE: 40	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVSA ISGSGGSTYY	60
ADSVKGRTI SRDMSKNTLY LQMNSLRAEDTA TAVYYCARDF DYWGQGTLVT VTSSASTKGP	120
SVFPLAPSSK STSGGTAA ALG CLVKDYFPEP VTVSNWS GAL TSGVHTFP AV LQSSGLYSL	180
SVTVVPSSS GTQTYICNVN HKPSNTKVDK KVEPKSCDKT HTCPCPAPAE AAGAPS VFL	240
PKPKKD TLMIS SRTPEVTCV VDVSHEDPEV KFNWYVDGVE VNNAKTKP R EQYNSTYRV	300
SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQ PR EPQVYTLPP CRDELTKNQV	360
SLWCLVKG YPSDIAVEWE NGQPENNYK TPPVLDSDGS FFLYSLKLTVD KSRWQGNV F	420
SCSVHEALHN HYTQKSLSLSPGEPEA	447
SEQ ID NO: 41	moltype = AA length = 216
FEATURE	Location/Qualifiers
source	1..216
	mol_type = protein
	organism = synthetic construct
 SEQUENCE: 41	
QSVLTQPPSA SGTPGQRVTI SCGSSSNIG SNVYVWYQQL PGTAPKLLIY GNINRPSGV	60
DRPSGSKSGT SASLAISGLR SEDEADYYCA AWDDSLNGRV FGGGTLTVL GQPKAAPS V	120
LFPPSSEELQ ANKATLVCLI SDFYGPAGTV AWKADSSPVK AGVETTPSK QSNNKYAASS	180
YLSLTPEQWK SHRSYSQC QT HEGSTVEKTV APTECS	216
SEQ ID NO: 42	moltype = AA length = 474
FEATURE	Location/Qualifiers

-continued

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source          1..474
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 42
EVQLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGSGGSTYY 60
ADSVKGRTI SRDNSKNTLY LQMNSLRAED TAVYYCARDF DYWGQGTLVT VTSSGGGGSG 120
GGGGGGGGSQ SVLTQPPSAS GTPGQRVTIS CSGSSSNIGS NYVWYQQLP GTAPKLLIYG 180
NINRPGSPVD RFSGSKSGTS SASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTAKLTVL 240
KTHTCPCPCA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEPD EVKFNWYVG 300
VEVHNNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG 360
QPREPQVCTL PPSRDELTKN QVSLSCAVKG FYPSDIAVEW ESNGQPENNY KTPPVLDSD 420
GSFFLVSKL VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGKWSHP QFEK        474

SEQ ID NO: 43      moltype = AA length = 456
FEATURE           Location/Qualifiers
source            1..456
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 43
EVOLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSSYIYY 60
ADSVKGRTI SRDNSKNTLY LQMNSLRAED TAVYYCARAV AAGGMFWGLD QWGQGTLVTV 120
TSSASTKGPS VPPLAPSSKS TSGGTAALGCC LVKDYFPEPV TVSWNSGALT SGVHTFPVAL 180
QSSGLYSLSS VVTVPSSSLG TQTYICCNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEA 240
AGAPSVLFLP PKPKDITLMIS RTPEVTCVVV DVSHEDPEVKV FNWYVDGVEV HNAKTKPREE 300
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPC 360
RDELTKNQVS LWCLVKGFYI SDIAVEWESN QOPENNNYKTT PPVLDSDGSF FLYSKLTVDK 420
SRWQQGNVFS CSVMHEALHN HYTQKSL SLSL PGEPEA                           456

SEQ ID NO: 44      moltype = AA length = 217
FEATURE           Location/Qualifiers
source            1..217
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 44
QSVLTQPPSA SGTPGQRVTI SCGSRSNIG SNSVHWYQQL PGTAPKLLIY GNSNRPSGVP 60
DRFSGSKSGT SASLAISGLR SEDEADYYCQ SYDSSLNDHV VRGGGTLTV LGQPKAAPSV 120
TLFPPSEEL QANKATLVCL ISDFYPGAVT VAWKADSSPV KAGVETTPS KQSNNKYAAS 180
SYLSLTPEQW KSHRSYSCQV THEGSTVEKT VAPTECS                           217

SEQ ID NO: 45      moltype = AA length = 484
FEATURE           Location/Qualifiers
source            1..484
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 45
EVQLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSSYIYY 60
ADSVKGRTI SRDNSKNTLY LQMNSLRAED TAVYYCARAV AAGGMFWGLD QWGQGTLVTV 120
TSSGGGGGG CGGGGGGGSQ VLTQPPSASG TPGRVTISC SGSSRNIGSN SVHWYQQLPG 180
TAPKLLIYGN SNRPGVPD FSGSKSGTSASLAIISGLRSE DEADYYCQST DSSLNDHVVF 240
GGGTAKLTVL KTHTCPCPCA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEPD 300
EVKFNWYVG  VEVHNNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP 360
IEKTISKAKG QPREGQVCTL PPSRDELTKN QVSLSCAVKG FYPSDIAVEW ESNGQPENNY 420
KTPPVLDSD GSFFLVSKL VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGKWSHP 480
QFEK                                         484

SEQ ID NO: 46      moltype = AA length = 447
FEATURE           Location/Qualifiers
source            1..447
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 46
EVQLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY 60
VDSMRGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAREF DYWGQGTLVT VTSSASTKGP 120
SVFPLAPSSK STSGGTAALG CLVKDYFPEPV TVSWNSGAL TSGVHTFPAV LQSSGLYSL 180
SVVTVPSSLG GTQTYICCNVH KPSNTKVDK VEPKSCDKTH HTCPPCPAPE AAGAPSVFLF 240
PPKPKDITLMIS RTPEVTCVVV DVSHEDPEVKV FNWYVDGVEV VHNAKTKPRE EYQNSTYRVV 300
SVLTVLHQDWL LNGKEYKCKV SNKALPAPIE TISKAKGQPR REPQVYTLPP CRDELTKNQV 360
SLWCLVKGFYI PSDIAVEWESN NGQOPENNNYKTT TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF 420
SCSVMHEALHN NHYTQKSL SLSL PGEPEA                                     447

SEQ ID NO: 47      moltype = AA length = 216
FEATURE           Location/Qualifiers
source            1..216
               mol_type = protein
               organism = synthetic construct
SEQUENCE: 47

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QSVLAQPPSA SGTPGQRVTI SCSGSSSNIG SNVYVWYQQL PGTAPKLLIY GNNKRPGVP 60	
DRFRSGSKSGT SASLAIISGLR SEDEADYYCA AWDDSLNGRV FGGGTLTQL GQPKAAPSVD 120	
LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTPSK QSNNKYAASS 180	
YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS 216	
SEQ ID NO: 48	moltype = AA length = 474
FEATURE	Location/Qualifiers
source	1..474
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 48	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY 60	
VDSMRGRFTI SRDNSKNLTY LQMNLSRAED TAVYYCAREF DYWGQGTLVT VTSSGGGSG 120	
GGGGGGGGSQ SVLAQPPSAS GTPGQRVTI CSGSSSNIGS NYVYVWYQQLP GTAPKLLIYG 180	
NNKRPGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAAW DDSSLNGRVF GGGTKLTVLD 240	
KTHTCPPCPA PEAAGAPSVE LFPPPKDQL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG 300	
VEVHNAKTPK REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG 360	
QPREPVQVTL PPSRDELTKN QVSLSCAVKG FYPSDIAVEW ESNQOPENNY KTTPPVLDSD 420	
GSFFLVSQKLT VDKSRWQGN VFSCVMHEA LHNNHYTQKSL SLSPGKWSHP QFEK 474	
SEQ ID NO: 49	moltype = AA length = 455
FEATURE	Location/Qualifiers
source	1..455
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 49	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYMTWIRQA PGKGLEWVSS ISGGSTYYAD 60	
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDPGV AGWFGQYGMV VWGQGTLTV 120	
SSASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPV VSWNSGALTS GVHTFPVALQ 180	
SSGLYVSLSSV VTFPSSSLGT QTYCICNVNHK PSNTKVDDKKV EPKSCDKTHT CPPCPAPEAA 240	
GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEHV NAKTKPREEQ 300	
YNSTYRVVSV LTVLHQDWLN GKEYCKVSN KALPAPIEKT ISKAKQOPRE PQVYLPPCR 360	
DELTKNQVSL WCLVKGFYPS DIAVEWESNG QOPENNYKTTP PVLDSDGSFF LYSKLTVDKS 420	
RWQOGNVFSC SVMHEALHNH YTQKSLSLSP GEPEA 455	
SEQ ID NO: 50	moltype = AA length = 216
FEATURE	Location/Qualifiers
source	1..216
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 50	
QSVLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI YRSNQRPSGV 60	
PDRFSGSKSG TSASLAIISGL RSEDEADYYC SSYAGNMYNLV FGGGTLTQL GQPKAAPSVD 120	
LFPPSSEELQ ANKATLVCLI SDFYPGAVTV AWKADSSPVK AGVETTPSK QSNNKYAASS 180	
YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS 216	
SEQ ID NO: 51	moltype = AA length = 482
FEATURE	Location/Qualifiers
source	1..482
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 51	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYMTWIRQA PGKGLEWVSS ISGGSTYYAD 60	
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDPGV AGWFGQYGMV VWGQGTLTV 120	
SSGGGGSGGG GSGGGGSQSV LTQPSASGT PGQRVTISCT GSSSNIGAGY DVHWYQQLPG 180	
TAPKLLIYRS NQRPSGVPDF FSGSKSGTS SLAISGLRS DEADYYCSSY AGNYNLVFGG 240	
GTKLTVDLKT HTCPCPAPE AAGAPSFLF PPKPKDTLMI SRTPEVTCVV VDVSHEDEPV 300	
KFNWYVGDVE VHNAKTPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE 360	
KTISKAKQGP REPQVCTLPP SRDELTKNOV SLSCAVKGFY PSDIAVEWES NGQOPENNYKT 420	
TPPVLDSDGS FFLVSKLTVQ KSRWQGQNVF SCVMHEALHNH NYHTQKSLSL SPGKWSHPQF 480	
EK 482	
SEQ ID NO: 52	moltype = AA length = 455
FEATURE	Location/Qualifiers
source	1..455
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 52	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVSA ISGSGSTYY 60	
ADSVKGRFTI SRDNSKNLTY LQMNLSRAED TAVYYCARDF DYWGQGTLVT VTSSASVAAP 120	
SFVIFPPPSDE QLKSGTASVV CLLNNFYPRE AKVQWVKDNA LQSGNSQESV TEQDSKDSTY 180	
SLSSTLTLSK ADYEKHKVYA CEVTHQGLSS PVTKSFNRRGE CDKHTCPA PAPEAAGAPS 240	
VFLFPPPKD TLMSRTPEV TCVVVDVSH DPEVFKNWWV DGVEVHNKTPKREEQYNST 300	
YRVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPVQVC TLPPSRDELT 360	
KNQVSLSCAV KGFPYPSDIAV EWESNGQOPEN NYKTTPPVLD SDGSFFLVSQKLTVDKSRWQ 420	
GNVFSCVMHEALHNHYTQK SLSPGKWSHP QFEK 455	

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SEQ ID NO: 53      moltype = AA  length = 215
FEATURE
source          Location/Qualifiers
1..215
mol_type = protein
organism = synthetic construct
SEQUENCE: 53
QSVLTQPPSA SGTPGQRVTI SCSGSSSNIG SNYVYWYQQL PGTAPKLLIY GNINRPGSPV 60
DRFSGSKSGT SASLAISGLR SEDEADYYCA AWDDSLNGRV FGGGTLTVL SSASTKGPSV 120
FPLAPSSKST SGGTAALGCL VKDYFPEPV VSWNSGALT GVHTFPAVLQ SSGLYSLSSV 180
VTPVSSSLGT QTYICCNVNHK PSNTKVDKKV EPKSC 215

SEQ ID NO: 54      moltype = AA  length = 456
FEATURE
source          Location/Qualifiers
1..456
mol_type = protein
organism = synthetic construct
SEQUENCE: 54
EVQLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSYYIYY 60
ADSVVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARAV AAGGMFWGLD QWGQGTLVTV 120
TSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV TVSWNSGALT SGVHTFPABL 180
QSSGLYSLSS VVTVPSSSLT QTQYICCNVNHH KPSNTKVDKKV VEPKSCDKTH TCPPCPAPEA 240
AGAPSVFLFP PKPKDTLMIS RTPEVTCVVV DVSHEDPEVKF FNWYVDGVEV HNAKTKPREE 300
QYNSTYRVVS LTIVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPC 360
RDELTKNQVS LWCLVKGFYP SDIAVEWESN QOPENNYKTT PPVLDSDGSF FLYSKLTVDK 420
SRWQQGNVFS CSVMEALHN HYTQKSLSLS PGEPEA 456

SEQ ID NO: 55      moltype = AA  length = 217
FEATURE
source          Location/Qualifiers
1..217
mol_type = protein
organism = synthetic construct
SEQUENCE: 55
QSVLTQPPSA SGTPGQRVTI SCSGSRSNIG SNSVHWYQQL PGTAPKLLIY GNSNRPGSPV 60
DRFSGSKSGT SASLAISGLR SEDEADYYCA SYDSSLNDHV FVGGGTLTV LGQPKAAPSV 120
TLPSSSEEL QANKATLVCL ISDFYPGAVT VAWKADSSPV KAGVETTPS KQSNNKYAAS 180
SYLSLTPEQW KSHRSYSCQV THEGSTVEKT VAPTECS 217

SEQ ID NO: 56      moltype = AA  length = 455
FEATURE
source          Location/Qualifiers
1..455
mol_type = protein
organism = synthetic construct
SEQUENCE: 56
EVOLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY 60
VDSMRGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAREF DYWGQGTLVTV VTSSASVAAP 120
SVIFNPSSDE QLKSGTASV CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY 180
SLSSTTLTSK ADYEHWKVA CEVTHQGLSS PVTKSFNRGE CDKTHTCPFC PAPEAAGAPS 240
VFLLFPKPKD TLMISRTPEV TCVVVDVSHB DPEVKFNWYV DGVEVHNAKT KPREEQYNST 300
YRVSVSLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVC TLPPSRDELT 360
KNQVSLSCAV KGFYPSDIAV EWESNGQOPEN NYKTTPPVLD SDGSFFLVSK LTVDKSRWQQ 420
GNVFSCSVMH EALHNHYTQK SLSLSPGWSH PQFEK 455

SEQ ID NO: 57      moltype = AA  length = 215
FEATURE
source          Location/Qualifiers
1..215
mol_type = protein
organism = synthetic construct
SEQUENCE: 57
QSVLAQPPSA SGTPGQRVTI SCSGSSSNIG SNYVYWYQQL PGTAPKLLIY GNNKRPGSPV 60
DRFSGSKSGT SASLAISGLR SEDEADYYCA AWDDSLNGRV FGGGTLTVL SSASTKGPSV 120
FPLAPSSKST SGGTAALGCL VKDYFPEPV VSWNSGALT GVHTFPAVLQ SSGLYSLSSV 180
VTPVSSSLGT QTYICCNVNHK PSNTKVDKKV EPKSC 215

SEQ ID NO: 58      moltype = AA  length = 455
FEATURE
source          Location/Qualifiers
1..455
mol_type = protein
organism = synthetic construct
SEQUENCE: 58
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIRQA PGKGLEWVSS ISGGSTYYAD 60
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMW VWGQGTLVTV 120
SSASTKGPSV FPLAPSSKST SGGTAALGCL VKDYFPEPV VSWNSGALT GVHTFPAVLQ 180
SSGLYSLSSV VTPVSSSLGT QTYICCNVNHK PSNTKVDKKV EPKSCDKTHT CPPCPAPEAA 240
GAPSVFLFP PKPKDTLMISR TPEVTCVVV DVSHEDPEVKF NWYVDGVEVH NAKTKPREEQ 300
YNTSTYRVVSV LTIVLHQDWL NGKEYKCKVSN KALPAPIEK TISKAKGQPR PQVYTLPPC 360

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DELTKNQVSL WCLVKGFYPS DIAVEWESNG QPENNYKTPP PVLDSDGSFF LYSKLTVDKS	420
RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GEPEA	455
SEQ ID NO: 59	moltype = AA length = 216
FEATURE	Location/Qualifiers
source	1..216
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 59	
QSVLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI YRSNQRPSGV	60
PDRFSGSKSG RSEDEADYYC SSYAGNNYLW FGGTAKLTVL GQPKAAPSVD	120
LFPSSSEELQ ANKATLVCLI SDFYPAVTV AWKADSSPVK AGVETTTPSK QSNNKYAASS	180
YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS	216
SEQ ID NO: 60	moltype = AA length = 730
FEATURE	Location/Qualifiers
source	1..730
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 60	
EVLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGSGGSTYY	60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDF DYWGQGTLVT VTSSGGGGSG	120
GGGSGGGGSQ SVLNTQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180
NINRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTAKLTVLD	240
KGPSVFPLAP EPKSSEVQLL ESGGGLVQPG GSLRLSCAAS GFTFSNAWMN WVRQAPGKGL	300
EVVSSISSSS SYIYADSVK GRFTISRDNS KNTLYLQMNS LRAEDTAVYY CARAVAAGGM	360
FWGLDQWQGC TLTVTVTSSG GGSGGGGSGG GGSQSVLTQ PPSASGTPGQR VTISCGSRS	420
NIGSNSVHWY QQLPGTAPKL LIYGNNSNRPV GVPDRFSGSK SGTSASLAIS GLRSEDEADYY	480
YCQSYDSSL DHVVFPGGTK LTIVLDKHTC PPCPAPEAAAG APSVFLFPK PKDTLMISRT	540
PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG	600
KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRD ELTKNQVSLT CLVKGFYPSD	660
IAVEWESNGQ PENNYKTPP VLDSDGFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY	720
TQKSLSLSPG	730
SEQ ID NO: 61	moltype = AA length = 730
FEATURE	Location/Qualifiers
source	1..730
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 61	
EVLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSSYIYY	60
ADSVKGRFTI SRDNNSKNTLY LQMNSLRAED TAVYYCARAV AAGGMFWGLD QWGQGTLVTV	120
TSSGGGGSGG CGSGGGGSQS VLTQPPSASG TPQGQRTVTC SGSRNSNIGSN SVHWYQQLPG	180
TAPKLLIYG DNRPSGVPD RFSGSKSGTS ASLAISGLRS DEADYYCQSY DSSLNDHVVF	240
GGGTAKLTVLD KGPSVFPLAP EPKSSEVQLL ESGGGLVQPG GSLRLSCAAS GFTFSIYAMS	300
WVRQAPGKGL EWVSAISGSG GSTYYADSVK GRFTISRDNS KNTLYLQMNS LRAEDTAVYY	360
CARDFDWQGC TLTVTVTSSG GGGGGGGGG GGGSQSVLTQ PPSASGTPGQ RVTISCGS	420
SNIGSNSVHWY QQLPGTAPKL LIYGNINRPV SGVPDRFSGS KSGTSASLAIS GLRSEDEADYY	480
YYCAAWDDSL NGRVFGGGTK LTIVLDKHTC PPCPAPEAAAG APSVFLFPK PKDTLMISRT	540
PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY NSTYRVVSVL TVLHQDWLNG	600
KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRD ELTKNQVSLT CLVKGFYPSD	660
IAVEWESNGQ PENNYKTPP VLDSDGFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY	720
TQKSLSLSPG	730
SEQ ID NO: 62	moltype = AA length = 728
FEATURE	Location/Qualifiers
source	1..728
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 62	
EVLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY	60
VDSMRGRFTI SRDNNSKNTLY LQMNSLRAED TAVYYCAREF DYWGQGTLVT VTSSGGGGSG	120
GGGSGGGGSQ SVLAQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180
NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTAKLTVLD	240
KGPSVFPLAP EPKSSEVQLL ESGGGLVQPG GSLRLSCAAS GFTFSDYMMT WIRQAPGKGL	300
EVVSSISCGS TTYYADSRKG FTISRDNSEN TLVYLMQNSLR AEDTAVYYCA RDFGVAGWFG	360
QYGMDDVWQGC TLTVVSSGGG GSQGGGGGGG GSQSVLTQPP SASGTPGQRV TISCTGSSN	420
IGAGYDVHWY QQLPGTAPKL LIYRSNQRPS GVPDRFSGSK SGTSASLAIS GLRSEDEADYY	480
YCCSYAGNNY LVFGGGTAKL VLDKTHTCPP CPAPEAAAGAP SVFLFPKPK DTLMISRTPE	540
VTCVVVDVSH EDPEVKFNWY DGVEVHNAK TKPREEQYNS TYRVRVSVLTV LHQDWLNGKE	600
YCKKVSNKAL PAPIEKTI SKAKGQPREPQV YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA	660
VEWESNGQPE NNYKTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCVM HEALHNHYTQ	720
KSLSLSPG	728
SEQ ID NO: 63	moltype = AA length = 728
FEATURE	Location/Qualifiers

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source          1..728
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 63
EVQLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIRQA PGKGLEWSS ISGGSTYYAD 60
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYVYCARDFGV AGWFQGYGMD VWGQGTLVT 120
SSGGGGGGGG GSQSVLQSQSV LTQPPSASGT PGQRVTISCT CGSSSNIGAGY DVHWWYQQLPG 180
TAPKLLIYRS NQRPSPGPDR FSGSKSGTS SLAISGLRSE DEADYYCSSL AGNYNLVFGG 240
GTKLTVLDKG PSVFPLAPEP KSSEVQLLES GGGLVQPGGS LRLSCAASGF TFSSYAMSWV 300
RQAPGKGLEW VANINQDGSE KNYVDSMRGR FTISRDNSKN TLYLQMNLSR AEDTAVYYCA 360
REFPDYWQGQ 1YTWTQSGGG GSQSVLAQPP SASGTPQQRV TISCSCGSSN 420
IGSNYVWYQ QLPGTAPKLL IYGNNKRPSPG VPDRFSGSKS GTSASLAISG LRSEDEADYY 480
CAAWDDSLNG RVFGGGTKLT VLDKHTCPP CPAPEAAGAP SVFLFPKP KDTLMSRTPE 540
VTCVVVDVSH EDPEVKFNWV DVGVEVHNNAK TKPREEQYNS TYRVRVSVLTV LHQDWLNKG 600
YKCKVSNKAL PAPIKEKAKG QKGPQPVQV YTLPSSRDEL TKNQVSLTCL VKGFYPSDIA 660
VIEWESNCQPE MNYKTTPPVLD SDGSFFFLYS KLTVDKSRWQ QGNVFCSSVM HEALHNHYTQ 720
KSLSLSPG                                         728

SEQ ID NO: 64          moltype = AA length = 724
FEATURE
source          1..724
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 64
EVQLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGSGGSTYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDF DYWGQGTLVT VTSSGGGGSG 120
GGGGGGGGSQ SVLTQPPSAS GTPQRVTIS CGSSSNIGS NYVYVWYQQLP GTAPKLLIYG 180
NNIRPSPGPDR FSGSKSGTS SLAISGLRS EDEADYYCAA WDDSLNCRVF GGGTKLTVLD 240
KTHTCPCPA PEAAGAPSVP LFPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKPNWYVDG 300
VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG 360
QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSPDIAREW ESNQOPENNY KTPPVLDSD 420
GSFFFLYSLKT DVKSRSWQGN VFSCSVMHEA LHNHYTQKSL SLSPGGGGGS GGGGSEVQLL 480
ESGGGLVQPG GSRLSCAAS GFTFSNAWMN WVRQAPGKGL EWVSSISSSS SYIYYADSVK 540
GRFTISRDNS KNTLYLQMN LRAEDTAVYY CARAVAAGM FWGLDQWQG TLVTVTSSGG 600
GGGGGGGGGG GGSQSVLTQ PPSASGTPQV VTISCGSRS NIGNSNSVHWY QQLPGTAPKL 660
LIYGNNSNRP S GVPDRFSGSK SGTASLASI GLRSEDEAD YYCAAWDDSL DHVVFGGT 720
LTVL                                         724

SEQ ID NO: 65          moltype = AA length = 724
FEATURE
source          1..724
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 65
EVQLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSSYIYY 60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARAV AAGGMFWGLD QWGQGTLVT 120
TSSGGGGGG GSQSVLQSQSV LTQPPSASG TPQQRVTIS CGSRSNIGSN SVHWWYQQLPG 180
TAPKLLIYGN NQRPSPGPDR FSGSKSGTS SLAISGLRSE DEADYYCQSY DSSLNDHVVF 240
GGGTKLTVLD KTHTCPCPA PEAAGAPSVP LFPPPKPKDTL MISRTPEVTC VVVDVSHEDP 300
EVKPNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP 360
IEKTISKAKG QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSPDIAREW ESNQOPENNY 420
KTPPVLDSD GSFFFLYSLKT DVKSRSWQGN VFSCSVMHEA LHNHYTQKSL SLSPGGGGGS 480
GGGGSEVQLL ESGGGLVQPG GSRLSCAAS GFTFSIYAMS WVRQAPGKGL EWVSAISGSG 540
GSTYYADSVK GRFTISRDNS KNTLYLQMN LRAEDTAVYY CARDFDYWQ TLTVVTSSGG 600
GGGGGGGGGG GGSQSVLTQ PPSASGTPQV RVTISCGSRS SNIGSNVWY YQQLPGTAPK 660
LIYGNINRP S GVPDRFSGSK SGTASLASI SGLRSEDEAD YYCAAWDDSL NGRVFGGGT 720
LTVL                                         724

SEQ ID NO: 66          moltype = AA length = 722
FEATURE
source          1..722
               mol_type = protein
               organism = synthetic construct

SEQUENCE: 66
EVQLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY 60
VDSMRGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAREF DYWGQGTLVT VTSSGGGGSG 120
GGGGGGGGSQ SVLAQPPSAS GTPQRVTIS CGSSSNIGS NYVYVWYQQLP GTAPKLLIYG 180
NNIRPSPGPDR FSGSKSGTS SLAISGLRS EDEADYYCAA WDDSLNCRVF GGGTKLTVLD 240
KTHTCPCPA PEAAGAPSVP LFPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKPNWYVDG 300
VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG 360
QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSPDIAREW ESNQOPENNY KTPPVLDSD 420
GSFFFLYSLKT DVKSRSWQGN VFSCSVMHEA LHNHYTQKSL SLSPGGGGGS GGGGSEVQLL 480
ESGGGLVQPG GSRLSCAAS GFTFSDYMMT WIRQAPGKGL EWVSSISGGS TYYADSRKGR 540
FTISRDNSEN TLYLQMNLSR AEDTAVYYCA RDGVAGWFG QYGMWDWQG TLTVVSSGG 600
GGGGGGGGGG GSQSVLTQPP SASGTPQVRV TISCTGSSSN IGAGYDVHWY QQLPGTAPKL 660
LIYRSNQRPS S GVPDRFSGSK SGTASLASI SGLRSEDEAD YYCAAWDDSL NGRVFGGGT 720
LTVL                                         720

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VL		722
SEQ ID NO: 67	moltype = AA length = 722	
FEATURE	Location/Qualifiers	
source	1..722	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 67		
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIRQA PGKGLEWSS ISGGSTYYAD 60		
SRKGKGRFTISR DNSENTLYLQ MNSLRAEDTA VYVYCARDGFG AGWFGQYGMW VWGQGTLVT 120		
SSCGGGSGGG SGGGGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHWFQQLPG 180		
TAPKLILYRS NQRPSGVPDF FSGSKSGTS SLAISGLRSE DEADYYCSS AGNYNLVFGG 240		
GTKLTVDLDT HTCPCPAPE AAGAPSFLF PPCKPKDLM1 SRTPEVTCVV VDVSHEDPEV 300		
KFNVWYDVGVE VHNAKTKPQE EQYNTSYR VSVLTVLHQDW LNGKEYKCKV SNKALPAPIE 360		
KTISKAKGQEP REPQVYTLPP SRDELTKNQV SLTCLVKGFY PSDIAWEWS NGQPENNYKT 420		
TPPPVLDSDGS FFLYSKLTVD KSRWQGQNVF SCSCVMHEALTH NHYTQKSLSL SPGGGGGGGG 480		
GGSEVQLLES GGGLVQPGGS LRLSCAASGF TFSSYAMSWW RQAPGKGLEW VANINQDGSE 540		
KNYVDSMRGR PTISRDNSR TLYLQMNSLR AEDTAVYYCA REFIDYWGQGT LVTVTSSGGG 600		
GSGGGGGGGG GSQSVAQPP SASGTPGQRV TISCSCGSSSN IGSNYVYWWQ QLPGTAPKLL 660		
IYGNNNKRPSG VPDRFSGSKS GTSASLAISG LRSEDEADYY CAAWDDSLNG RVFGGGTAKLT 720		
VL		722
SEQ ID NO: 68	moltype = AA length = 575	
FEATURE	Location/Qualifiers	
source	1..575	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 68		
EVQLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGSGGSTYY 60		
ADSVVKGRFTI SRDNKNTLY LQMNSLRAED TAVYYCARDF DYWGQGTLVT VTSSPAPNLL 120		
GGPEVQLLES GGGLVQPGGS LRLSCAASGF TFSNAWMNWV RQAPGKGLEW VSSISSSSY 180		
IYVADSVKGR FTISRDNSKN TLYLQMNSLR AEDTAVYYCA RAVAAGGMFW GLDQWGQGTL 240		
VTVTSSASTK GPSVFPPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVWSNNG ALTSGVHTFP 300		
AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHHKPSNTKV DKKVEPKSCD KTHTCPPCPA 360		
PEAAGAPSFSV LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP 420		
REEQYNSTYR VVSVLTVLHQ DWLNKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL 480		
PPSRDELTKN QVSLTCLVKG FYPSPDIAREV ESNQGPENNY KTTTPVLDSD GSFFFLYSKLT 540		
VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPG		575
SEQ ID NO: 69	moltype = AA length = 336	
FEATURE	Location/Qualifiers	
source	1..336	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 69		
QSVLTQPPSA SGTPGQRVTI SCSCGSSSNIG SNVYVWYQQL PGTAPKLLIV GNINRPSGVP 60		
DRFGSGKSGT SASLAISGLR SEDEADYYCA AWDDSLNDRFG FGGGTKLTVL PAPNLLGGPQ 120		
SVLTQPPSAS GTPGQRVTIS CSGRSRNIGS NSVHWYQQLP GTAPKLLIVY NSNRPSGVPD 180		
RFGSGKSGTS ASLAISGLRS EDEADYYCOS YDSSLNDHV FGGGTKLTVL GQPKAAPSVT 240		
LFPPSSEELQ ANKATLVCCLI SDFYPGAVTV AWKADSSPVK AGVETTPSK QSNNKYAASS 300		
YLSLTPEQWK SHRSYSCQVT HEGSTVEKTV APTECS		336
SEQ ID NO: 70	moltype = AA length = 575	
FEATURE	Location/Qualifiers	
source	1..575	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 70		
EVOLLESGGG LVQPGGSLRL SCAASGFTFS NAWMMNWVRQA PGKGLEWVSS ISSSSSYIY 60		
ADSVVKGRFTI SRDNKNTLY LQMNSLRAED TAVYYCARAV AAGGMFWGLD QWGQGTLVT 120		
TSSPAPNLLG GPEVQLLES GGLVQPGGS RLSCAASGF PSIYAMSWR QAPGKGLEWV 180		
SAISGSGST YYADSVKGRF TISRDNSKN TLYLQMNSLR EDTAVYYCAR DFDPYWGQGTL 240		
VTVTSSASTK GPSVFPPLAPS SKSTSGGTAA LGCLVKDYFP EPVTVWSNNG ALTSGVHTFP 300		
AVLQSSGLYS LSSVVTVPSS SLGTQTYICN VNHHKPSNTKV DKKVEPKSCD KTHTCPPCPA 360		
PEAAGAPSFSV LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP 420		
REEQYNSTYR VVSVLTVLHQ DWLNKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL 480		
PPSRDELTKN QVSLTCLVKG FYPSPDIAREV ESNQGPENNY KTTTPVLDSD GSFFFLYSKLT 540		
VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPG		575
SEQ ID NO: 71	moltype = AA length = 336	
FEATURE	Location/Qualifiers	
source	1..336	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 71		
QSVLTQPPSA SGTPGQRVTI SCSCGSRNIG SNSVHWYQQL PGTAPKLLIV GNSNRPSGVP 60		

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DRFSGSKSGT SASLAISGLR SEDEADYYCQ SYDSSLNDHV VFGGGTKLTV LPAPNLLGGP 120
QSVLTQPPSA SGTPGQRVTI SCGSSSNIG SNVYVWYQQL PGTAPKLLIY GNINRPGVP 180
DRFSGSKSGT SASLAISGLR SEDEADYYCA AWDDSLNGRV FGGGTLTVL GQPKAAPSVT 240
LFPSSSEELQ ANKATLVLCL SDFYPGAVTV AWKADSSPVK AGVETTPSK QSNNKYAASS 300
YSLTPEQWK HRSYSCQVT HEGSTVEKTV APTECS 336
SEQ ID NO: 72 moltype = AA length = 574
FEATURE Location/Qualifiers
source 1..574
mol_type = protein
organism = synthetic construct
SEQUENCE: 72
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY 60
VDSMRGRTFI SRDNSKNTLY LQMNLSLRAED TAVYYCAREF DYWGQGTLVT VTSSPAPNLL 120
GGPEVQLLES GGGLVQPGGS LRLMSAASGF TFSDDYMTWI RQAPGKGLEW VSSISGGSTY 180
YADSRKGRTF ISRDNSENTL YLQMNLSLRAE DTAVYYCARD FGVAGWFGQY GMWDVWQGTL 240
VTVSSASTKG PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTWSWNSGA LTSGVHTFP 300
VLOQSSGLYSL SSVVTPVSSS LGTQTYICNV NHKPSNTKVD KKVEPKSCDK THTCPCCPAP 360
EAAGAPSFL FPPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR 420
EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPOVYTL 480
PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TPPVLDSDG SFFLYSKLT 540
DKSRWQQGNV FSCSVMHEAL HNHYTQKSL S LSPG 574
SEQ ID NO: 73 moltype = AA length = 335
FEATURE Location/Qualifiers
source 1..335
mol_type = protein
organism = synthetic construct
SEQUENCE: 73
QSVLQAOPPSA SGTPGQRVTI SCGSSSNIG SNVYVWYQQL PGTAPKLLIY GNINRPGVP 60
DRFSGSKSGT SASLAISGLR SEDEADYYCA AWDDSLNGRV FGGGTLTVL PAPNLLGGPQ 120
SVLTQPPSAS GTPGQRVTIS CTGSSSNIGA GYDVHWYQQL PGTAPKLLIY RSNRPGVP 180
DRFSGSKSGT SASLAISGLR SEDEADYYCS SYAGNYNLNFV GGGTKLTVLG QPKAAPSVT 240
FPPSSEELQA NKATLVLCLIS DFYPGAVTVKA WKADSSPVKA GVETTPSKQ SNNKYAASSY 300
YSLTPEQWK HRSYSCQVT EGSTVEKTV PTECS 335
SEQ ID NO: 74 moltype = AA length = 574
FEATURE Location/Qualifiers
source 1..574
mol_type = protein
organism = synthetic construct
SEQUENCE: 74
EVQLLESGGG DVQPGGSLRL SCAASGFTFS DYMMTWIRQA PGKGLEWVSS ISGGSTYYAD 60
SRKGRFTISR DNSENTLYLQ MSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVT 120
SSPAPNLLGG PEVQLLES GG GLVQPGGSLR LSCAASGFTF SSYAMSWVRQ APGKGLEWVA 180
NINQDGSEKN YVDSMRGRTF ISRDNSKNTL YLQMNLSLRAE DTAVYYCARE FDYWGQGTL 240
TVTSSASTKG PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTWSWNSGA LTSGVHTFP 300
VLOQSSGLYSL SSVVTPVSSS LGTQTYICNV NHKPSNTKVD KKVEPKSCDK THTCPCCPAP 360
EAAGAPSFL FPPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR 420
EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPOVYTL 480
PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TPPVLDSDG SFFLYSKLT 540
DKSRWQQGNV FSCSVMHEAL HNHYTQKSL S LSPG 574
SEQ ID NO: 75 moltype = AA length = 335
FEATURE Location/Qualifiers
source 1..335
mol_type = protein
organism = synthetic construct
SEQUENCE: 75
QSVLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI YRSNQRPSPV 60
PDRFSGSKSG TSASLAISGL RSEDEADYYC SSYAGNYNLW FGGGTLTVL PAPNLLGGPQ 120
SVLAQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYVWYQQLP GTAPKLLIYG NNKRPGVPD 180
RFGSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLG QPKAAPSVT 240
FPPSSEELQA NKATLVLCLIS DFYPGAVTVKA WKADSSPVKA GVETTPSKQ SNNKYAASSY 300
YSLTPEQWK HRSYSCQVT EGSTVEKTV PTECS 335
SEQ ID NO: 76 moltype = AA length = 469
FEATURE Location/Qualifiers
source 1..469
mol_type = protein
organism = synthetic construct
SEQUENCE: 76
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYAMSWVRQA PGKGLEWVSA ISGSGGVTVY 60
ADSVKGRTFI SRDNSKNTLY LQMNLSLRAED TAVYYCAREF DWWGQGTLVT VTSSGGGGSG 120
GGGSGGGGSQ SVLTQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYVWYQQLP GTAPKLLIYG 180
NINRPGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD 240

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KTHTCPPCPA	PEAACAPSVF	LFPPPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVG	300
VEVHNAKTP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPVYVT	PPCRDELTKN	QVSLWCLVKG	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 77	moltype = AA length = 469					
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 77						
EVQLLESGGG	LVQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVSA	ISGSGGSTYY	60
ADSVKGRFTI	SRDNSKNTLY	LQMNSLRAED	TAVYYCAREF	DWYGQGTLVT	VTSSGGGSG	120
GGGSGGGGSQ	SVLTQPPSAS	GTPGQRVTIS	CSGSSSNIGS	NYVYWYQQLP	GTAPKLLIYG	180
NINRPSGVPD	RFGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGTKLTVD	240
KTHTCPPCPA	PEAACAPSVF	LFPPPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVG	300
VEVHNAKTP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPVYVT	PPCRDELTKN	QVSLWCLVKG	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 78	moltype = AA length = 469					
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 78						
EVQLLESGGG	LVQPGGSLRL	SCAASGFTFS	DYAMSWVRQA	PGKGLEWVSA	ISGSGGATYY	60
ADSVKGRFTI	SRDNSKNTLY	LQMNSLRAED	TAVYYCAREF	DYWGQGTLVT	VTSSGGGSG	120
GGGSGGGGSQ	SVLTQPPSAS	GTPGQRVTIS	CSGSSSNIGS	NYVYWYQQLP	GTAPKLLIYG	180
NINRPSGVPD	RFGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGTKLTVD	240
KTHTCPPCPA	PEAACAPSVF	LFPPPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVG	300
VEVHNAKTP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPVYVT	PPCRDELTKN	QVSLWCLVKG	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 79	moltype = AA length = 469					
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 79						
EVQLLESGGG	LVQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVAN	INQDGSEKNY	60
VDSMRGRFTI	SRDNSKNTLY	LQMNSLRAED	TAVYYCARDY	RYWGQGTLVT	VTSSGGGSG	120
GGGSGGGGSQ	SVLAQPPSAS	GTPGQRVTIS	CSGSSSNIGS	NYVYWYQQLP	GTAPKLLIYG	180
NNKRPSGVPD	RFGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGTKLTVD	240
KTHTCPPCPA	PEAACAPSVF	LFPPPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVG	300
VEVHNAKTP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPVYVT	PPCRDELTKN	QVSLWCLVKG	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 80	moltype = AA length = 469					
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 80						
EVQLLESGGG	LVQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVAN	INQDGSEKNY	60
VDSMRGRFTI	SRDNSKNTLY	LQMNSLRAED	TAVYYCARY	KYWGQGTLVT	VTSSGGGSG	120
GGGSGGGGSQ	SVLAQPPSAS	GTPGQRVTIS	CSGSSSNIGS	NYVYWYQQLP	GTAPKLLIYG	180
NNKRPSGVPD	RFGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGTKLTVD	240
KTHTCPPCPA	PEAACAPSVF	LFPPPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVG	300
VEVHNAKTP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPVYVT	PPCRDELTKN	QVSLWCLVKG	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 81	moltype = AA length = 469					
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 81						
EVQLLESGGG	LVQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVAN	INQDGSEKNY	60
VDSMRGRFTI	SRDNSKNTLY	LQMNSLRAED	TAVYYCAREY	KYWGQGTLVT	VTSSGGGSG	120
GGGSGGGGSQ	SVLAQPPSAS	GTPGQRVTIS	CSGSSSNIGS	NYVYWYQQLP	GTAPKLLIYG	180
NNKRPSGVPD	RFGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGTKLTVD	240
KTHTCPPCPA	PEAACAPSVF	LFPPPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVG	300

GSFFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469
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VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG	360
QPREPQVYTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469

SEQ ID NO: 82	moltype = AA length = 469
FEATURE	Location/Qualifiers
source	1..469
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 82	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY	60
VDSMGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCAREY QYWQGQTLVT VTSSGGGSG	120
GGGSGGGGSQ SVLAQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180
NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG	300
VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG	360
QPREPQVYTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469

SEQ ID NO: 83	moltype = AA length = 469
FEATURE	Location/Qualifiers
source	1..469
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 83	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY	60
VDSMGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARNY QYWQGQTLVT VTSSGGGSG	120
GGGSGGGGSQ SVLAQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180
NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG	300
VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG	360
QPREPQVYTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469

SEQ ID NO: 84	moltype = AA length = 469
FEATURE	Location/Qualifiers
source	1..469
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 84	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY	60
VDSMGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARNY QYWQGQTLVT VTSSGGGSG	120
GGGSGGGGSQ SVLAQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180
NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG	300
VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG	360
QPREPQVYTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469

SEQ ID NO: 85	moltype = AA length = 469
FEATURE	Location/Qualifiers
source	1..469
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 85	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGSGGSTYY	60
ADSVKGRTI SRDNSKNTLY LQMNLSRAED TAVYYCARDG LYWGQGQTLVT VTSSGGGSG	120
GGGSGGGGSQ SVLTQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180
NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG	300
VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG	360
QPREPQVYTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469

SEQ ID NO: 86	moltype = AA length = 469
FEATURE	Location/Qualifiers
source	1..469
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 86	

EVOLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGSGGSTYY	60
ADSVKGRTI SRDNSKNTLY LQMNLSRAED TAVYYCARNW DYWGQGQTLVT VTSSGGGSG	120
GGGSGGGGSQ SVLTQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180
NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG	300
VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG	360

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QPREPQVYTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469
SEQ ID NO: 87	moltype = AA length = 469
FEATURE	Location/Qualifiers
source	1..469
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 87	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGSGGSTYY	60
ADSVKGRTI SRDNSKNTLY LQMNLSRAED TAVYYCARNQ DWFGQGTLVT VTSSGGGSG	120
GGGGGGGGSQ SVLTQPPSAS GTPGQRTVIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180
NINRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPSFL FPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG	300
VEVHNAKTTP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC VVSNKALPAP IEKTISKAKG	360
QPREPQVYTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469
SEQ ID NO: 88	moltype = AA length = 469
FEATURE	Location/Qualifiers
source	1..469
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 88	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGSGGSTYY	60
ADSVKGRTI SRDNSKNTLY LQMNLSRAED TAVYYCARNQ DWFGQGTLVT VTSSGGGSG	120
GGGGGGGGSQ SVLTQPPSAS GTPGQRTVIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180
NINRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPSFL FPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG	300
VEVHNAKTTP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC VVSNKALPAP IEKTISKAKG	360
QPREPQVYTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469
SEQ ID NO: 89	moltype = AA length = 469
FEATURE	Location/Qualifiers
source	1..469
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 89	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVA ISGSGGSTYY	60
ADSVKGRTI SRDNSKNTLY LQMNLSRAED TAVYYCARNQ DWFGQGTLVT VTSSGGGSG	120
GGGGGGGGSQ SVLTQPPSAS GTPGQRTVIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180
NINRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPSFL FPPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG	300
VEVHNAKTTP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC VVSNKALPAP IEKTISKAKG	360
QPREPQVYTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469
SEQ ID NO: 90	moltype = AA length = 468
FEATURE	Location/Qualifiers
source	1..468
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 90	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYWMSWVRQA PGKGLEWVAN IKQDGSEKNY	60
VDSMRGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCAREY DYWGQGTLVT VTSGGGGSG	120
GGGGGGGSQS VLAQPPSASG TPQGQRTISC SGSSSNIGSN YVYWYQQLPG TAPKLLIYGN	180
NKRPSGVPDF FSGSKSGTS ASLAISGLRSE DEADYYCAA DDSSLNGRVFG GGTKLTVLDK	240
THTCPPCPAP EAAGAPSFL FPPPKPKDTLM ISRTPEVTC VVVDVSHEDPE VKFNWYVDG	300
EVHNAKTTPK REEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ	360
PREPQVYTL PPCRDELTKNQ VSLWCLVKGF YPSDIAVEWE SNGQGPENNYK TTPPVLDSDG	420
SFFFLYSKLT DKSRSWQGN VFSCSVMHEAL HNHYTQKSL SLSPGEPEA	468
SEQ ID NO: 91	moltype = AA length = 468
FEATURE	Location/Qualifiers
source	1..468
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 91	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYWMSWVRQA PGKGLEWVAN INQDGSEKYY	60
VDSMRGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCAREY DYWGQGTLVT VTSGGGGSG	120
GGGGGGGSQS VLAQPPSASG TPQGQRTISC SGSSSNIGSN YVYWYQQLPG TAPKLLIYGN	180
NKRPSGVPDF FSGSKSGTS ASLAISGLRSE DEADYYCAA DDSSLNGRVFG GGTKLTVLDK	240
THTCPPCPAP EAAGAPSFL FPPPKPKDTLM ISRTPEVTC VVVDVSHEDPE VKFNWYVDG	300
EVHNAKTTPK REEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ	360
PREPQVYTL PPCRDELTKNQ VSLWCLVKGF YPSDIAVEWE SNGQGPENNYK TTPPVLDSDG	420

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SFFFLYSKLT	V DKSRWQQGN	FSCSVMHEAL	HNHYTQKSLS	LSPGEPEA	468
SEQ ID NO: 92		moltype = AA	length = 468		
FEATURE		Location/Qualifiers			
source		1..468			
		mol_type = protein			
		organism = synthetic construct			
SEQUENCE: 92					
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS	SYWMSWVRQA	PGKGLEWVAN	IKQDGSEKNY	60
VDSMRGRFTI SRDNSKNTLY	LQMNSLRAED	TAVYYCAREF	DWWGQGTLVT	VSSGGGGSGG	120
GGGGGGGSQS VLAQPPSASC	GTPQRVTIS	CSGSSSNIGNS	YVYWYQQLPG	TAPKLLIYGN	180
NKRPSGVPDF FSGSKSGTS	SLAISGLRSE	DEADYYCAAW	DDSLNGRVFG	GGTKLTVLDK	240
THTCPPCPAP EAAGAPSFL	FPPPKDTL	ISRTPEVTCV	VVDVSHEDPE	VKFNWYVDGV	300
EVHNAKTKP REEQYNSTYR	VSVLTVLHQD	WLNGKEYKCK	VSNKALPAPI	EKTISKAKGQ	360
PREPQVYTL PCRDELTKN	VSLWCLVKGF	YPSDIAVEWES	SNQOPENNYK	TTPPVLDSDG	420
SFFFLYSKLT	V DKSRWQQGN	FSCSVMHEAL	HNHYTQKSLS	LSPGEPEA	468
SEQ ID NO: 93		moltype = AA	length = 469		
FEATURE		Location/Qualifiers			
source		1..469			
		mol_type = protein			
		organism = synthetic construct			
SEQUENCE: 93					
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS	DYAMSWVRQA	PGKGLEWVAN	INQDGSEKNY	60
VDSMRGRFTI SRDNSKNTLY	LQMNSLRAED	TAVYYCAREF	DWWGQGTLVT	VSSGGGGSGG	120
GGGGGGGSQ SVLAQPPSAS	GTPQRVTIS	CSGSSSNIGNS	YVYWYQQLPG	GTAPKLLIYG	180
NNKRPSGVPD FSGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPSFL	LFPPKPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVDG	300
VEVHNAKTKP REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKCK	KVSNKALPAP	IEKTISKAKG	360
QREPQVYTL PCRDELTKN	QVSLWCLVKG	FYPSDIAVEWES	SNQOPENNYK	TTPPVLDSDG	420
GSFFFLYSKLT VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSLS	SLSPGEPEA		469
SEQ ID NO: 94		moltype = AA	length = 469		
FEATURE		Location/Qualifiers			
source		1..469			
		mol_type = protein			
		organism = synthetic construct			
SEQUENCE: 94					
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS	DYAMSWVRQA	PGKGLEWVAN	INQDGSEKNY	60
VDSMRGRFTI SRDNSKNTLY	LQMNSLRAED	TAVYYCAREF	DWWGQGTLVT	VSSGGGGSGG	120
GGGGGGGSQ SVLAQPPSAS	GTPQRVTIS	CSGSSSNIGNS	YVYWYQQLPG	GTAPKLLIYG	180
NNKRPSGVPD FSGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPSFL	LFPPKPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVDG	300
VEVHNAKTKP REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKCK	KVSNKALPAP	IEKTISKAKG	360
QREPQVYTL PCRDELTKN	QVSLWCLVKG	FYPSDIAVEWES	SNQOPENNYK	TTPPVLDSDG	420
GSFFFLYSKLT VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSLS	SLSPGEPEA		469
SEQ ID NO: 95		moltype = AA	length = 481		
FEATURE		Location/Qualifiers			
source		1..481			
		mol_type = protein			
		organism = synthetic construct			
SEQUENCE: 95					
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS	DYYMTWIROA	PGKGLEWVSS	ISGGSTYYAD	60
SRKGRTISR DNSENTLYR	MNSLRAEDTA	VYYCARDFGV	AGWFQGYGMD	VWGQGTLVT	120
SSGGGGGGGG GGGGGGSQSV	LTPQPPSASGT	PGQRVTISCT	GSSENIGAGY	DVHWYQQLPG	180
TAPKLLIYRS NQRPSGPDR	FSGSKSGTS	SLAISGLRSE	DEADYYCSSY	AGNYNLVFGG	240
GTKLTVLDKT HTCPCPAPE	AAGAPSFLF	PPPKPKDTLM	SRTPEVTCVV	VDVSHEDPEV	300
KFNWYVDGVE VHNAKTKP	EQYNSTYRVV	SVLTVLHQDWLNGKEYKCKV	SNKALPAPIE	360	
KTISKAKGQP REPQVCLLPP	SRDELTKNQV	SLSCAVKGFY	PSDIAVEWES	NGQOPENNYKT	420
TPPPVLDSDGS FFLVSKLTV	DKSRWQQGNFV	SCSVMHEALH	HNHYTQKSLSL	SPGWSHPQFE	480
K					481
SEQ ID NO: 96		moltype = AA	length = 481		
FEATURE		Location/Qualifiers			
source		1..481			
		mol_type = protein			
		organism = synthetic construct			
SEQUENCE: 96					
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS	DYYMTWIROA	PGKGLEWVSS	ISGGSTYYAD	60
SRKGRTISR DNSENTLYLQ	MNSLRAEDTA	VYYCARWETS	SGGFGSGGLS	HWGQGTLVT	120
SSGGGGGGGG GGGGGGSQSV	LTPQPPSASGT	PGQRVTISCT	GSSENIGAGY	DVHWYQQLPG	180
TAPKLLIYRS NQRPSGPDR	FSGSKSGTS	SLAISGLRSE	DEADYYCSSY	AGNYNLVFGG	240
GTKLTVLDKT HTCPCPAPE	AAGAPSFLF	PPPKPKDTLM	SRTPEVTCVV	VDVSHEDPEV	300
KFNWYVDGVE VHNAKTKP	EQYNSTYRVV	SVLTVLHQDWLNGKEYKCKV	SNKALPAPIE	360	
KTISKAKGQP REPQVCLLPP	SRDELTKNQV	SLSCAVKGFY	PSDIAVEWES	NGQOPENNYKT	420

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TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE	480
K	481
SEQ ID NO: 97	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 97	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD	60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARLTVD GGGYGSGLD LWGQGTLVT	120
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSNNIGAGY DVHWYQQLPG	180
TAPKLLIYRS NQRPSGPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFVGG	240
GTKLTVLDKT HTCPCPAPE AAGAPSFLP PPKPKDTLM SRTPEVTCVV VDVSCHEDPEV	300
KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360
KTISKAKGQP REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420
TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE	480
K	481
SEQ ID NO: 98	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 98	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD	60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARNEVS GGYGEFGLS LWGQGTLVT	120
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSNNIGAGY DVHWYQQLPG	180
TAPKLLIYRS NQRPSGPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFVGG	240
GTKLTVLDKT HTCPCPAPE AAGAPSFLP PPKPKDTLM SRTPEVTCVV VDVSCHEDPEV	300
KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360
KTISKAKGQP REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420
TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE	480
K	481
SEQ ID NO: 99	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 99	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD	60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARNTA GGYFGSFGLD LWGQGTLVT	120
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSNNIGAGY DVHWYQQLPG	180
TAPKLLIYRS NQRPSGPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFVGG	240
GTKLTVLDKT HTCPCPAPE AAGAPSFLP PPKPKDTLM SRTPEVTCVV VDVSCHEDPEV	300
KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360
KTISKAKGQP REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420
TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE	480
K	481
SEQ ID NO: 100	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 100	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD	60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARNETS GGYFGSFGLD IWGQGTLVT	120
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSNNIGAGY DVHWYQQLPG	180
TAPKLLIYRS NQRPSGPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFVGG	240
GTKLTVLDKT HTCPCPAPE AAGAPSFLP PPKPKDTLM SRTPEVTCVV VDVSCHEDPEV	300
KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360
KTISKAKGQP REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420
TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE	480
K	481
SEQ ID NO: 101	moltype = AA length = 483
FEATURE	Location/Qualifiers
source	1..483
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 101	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSSYIY	60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARAV AAGGMFWGLD QWGQGTLVT	120
TSSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT SGSRSNIGSN DVHWYQQLPG	180

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TAPKLLIYGN SNRPGVPDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLMNDHVFV GGGTKLTVLD KTHTCPCCPA PEAAGAPSVP LFPPPKPDKL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISAKAG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPDSIAVEW ESNQGPENNY KTPPPVLDSD GSFFLVSKLTD VDKSRWQQGN VFSCSVMHM A LHNHYTQKSL SLSPGWSHPQ FEK	240 300 360 420 480 483
SEQ ID NO: 102	moltype = AA length = 483
FEATURE	Location/Qualifiers
source	1..483
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 102	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWRQ A PGKGLEWVSS ISSSSYYIY ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARSN GSGGSDYPLD LWGQGTLVT TSSGGGGSGG GGSGGGGSQS VLTQPPSASG TPQQRVTISC SGSRSNIGSN SVHWYQQLPG TAPKLLIYGN SNRPGVPDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLMNDHVFV GGGTKLTVLD KTHTCPCCPA PEAAGAPSVP LFPPPKPDKL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISAKAG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPDSIAVEW ESNQGPENNY KTPPPVLDSD GSFFLVSKLTD VDKSRWQQGN VFSCSVMHM A LHNHYTQKSL SLSPGWSHPQ FEK	60 120 180 240 300 360 420 480 483
SEQ ID NO: 103	moltype = AA length = 483
FEATURE	Location/Qualifiers
source	1..483
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 103	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWRQ A PGKGLEWVSS ISSSSYYIY ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARSN GSGGSDYPLD LWGQGTLVT TSSGGGGSGG GGSGGGGSQS VLTQPPSASG TPQQRVTISC SGSRSNIGSN SVHWYQQLPG TAPKLLIYGN SNRPGVPDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLMNDHVFV GGGTKLTVLD KTHTCPCCPA PEAAGAPSVP LFPPPKPDKL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISAKAG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPDSIAVEW ESNQGPENNY KTPPPVLDSD GSFFLVSKLTD VDKSRWQQGN VFSCSVMHM A LHNHYTQKSL SLSPGWSHPQ FEK	60 120 180 240 300 360 420 480 483
SEQ ID NO: 104	moltype = AA length = 483
FEATURE	Location/Qualifiers
source	1..483
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 104	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWRQ A PGKGLEWVSS ISSSSYYIY ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARSN GSGGSDYPLD LWGQGTLVT TSSGGGGSGG GGSGGGGSQS VLTQPPSASG TPQQRVTISC SGSRSNIGSN SVHWYQQLPG TAPKLLIYGN SNRPGVPDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLMNDHVFV GGGTKLTVLD KTHTCPCCPA PEAAGAPSVP LFPPPKPDKL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISAKAG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPDSIAVEW ESNQGPENNY KTPPPVLDSD GSFFLVSKLTD VDKSRWQQGN VFSCSVMHM A LHNHYTQKSL SLSPGWSHPQ FEK	60 120 180 240 300 360 420 480 483
SEQ ID NO: 105	moltype = AA length = 483
FEATURE	Location/Qualifiers
source	1..483
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 105	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWRQ A PGKGLEWVSS ISSSSYYIY ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARAV AGTSMWYGLD QWGQGTLVT TSSGGGGSGG GGSGGGGSQS VLTQPPSASG TPQQRVTISC SGSRSNIGSN SVHWYQQLPG TAPKLLIYGN SNRPGVPDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLMNDHVFV GGGTKLTVLD KTHTCPCCPA PEAAGAPSVP LFPPPKPDKL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISAKAG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPDSIAVEW ESNQGPENNY KTPPPVLDSD GSFFLVSKLTD VDKSRWQQGN VFSCSVMHM A LHNHYTQKSL SLSPGWSHPQ FEK	60 120 180 240 300 360 420 480 483
SEQ ID NO: 106	moltype = AA length = 483
FEATURE	Location/Qualifiers
source	1..483
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 106	

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SEQUENCE: 106	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSSYIYY	60
ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARAV GASTVYFGLD QWGQGTLVTV	120
TSSGGGGSGG CGSGGGGSQS VLTOQPSASG TPQQRVTISC SGSRSNIGSN SVHWFQQLPG	180
TAPKLLIYGN SNRPSGVDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLNDHVVF	240
GGGTKLTVLD KTHTCPCPA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEPD	300
EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP	360
IEKTISKAKG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPSPDIAVEW ESNQGPENNY	420
KTPPPVLDSD GSFFLVSCLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGWSHPQ	480
FEK	483
SEQ ID NO: 107	moltype = AA length = 483
FEATURE	Location/Qualifiers
source	1..483
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 107	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSSYIYY	60
ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARAV AAGGFFFWGLD QWGQGTLVTV	120
TSSGGGGSGG CGSGGGGSQS VLTOQPSASG TPQQRVTISC SGSRSNIGSN SVHWFQQLPG	180
TAPKLLIYGN SNRPSGVDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLNDHVVF	240
GGGTKLTVLD KTHTCPCPA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEPD	300
EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP	360
IEKTISKAKG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPSPDIAVEW ESNQGPENNY	420
KTPPPVLDSD GSFFLVSCLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGWSHPQ	480
FEK	483
SEQ ID NO: 108	moltype = AA length = 483
FEATURE	Location/Qualifiers
source	1..483
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 108	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSSYIYY	60
ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARAV AAGGFFFWGLD QWGQGTLVTV	120
TSSGGGGSGG CGSGGGGSQS VLTOQPSASG TPQQRVTISC SGSRSNIGSN SVHWFQQLPG	180
TAPKLLIYGN SNRPSGVDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLNDHVVF	240
GGGTKLTVLD KTHTCPCPA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEPD	300
EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP	360
IEKTISKAKG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPSPDIAVEW ESNQGPENNY	420
KTPPPVLDSD GSFFLVSCLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGWSHPQ	480
FEK	483
SEQ ID NO: 109	moltype = AA length = 483
FEATURE	Location/Qualifiers
source	1..483
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 109	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS LAWMNWVRQA PGKGLEWVSS ISSSTSYYIYY	60
ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARAV AAGGGMFWGLD QWGQGTLVTV	120
TSSGGGGSGG CGSGGGGSQS VLTOQPSASG TPQQRVTISC SGSRSNIGSN SVHWFQQLPG	180
TAPKLLIYGN SNRPSGVDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLNDHVVF	240
GGGTKLTVLD KTHTCPCPA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEPD	300
EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP	360
IEKTISKAKG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPSPDIAVEW ESNQGPENNY	420
KTPPPVLDSD GSFFLVSCLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGWSHPQ	480
FEK	483
SEQ ID NO: 110	moltype = AA length = 483
FEATURE	Location/Qualifiers
source	1..483
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 110	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS LAWMNWVRQA PGKGLEWVSS ISSSTSYYIYY	60
ADSVKGRFTI SRDNSKNTLY LQMNLSRAED TAVYYCARAV AAGGFFFWGLD QWGQGTLVTV	120
TSSGGGGSGG CGSGGGGSQS VLTOQPSASG TPQQRVTISC SGSRSNIGSN SVHWFQQLPG	180
TAPKLLIYGN SNRPSGVDR FSGSKSGTSA SLAISGLRSE DEADYYCQSY DSSLNDHVVF	240
GGGTKLTVLD KTHTCPCPA PEAAGAPSVF LFPPPKPKDTL MISRTPEVTC VVVDVSHEPD	300
EVKFNWYVDG VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP	360
IEKTISKAKG QPREPVQVCTL PPSRDELTKN QVSLSCAVKG FYPSPDIAVEW ESNQGPENNY	420
KTPPPVLDSD GSFFLVSCLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGWSHPQ	480
FEK	483
SEQ ID NO: 111	moltype = AA length = 481

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FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 111	
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SVKGRFTISR DNSENTLYLQ	MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV 120
SSGGGGSGGG GSgggggSQSV	LTPQPPSASGT PGQRVTISCT GSSSNIGAGY DVHwyQQLPG 180
TAPKLLIYRS NQRPSGPDR	FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFVGG 240
GTKLTVDLKT HTCPCPAPE	AAGAPSvFLF PPkPKDTLMi SRTPEVTCVV VDVSHEDEPV 300
KFNWYVDGVE VHNAKTPRE	EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE 360
KTISKAKGQP REPQVCTLPP	SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT 420
TPPVLDSDGS FFLVSKLTVD	KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE 480
K	481
SEQ ID NO: 112	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 112	
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS DSYMSWIROA PGKGLEWVSS ISGGSTYYAD 60
SVKGRFTISR DNSENTLYLQ	MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV 120
SSGGGGSGGG GSgggggSQSV	LTPQPPSASGT PGQRVTISCT GSSSNIGAGY DVHwyQQLPG 180
TAPKLLIYRS NQRPSGPDR	FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFVGG 240
GTKLTVDLKT HTCPCPAPE	AAGAPSvFLF PPkPKDTLMi SRTPEVTCVV VDVSHEDEPV 300
KFNWYVDGVE VHNAKTPRE	EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE 360
KTISKAKGQP REPQVCTLPP	SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT 420
TPPVLDSDGS FFLVSKLTVD	KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE 480
K	481
SEQ ID NO: 113	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 113	
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS DYYMNWIROA PGKGLEWVSS ISGGSTYYAD 60
SVKGRFTISR DNSENTLYLQ	MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV 120
SSGGGGSGGG GSgggggSQSV	LTPQPPSASGT PGQRVTISCT GSSSNIGAGY DVHwyQQLPG 180
TAPKLLIYRS NQRPSGPDR	FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFVGG 240
GTKLTVDLKT HTCPCPAPE	AAGAPSvFLF PPkPKDTLMi SRTPEVTCVV VDVSHEDEPV 300
KFNWYVDGVE VHNAKTPRE	EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE 360
KTISKAKGQP REPQVCTLPP	SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT 420
TPPVLDSDGS FFLVSKLTVD	KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE 480
K	481
SEQ ID NO: 114	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 114	
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD 60
SRKGRFTISR DNSENTLYLQ	MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV 120
SSGGGGSGGG GSgggggSQSV	LTPQPPSASGT PGQRVTISCT GSSSNIGAGY DVHwyQQLPG 180
TAPKLLIYRS NQRPSGPDR	FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFVGG 240
GTKLTVDLKT HTCPCPAPE	AAGAPSvFLF PPkPKDTLMi SRTPEVTCVV VDVSHEDEPV 300
KFNWYVDGVE VHNAKTPRE	EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE 360
KTISKAKGQP REPQVCTLPP	SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT 420
TPPVLDSDGS FFLVSKLTVD	KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE 480
K	481
SEQ ID NO: 115	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 115	
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SRKGRFTISR DNSENTLYLQ	MNSLRAEDTA VYYCARDFGV SGWFGQYGMV VWGQGTLVTV 120
SSGGGGSGGG GSgggggSQSV	LTPQPPSASGT PGQRVTISCT GSSSNIGAGY DVHwyQQLPG 180
TAPKLLIYRS NQRPSGPDR	FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFVGG 240
GTKLTVDLKT HTCPCPAPE	AAGAPSvFLF PPkPKDTLMi SRTPEVTCVV VDVSHEDEPV 300
KFNWYVDGVE VHNAKTPRE	EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE 360
KTISKAKGQP REPQVCTLPP	SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT 420

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TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE	480
K	481
SEQ ID NO: 116	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 116	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYWMWTIIRQA PGKGLEWVSS ISGGTTYYAD	60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV	120
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHWYQQLPG	180
TAPKLLIYRS NQRPSGPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSL AGNYNLVFGG	240
GTKLTVLDKT HTCPCPAPE AAGAPSFLP PPKPKDTLMI SRTPEVTCVV VDVSCHEDPEV	300
KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360
KTISKAKGQP REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420
TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE	480
K	481
SEQ ID NO: 117	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 117	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYWMWTIIRQA PGKGLEWVSS ISGGTTYYAD	60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV	120
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHWYQQLPG	180
TAPKLLIYRS NQRPSGPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSL AGNYNLVFGG	240
GTKLTVLDKT HTCPCPAPE AAGAPSFLP PPKPKDTLMI SRTPEVTCVV VDVSCHEDPEV	300
KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360
KTISKAKGQP REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420
TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE	480
K	481
SEQ ID NO: 118	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 118	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYWMWTIIRQA PGKGLEWVSS ISGGTTYYAD	60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV	120
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHWYQQLPG	180
TAPKLLIYRS NQRPSGPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSL AGNYNLVFGG	240
GTKLTVLDKT HTCPCPAPE AAGAPSFLP PPKPKDTLMI SRTPEVTCVV VDVSCHEDPEV	300
KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360
KTISKAKGQP REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420
TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE	480
K	481
SEQ ID NO: 119	moltype = AA length = 481
FEATURE	Location/Qualifiers
source	1..481
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 119	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYWMWTIIRQA PGKGLEWVSS ISGGTTYYAD	60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV SGWFGQYGMV VWGQGTLVTV	120
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHWYQQLPG	180
TAPKLLIYRS NQRPSGPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSL AGNYNLVFGG	240
GTKLTVLDKT HTCPCPAPE AAGAPSFLP PPKPKDTLMI SRTPEVTCVV VDVSCHEDPEV	300
KFNWYVDGVE VHNAKTKPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360
KTISKAKGQP REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420
TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SCSTMHEALH NHYTQKSLSL SPGWSHPQFE	480
K	481
SEQ ID NO: 120	moltype = AA length = 469
FEATURE	Location/Qualifiers
source	1..469
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 120	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS IYAMSWVRQA PGKGLEWVSA ISGGGGSTYY	60
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDF DYWGQGTLVT VTSSGGGGSG	120
GGGGGGGGSQ SVLTQPPSAS GTGPGQRTIS CSGSSSNIGS NYVYWYQQLP GTAPKLLIYG	180

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NINRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPS VF LFPPPKD TL MISRTPEVTC VVVDVSHEDP EVKFNWYVG D	300
VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG	360
QPREPVQVTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469
SEQ ID NO: 121 moltype = AA length = 483	
FEATURE Location/Qualifiers	
source 1..483	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 121	
EVLLESGGG LVQPGGSLRL SCAASGFTFS NAWMNWVRQA PGKGLEWVSS ISSSSYYI YY	60
ADSVKGRFTI SRDNSKNTLY LQMNLSLRAED TAVYYCARAV AAGGMFWGLD QWGQGTLVTV	120
TSSGGGGSGG GGSGGGGSQS VLTQPPSASG TPQRVTISC SGSRNSNIGSN SVHWYQQLPG	180
TAPKLLIYGN SNGRPSGVPD FSGSKSGTS SLAISGLRSE DEADYYCQSY DSSLNDHVV F	240
GGGTKLTVLD KTHTCPPCPA PEAAGAPS VF LFPPPKD TL MISRTPEVTC VVVDVSHEDP	300
EVKFNWYVG D VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP	360
IEKTISKAKG QPREPVQVTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY	420
KTPPVLDSD GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGWHPQ	480
FEK	483
SEQ ID NO: 122 moltype = AA length = 469	
FEATURE Location/Qualifiers	
source 1..469	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 122	
EVLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKN Y	60
VDSMRGRFTI SRDN SKNTLY LQMNLSLRAED TAVYYCAREF DYWGQGTLVT VTSSGGGGSG	120
GGGGGGGGSQ SVLAQPPSAS GTPQRVTISC CSGSSSNIGS NYVWYQQLP GTAPKLLIYG	180
NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPS VF LFPPPKD TL MISRTPEVTC VVVDVSHEDP EVKFNWYVG D	300
VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG	360
QPREPVQVTL PPCRDELTKN QVSLWCLVKG FYPSDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469
SEQ ID NO: 123 moltype = AA length = 481	
FEATURE Location/Qualifiers	
source 1..481	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 123	
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SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGM D VWGQGTLVTV	120
SSGGGGGGGG GS GGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHWYQQLPG	180
TAPKLLIYGN QRSRPSGVPD FSGSKSGTS SLAISGLRSE DEADYYCSSY AGNYNLVFGG	240
GTLTVLDK T CPCPAPE AAGAPS VFLP PP KPKDTLM SRTPEVTCVV VDVSHEDPEV	300
KFNWYVG DVE VHNAKTKP RE EQYNSTYRV SVLTVLHDW LNGKEYCKV SNKALPAPIE	360
KTISKAKGQP REPQVCTLPP SRDELTKNQV SLSCAVKG F PSDIAVEWES NGQGPENNYKT	420
TPPVLDSDGS FFLVSKLTVD KSRWQQGNVF SC S VMHEAL NHYTQKSL SLPGWHPQFE	480
K	481
SEQ ID NO: 124 moltype = AA length = 469	
FEATURE Location/Qualifiers	
source 1..469	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 124	
EVLLESGGG LVQPGGSLRL SCAASGFTFS DYAMSWVRQA PGKGLEWVAN INQSGSEKN Y	60
VDSMRGRFTI SRDN SKNTLY LQMNLSLRAED TAVYYCAREF DWWGQGTLVT VSSSGGGGSG	120
GGGGGGGGSQ SVLAQPPSAS GTPQRVTIS CSGSASNIGS NYVWYQQLP GTAPKLLIYG	180
NNKRPSGVPD RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLD	240
KTHTCPPCPA PEAAGAPS VF LFPPPKD TL MISRTPEVTC VVVDVSHEDP EVKFNWYVG D	300
VEVHNAKTKP REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG	360
QPREPVQVTL PPCRDELTKN QVSLWCLVKG FYP SDIAVEW ESNQGPENNY KTPPVLDSD	420
GSFFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGEPEA	469
SEQ ID NO: 125 moltype = AA length = 469	
FEATURE Location/Qualifiers	
source 1..469	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 125	
EVLLESGGG LVQPGGSLRL SCAASGFTFS DYAMSWVRQA PGKGLEWVAN INQSGSEKN Y	60
VDSMRGRFTI SRDN SKNTLY LQMNLSLRAED TAVYYCAREF DWWGQGTLVT VSSSGGGGSG	120

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GGGSGGGGSQ	SVLAQPPSAS	GTPGQRTVIS	CSGSSNIGS	NYVYWYQQLP	GTAPKLLIYG	180
VDSMRGPAGV	PFSGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGKLTIVLD	240
KTHTCPPCPA	PEAAAGAPS	VLSLWCLVK	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	300
VEVHNAKTKP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPVYVT	PPCRDELT	QVSLWCLVK	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 126	moltype = AA	length = 469				
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 126						
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VDSMRGRFTI	SRDNSKNTLY	LQMNLSRAED	TAVYYCAREF	DWVGQGTLVT	VSSSGGGGSG	120
GGGSGGGGSQ	SVLAQPPSAS	GTPGQRTVIS	CSGSSNIGS	NYVYWYQQLP	GTAPKLLIYG	180
NNKRPAGV	PFSGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGKLTIVLD	240
KTHTCPPCPA	PEAAAGAPS	VLSLWCLVK	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	300
VEVHNAKTKP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPVYVT	PPCRDELT	QVSLWCLVK	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 127	moltype = AA	length = 469				
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 127						
EVOLLESGGG	LVQPGGSLRL	SCAASGFTFS	DYAMSWVRQA	PGKGLEWVAN	INQSGSEKNY	60
VDSMRGRFTI	SRDNSKNTLY	LQMNLSRAED	TAVYYCAREF	DWVGQGTLVT	VSSSGGGGSG	120
GGGSGGGGSQ	SVLAQPPSAS	GTPGQRTVIS	CSGSASNIGS	NYVYWYQQLP	GTAPKLLIYG	180
NNKRPAGV	PFSGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGKLTIVLD	240
KTHTCPPCPA	PEAAAGAPS	VLSLWCLVK	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	300
VEVHNAKTKP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPVYVT	PPCRDELT	QVSLWCLVK	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 128	moltype = AA	length = 469				
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 128						
EVOLLESGGG	LVQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVAN	INQDGSEKNY	60
VDSMRGRFTI	SRDNSKNTLY	LQMNLSRAED	TAVYYCAREF	DYWGQGTLVT	VSSSGGGGSG	120
GGGSGGGGSQ	SVLAQPPSAS	GTPGQRTVIS	CSGSASNIGS	NYVYWYQQLP	GTAPKLLIYG	180
NNKRPAGV	PFSGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGKLTIVLD	240
KTHTCPPCPA	PEAAAGAPS	VLSLWCLVK	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	300
VEVHNAKTKP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPVYVT	PPCRDELT	QVSLWCLVK	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 129	moltype = AA	length = 469				
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 129						
EVOLLESGGG	LVQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVAN	INQDGSEKNY	60
VDSMRGRFTI	SRDNSKNTLY	LQMNLSRAED	TAVYYCAREF	DYWGQGTLVT	VSSSGGGGSG	120
GGGSGGGGSQ	SVLAQPPSAS	GTPGQRTVIS	CSGSASNIGS	NYVYWYQQLP	GTAPKLLIYG	180
NNKRPAGV	PFSGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLNGRVF	GGGKLTIVLD	240
KTHTCPPCPA	PEAAAGAPS	VLSLWCLVK	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	300
VEVHNAKTKP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPVYVT	PPCRDELT	QVSLWCLVK	FYPSDIAVEW	ESNGQPENNY	KTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 130	moltype = AA	length = 469				
FEATURE	Location/Qualifiers					
source	1..469					
	mol_type = protein					
	organism = synthetic construct					
SEQUENCE: 130						
EVOLLESGGG	LVQPGGSLRL	SCAASGFTFS	SYAMSWVRQA	PGKGLEWVAN	INQDGSEKNY	60
VDSMRGRFTI	SRDNSKNTLY	LQMNLSRAED	TAVYYCAREF	DYWGQGTLVT	VSSSGGGGSG	120
GGGSGGGGSQ	SVLAQPPSAS	GTPGQRTVIS	CSGSASNIGS	NYVYWYQQLP	GTAPKLLIYG	180

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NNKRPSGVPD	RFSGSKSGTS	ASLAISGLRS	EDEADYYCAA	WDDSLSGRVF	GGGTKLTVLD	240
KTHTCPPCPA	PEAAGAPSVF	LFPPPKDTL	MISRTPEVTC	VVVDVSHEDP	EVKFNWYVDG	300
VEVHNAKTTP	REEQYNSTYR	VVSVLTVLHQ	DWLNGKEYKC	KVSNKALPAP	IEKTISKAKG	360
QPREPQVYTL	PPCRDELTKN	QVSLWCLVKG	FYPSDIAVEW	ESNGQPENNY	KTTPPVLDSD	420
GSFFFLYSKLT	VDKSRWQQGN	VFSCSVMHEA	LHNHYTQKSL	SLSPGEPEA		469

SEQ ID NO: 131	moltype = AA length = 469		
FEATURE	Location/Qualifiers		
source	1..469		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 131			
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY	60	
VDMSMRFTI SRDNKNTLY	LQMNLSRAEDTA TAVYYCAREP DYWGQGTLVT VSSSGGGGSG	120	
GGGGGGGGSQ	SQVLAQPPSAS GTPGQRVTLC	CSGSASNIGS NYVWYQQLP GTAPKLLIYG	180
NNKRPAVGVPD	RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLSGRVF	GGGTKLTVLD	240
KTHTCPPCPA	PEAAGAPSVF LFPPPKDTL MISRTPEVTC	VVVDVSHEDP EVKFNWYVDG	300
VEVHNAKTTP	REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC	KVSNKALPAP IEKTISKAKG	360
QPREPQVYTL	PPCRDELTKN QVSLWCLVKG FYPSDIAVEW	ESNGQPENNY KTTTPVLDSD	420
GSFFFLYSKLT	VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL	SLSPGEPEA	469

SEQ ID NO: 132	moltype = AA length = 481		
FEATURE	Location/Qualifiers		
source	1..481		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 132			
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS DYYMTWIRQA PGKGLEWVSS ISGGSTYYAD	60	
SRKGRFTISR DNSENTLYLQ	MNSLRAEDTA VYYCARDFGV AGWFQGYGMD VWGQGTLTV	120	
SSGGGGGGGG	GSGGGGGSQSV LTQPPSASGT PGQRVTISCT GSASNIGAGY DVHWYQQLPG	180	
TAPKLLIYRS	NQRPGVPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFGG	240	
GTKLTVDLDT	HTCPPCPAPE AAGAPSVFLF PPCKPKDTLMI SRTPEVTCVV	VDVSHEDPEV	300
KFNWYVDGVE	VHNAKTTPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360	
KTISKAKGQP	REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420	
TPPVLDSDGS	FFLVSKLTVK KSRWQQGNVF SCSCVMHEAL NHYTQKSLSL SPGWSHPQFE	480	
K		481	

SEQ ID NO: 133	moltype = AA length = 481		
FEATURE	Location/Qualifiers		
source	1..481		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 133			
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS DYYMTWIRQA PGKGLEWVSS ISGGSTYYAD	60	
SRKGRFTISR DNSENTLYLQ	MNSLRAEDTA VYYCARDFGV AGWFQGYGMD VWGQGTLTV	120	
SSGGGGGGGG	GSGGGGGSQSV LTQPPSASGT PGQRVTISCT GSASNIGAGY DVHWYQQLPG	180	
TAPKLLIYRS	NQRPGVPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGLYNLVFGG	240	
GTKLTVDLDT	HTCPPCPAPE AAGAPSVFLF PPCKPKDTLMI SRTPEVTCVV	VDVSHEDPEV	300
KFNWYVDGVE	VHNAKTTPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360	
KTISKAKGQP	REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420	
TPPVLDSDGS	FFLVSKLTVK KSRWQQGNVF SCSCVMHEAL NHYTQKSLSL SPGWSHPQFE	480	
K		481	

SEQ ID NO: 134	moltype = AA length = 481		
FEATURE	Location/Qualifiers		
source	1..481		
	mol_type = protein		
	organism = synthetic construct		
SEQUENCE: 134			
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS DYYMTWIRQA PGKGLEWVSS ISGGSTYYAD	60	
SRKGRFTISR DNSENTLYLQ	MNSLRAEDTA VYYCARDFGV AGWFQGYGMD VWGQGTLTV	120	
SSGGGGGGGG	GSGGGGGSQSV LTQPPSASGT PGQRVTISCT GSASNIGAGY DVHWYQQLPG	180	
TAPKLLIYRS	NQRPGVPDR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGLYNLVFGG	240	
GTKLTVDLDT	HTCPPCPAPE AAGAPSVFLF PPCKPKDTLMI SRTPEVTCVV	VDVSHEDPEV	300
KFNWYVDGVE	VHNAKTTPRE EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE	360	
KTISKAKGQP	REPQVCTLPP SRDELTKNQV SLSCAVKGFY PSDIAVEWES NGQPENNYKT	420	
TPPVLDSDGS	FFLVSKLTVK KSRWQQGNVF SCSCVMHEAL NHYTQKSLSL SPGWSHPQFE	480	
K		481	

SEQ ID NO: 135	moltype = AA length = 481	
FEATURE	Location/Qualifiers	
source	1..481	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 135		
EVQLLESGGG LVQPGGSLRL	SCAASGFTFS DYYMTWIRQA PGKGLEWVSS ISGGSTYYAD	60

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SRKGRFTISR	DNSENTLYLQ	MNSLRAEDTA	VYYCARDFGV	AGWFGQYGM	VWGQGLTV	120
SSGGGGSGGG	CGGGGGSQ	LTPQPPSASGT	PGQRVTISCT	GSASNIGAG	DVHWYQQLPG	180
TAPKLLIYRS	NQRPAGVPDF	FSGSKSGTS	SIAISGLRSE	DEADYYCSSL	AGLYNLVF	240
GTKLTVDLDT	HTCPPCPAPE	AAGAPSFLF	PPPKDITLMI	SRTPEVTCVV	VDVSHDPEV	300
KFNWYVGDVE	VHNAKTKPRE	EQYNSTYRVV	SVLTVLHQDW	LNGKEYKCKV	SNKALPAPIE	360
KTISKAKGQP	REPQVCTLPP	SRDELTKNOV	SLSCAVKGFY	PSDIAVEWES	NGQPENNYKT	420
TPPVLDSDGS	FFLVSKLTV	KSRWQQGNVF	SCSVMHEALH	NHYTQKSLSL	SPGWSHPQFE	480
K						481

SEQ ID NO: 136 moltype = AA length = 573
 FEATURE Location/Qualifiers
 source 1..573
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 136
 EVOLLESGG LVQPGGSLRL SCAASGFTFS DYYMTWIRQA PGKGLEWVSS ISGGSTYYAD 60
 SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGM

SSPAPNLLGG	PEVQPLLESGG	GLVQPGGSLR	LSCAASGTF	SSYAMSWVRQ	APGKGLEWVA	180
NINQDGSEKN	YLDSMGRFT	ISRDNSKNTL	SLRAEDTAVY	FDYWQGTLV	240	
TVSSASTKGP	SVFPLAPSS	STSGGTAALG	CLVKDYFPEP	VTWSWNSGAL	TSGVHTFP	300
LQSSGLYSL	SVVTVPSS	GTQTYICNVN	HKPNTKVDK	KVEPKSCDKT	HTCPPCPAPE	360
AAGAPSFLF	PPPKDITL	TREPEVTCVV	VDVSHDPEV	KFNWYVGDVE	VHNAKTKPRE	420
EQYNSTYRVV	SVLTVLHQDW	LNGKEYKCKV	SNKALPAPIE	KTISKAKGQP	REPQVYTLPP	480
SRDELTKNOV	SLTCLVKGFY	PSDIAVEWES	NGQPENNYKT	TPPVLDSDGS	FFLYSKLTV	540
KSRWQQGNVF	SCSVMHEALH	NHYTQKSLSL	SPG			573

SEQ ID NO: 137 moltype = AA length = 568
 FEATURE Location/Qualifiers
 source 1..568
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 137
 EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIRQA PGKGLEWVSS ISGGSTYYAD 60
 SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGM

SSPLADEVQL	LESGGGLVQ	GGSLRLSCAA	SGFTFSSYWM	SWVRQAPGKG	LEWVANINQD	180
GSEKNNYVDSM	RGRFTISRDN	SKNTLYLQMN	SLRAEDTAVY	YCAREDYWG	QGTLTVVSSA	240
STKGPSVFPL	APSSKSTSGG	TAALGCLVKD	YFPEPVTV	NSGALTSGVH	TFPAVLQSSG	300
LYSLSSVTV	PSSSLGQTQ	ICVNHNKPSN	TKVDKKVEPK	SCDKTHTCPP	CPAPEAAGAP	360
SVFLFPKPK	DTLYITREPE	TCVUVVDSH	EDPEVKFNWY	VDGVEVHN	AKGQPREPQV	420
TYRVVSVLTV	LHQDWLNGKE	YKCKVSNKAL	PAPIEKTI	AKGQPREPQV	YTLPPSRDEL	480
TKNQVSLTCL	VKGFYPSDIA	VEWESNGQPE	NNYKTTPPV	DSDGSFFLYS	KLTVDKSRWQ	540
QGNVFSCSVM	HEALHNHYTQ	KSLSLSPG				568

SEQ ID NO: 138 moltype = AA length = 568
 FEATURE Location/Qualifiers
 source 1..568
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 138
 EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMNWIROA PGKGLEWVSS ISGGSTYYAD 60
 SVKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQF

SSPLADEVQL	LESGGGLVQ	GGSLRLSCAA	SGFTFSSYWM	SWVRQAPGKG	LEWVANINQD	180
GSEKNNYVDSM	RGRFTISRDN	SKNTLYLQMN	SLRAEDTAVY	YCAREDYWG	QGTLTVVSSA	240
STKGPSVFPL	APSSKSTSGG	TAALGCLVKD	YFPEPVTV	NSGALTSGVH	TFPAVLQSSG	300
LYSLSSVTV	PSSSLGQTQ	ICVNHNKPSN	TKVDKKVEPK	SCDKTHTCPP	CPAPEAAGAP	360
SVFLFPKPK	DTLYITREPE	TCVUVVDSH	EDPEVKFNWY	VDGVEVHN	AKGQPREPQV	420
TYRVVSVLTV	LHQDWLNGKE	YKCKVSNKAL	PAPIEKTI	AKGQPREPQV	YTLPPSRDEL	480
TKNQVSLTCL	VKGFYPSDIA	VEWESNGQPE	NNYKTTPPV	DSDGSFFLYS	KLTVDKSRWQ	540
QGNVFSCSVM	HEALHNHYTQ	KSLSLSPG				568

SEQ ID NO: 139 moltype = AA length = 568
 FEATURE Location/Qualifiers
 source 1..568
 mol_type = protein
 organism = synthetic construct

SEQUENCE: 139
 EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMNWIROA PGKGLEWVSS ISGGSTYYAD 60
 SVKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQF

SSPLADEVQL	LESGGGLVQ	GGSLRLSCAA	SGFTFSSYWM	SWVRQAPGKG	LEWVANINQD	180
GSEKNNYVDSM	RGRFTISRDN	SKNTLYLQMN	SLRAEDTAVY	YCAREDYWG	QGTLTVVSSA	240
STKGPSVFPL	APSSKSTSGG	TAALGCLVKD	YFPEPVTV	NSGALTSGVH	TFPAVLQSSG	300
LYSLSSVTV	PSSSLGQTQ	ICVNHNKPSN	TKVDKKVEPK	SCDKTHTCPP	CPAPEAAGAP	360
SVFLFPKPK	DTLYITREPE	TCVUVVDSH	EDPEVKFNWY	VDGVEVHN	AKGQPREPQV	420
TYRVVSVLTV	LHQDWLNGKE	YKCKVSNKAL	PAPIEKTI	AKGQPREPQV	YTLPPSRDEL	480
TKNQVSLTCL	VKGFYPSDIA	VEWESNGQPE	NNYKTTPPV	DSDGSFFLYS	KLTVDKSRWQ	540
QGNVFSCSVM	HEALHNHYTQ	KSLSLSPG				568

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SEQ ID NO: 140      moltype = AA length = 568
FEATURE          Location/Qualifiers
source           1..568
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 140
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMNWIROA PGKGLEWVSS ISGGSTYYAD 60
SVKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGLTV 120
SSPLAPEVQL LESGGGLVQP GGSSLRSCAA SGFTFSSYWM SWVRQAPGKG LEWVANIQD 180
GSEKNYVDSM RGRFTISRDN SKNTLYLQMN SLRAEDTAVY YCAREDFFWG QGTLVTVSSA 240
STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG 300
LYSLSSVVTV PSSSLGTQTY ICNVNHNKPSN TKVDKKVEPK SCDKTHTCPP CPAPEAAGAP 360
SVFLFPPKPK DTLYITREPE VTCVVVDVSH EDPEVKFNWY VGVEVHNAK TKPREEQYNS 420
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL 480
TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVVL DSDGSFFLYS KLTVDKSRWQ 540
QGNVFSCSVM HEALHNHYTQ KSLSLSPG 568

SEQ ID NO: 141      moltype = AA length = 568
FEATURE          Location/Qualifiers
source           1..568
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 141
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMNWIROA PGKGLEWVSS ISGGSTYYAD 60
SVKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGLTV 120
SSPLAPEVQL LESGGGLVQP GGSSLRSCAA SGFTFSSYWM SWVRQAPGKG LEWVANIQD 180
GSEKNYVDSM RGRFTISRDN SKNTLYLQMN SLRAEDTAVY YCAREDFYWG QGTLVTVSSA 240
STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG 300
LYSLSSVVTV PSSSLGTQTY ICNVNHNKPSN TKVDKKVEPK SCDKTHTCPP CPAPEAAGAP 360
SVFLFPPKPK DTLYITREPE VTCVVVDVSH EDPEVKFNWY VGVEVHNAK TKPREEQYNS 420
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL 480
TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVVL DSDGSFFLYS KLTVDKSRWQ 540
QGNVFSCSVM HEALHNHYTQ KSLSLSPG 568

SEQ ID NO: 142      moltype = AA length = 568
FEATURE          Location/Qualifiers
source           1..568
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 142
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD 60
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGLTV 120
SSPLAPEVQL LESGGGLVQP GGSSLRSCAA SGFTFSSYAM SWVRQAPGKG LEWVANINQD 180
GSEKNYVDSM RGRFTISRDN SKNTLYLQMN SLRAEDTAVY YCAREDFYWG QGTLVTVSSA 240
STKGPSVFPL APSSKSTSGG TAALGCLVKD YFPEPVTVSW NSGALTSGVH TFPAVLQSSG 300
LYSLSSVVTV PSSSLGTQTY ICNVNHNKPSN TKVDKKVEPK SCDKTHTCPP CPAPEAAGAP 360
SVFLFPPKPK DTLYITREPE VTCVVVDVSH EDPEVKFNWY VGVEVHNAK TKPREEQYNS 420
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV YTLPPSRDEL 480
TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVVL DSDGSFFLYS KLTVDKSRWQ 540
QGNVFSCSVM HEALHNHYTQ KSLSLSPG 568

SEQ ID NO: 143      moltype = AA length = 335
FEATURE          Location/Qualifiers
source           1..335
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 143
QSVLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYDVHNYQQ LPGTAPKLII YRSNQRPSGV 60
PDRFSGSKSG TSASLAISGL RSEDEADYYC SSYAGLYNLV FGGGTKLTVL PAPNLLGGPQ 120
SVALAQPPSAS GTPGQRVTIS CSGSSSNIGS NYVWYWWQQLP CKTAPKLIIYG NNKRPSGVPD 180
RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVFV GGGTKLTVLG QPKAAPSTVL 240
FPPSSEELQA NKATLVCLIS DFYPGAVTVA WKADSSPVKA GVETTTPSKQ SNNKYAASSY 300
LSLTPEQWKHS HRSYSCQVTH EGSTVEKTVTA PTECS 335

SEQ ID NO: 144      moltype = AA length = 330
FEATURE          Location/Qualifiers
source           1..330
                  mol_type = protein
                  organism = synthetic construct
SEQUENCE: 144
QSVLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYDVHNYQQ LPGTAPKLII YRSNQRPSGV 60
PDRFSGSKSG TSASLAISGL RSEDEADYYC SSYAGLYNLV FGGGTKLTVL PLAPQSVLAQ 120
PPSASGTPGQ RVTISCGSS SNIGSNYVW YQQLPGTAPK LLIYGNKNRP SGVPDRFSGS 180
KSGTSASLAI SGLRSEDEAD YYCAAWDDSL SGRVFGGGTK LTVLGQPKAA PSVTLFPSS 240
EEQANKATL VCLISDFYPC AVTVAWKADS SPVKAGVETT TPSKQSNNKY AASSYSLTP 300

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SEQ ID NO: 145	moltype = AA length = 342	
FEATURE	Location/Qualifiers	
source	1..342	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 145		
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD 60		
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV 120		
SSGLAPQSVL AQPPSASGTQ GQRVTISCG SSSNIGNSNVV YWYQQLPCTGA PKLLIYGNNK 180		
RPSGVPDFRS GSCKSGTSASL AISGLRSEDE ADYVCAAWDD SLSGRVFGGG TKLTVLGQPK 240		
AAPSVTLFPP SSEEQANKA TLVCLISDFY PGAVTVAWKA DSSPVKAGVE TTPSKQSNN 300		
KYAASSYLSL TPEQWKSHRS YSCQVTHEGS TVEKTVAPTE CS 342		
SEQ ID NO: 146	moltype = AA length = 330	
FEATURE	Location/Qualifiers	
source	1..330	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 146		
QSVLTQPPSA SGTPGQRTI SCTGSSSNIG AGYDVHVVYQQ LPGTAKPLLI YRSNQRPSSGV 60		
PDRFSGSKGL RSEDEADYYC SSYAGNYNLV FGGTAKLTVL PLAPQSVLAQ 120		
PPSASGTPQQ RVTISCGSS SNIGSNYVW YQOLPGTAKP LLIYGNNKRPG SVGPDRFSGS 180		
KSGTSASLAI SGLRSEDEAD YYCAAWDDSL NGRVFGGGTK LTVLGQPKAA PSVTLFPSS 240		
EELQANKATL VCLISDFYPG AVTVAWKA SPVKAGVETT TPSKQSNNKY AASSYLSLTP 300		
EQWKSHRSYS CQVTHEGSTV EKTVPTECS 330		
SEQ ID NO: 147	moltype = AA length = 728	
FEATURE	Location/Qualifiers	
source	1..728	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 147		
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD 60		
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV 120		
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHWYQQLPG 180		
TAPKLLIYRS NQRPSGVPDFR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFGG 240		
GTKLTVLDKG PSVFPLAPEK KSSEVQLES GGGLVQPGGS LRLSCAASGF TFSSYAMSWV 300		
RQAPGKGLEW VANINQDGSE KNYVDSMGR FTISRDNSKN TLYLQMNSSLR AEDTAVYYCA 360		
REEDDYWGQGT LVTVTSSGG GSAGGGGSQSV GSQSVLAQPP SASGTPGQRV TISCSSGSSN 420		
IGSNYVYWWY QLPGTAKPLL IYGNNKRPSG VPDRFSGSKS GTSASLAISG LRSEDEADYY 480		
CAAWDDSLNG RVFGGGTAKLT VLDKHTCPP CPAPEAAGAP SVFLFPKPK DTLMSIRTPE 540		
VTCVVVDVSH RPDEVKFNWY VDGVEVHNKA TKPREEQYNS TYRVRVSVLTV LHQDWLNKGKE 600		
YCKKVSNKAL PAPIEKTIK AKGQPREPOV YTLPPSDEL TKNQVSLTCL VKGFYPSDIA 660		
VEWESNGQPE NNYKTTPPVL DSDGSFFLYS KLTVDKSRWQ QGNVFSCVM HEALHNHYTQ 720		
KSLSLSPG 728		
SEQ ID NO: 148	moltype = AA length = 723	
FEATURE	Location/Qualifiers	
source	1..723	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 148		
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD 60		
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV 120		
SSGGGGSGGG GSAGGGGSQSV LTQPPSASGT PGQRVTISCT GSSSNIGAGY DVHWYQQLPG 180		
TAPKLLIYRS NQRPSGVPDFR FSGSKSGTSA SLAISGLRSE DEADYYCSSY AGNYNLVFGG 240		
GTKLTVLDKG PSVFPLAPEK KSSEVQLES GGGLVQPGGS LRLSCAASGF TFSSYAMSWV 300		
RQAPGKGLEW VANINQDGSE KNYVDSMGR FTISRDNSKN TLYLQMNSSLR AEDTAVYYCA 360		
REEDDYWGQGT LVTVTSSGG GSAGGGGSQSV GSQSVLAQPP SASGTPGQRV TISCSSGSSN 420		
IGSNYVYWWY QLPGTAKPLL IYGNNKRPSG VPDRFSGSKS GTSASLAISG LRSEDEADYY 480		
CAAWDDSLNG RVFGGGTAKLT VLCPPCPAPE AAGAPSPLF PPKPDKTLMI SRTPEVTCVV 540		
VDVSHPDEPE KFNWYVDGVE VHNAKTKPRE EQYNSTYRUVV SVLTVLHQDW LNGKEYKCV 600		
SNKALPAPIE KTISKAKGQP REPQVYTLPP SRDELTKNQV SLTCLVKGFY PSDIAWEVES 660		
NGOPENNYKT TPPVLDSDGS FFYLSKLTVD KSRWQQGNVFC SCSVHMHEALH NYHTQKSLSL 720		
SPG 723		
SEQ ID NO: 149	moltype = AA length = 574	
FEATURE	Location/Qualifiers	
source	1..574	
	mol_type = protein	
	organism = synthetic construct	
SEQUENCE: 149		
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD 60		
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVTV 120		

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SSPAPNLLGG PEVQLLESQGG GLVQPGGSLR LSCAASGFTF SSYAMSWVRQ APGKGLEWVA	180
NIQDGSEKVN YDSDMRGRFT ISRDN SKNTL YLQMNNSLRAE DTAVYYCARE FDYWGQGTLV	240
TVTSSASTKG PSVFPLAPSS KSTSGGTAAL GCLVKDYFPE PVTVWSNSGA LTSGVHTFP	300
VIQSSGLYSL SSVTVPSSS LGTQTYICNV NHKPSNTKVD KKVEPKSCDK THTCP	360
EAAGAPS VFL PPPKPDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTPR	420
EQQYNSTYRV VS VLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPOVYTL	480
PSRDELTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK TPPVLDSDG SFFLYSKLT	540
DKSRWQQNVN FSCSVMHEAL HNHYTQKSLS LSPG	574
SEQ ID NO: 150 moltype = AA length = 335	
FEATURE Location/Qualifiers	
source 1..335	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 150	
QS VLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI YRSNQRPSGV	60
PDRFSGSKSG TSASLAISGL RSEDEADYYC SSYAGNLYNLV FGGGTKLTVL PAPNLLGGPQ	120
SVLAQPPSAS GTPGQRVTIS CSGSSSNIGS NYVYWWYQQLP GTAPKLLIYG NNKRPSGV	180
RFGSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNLRVFF GGGTKLTVLG QPKAAPSV	240
FPPSSEELQA NKATLVCLIS DFYPGAVTA WKADSSPVKA G VETTTPSKQ SNNKYAASSY	300
LSLTPEQWK HRSYSCQVTH EGSTVEKTV A PTECS	335
SEQ ID NO: 151 moltype = AA length = 569	
FEATURE Location/Qualifiers	
source 1..569	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 151	
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD	60
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDPGV AGWFGQYGMV VWGQGTLVTV	120
SSPLADEVQL LESGGGLVQP GGSLRSLCAA SGFTFSSYAM SWVRQAPGKG LEWVANINQD	180
GSEKNYVDSM RGRFTISRDN SKNTLYLQMN SLRAEDTAVY YCAREFDYWG QGTLVTVTSS	240
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS	300
GLYSLSSVVT VPSSSLGTQT YICNVNHNPKS NTKVDKKVEP KSCDKTHTCP PCPAPEAAGA	360
PSVFLFPPK P KDTLMISRTP EVT C VVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN	420
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTI KAKGQPREPQ VYTLPSSRDE	480
LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW	540
QQGNVFSCSV MHEALHNHYT QKSLSLSPG	569
SEQ ID NO: 152 moltype = AA length = 330	
FEATURE Location/Qualifiers	
source 1..330	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 152	
QS VLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI YRSNQRPSGV	60
PDRFSGSKSG TSASLAISGL RSEDEADYYC SSYAGNLYNLV FGGGTKLTVL PLAPOSVLAQ	120
PPSASGTPQ RVTISCGSS SNIGSNYYWV YQQLPGTAK LLIYGNKRP SGVPDRFSGS	180
KSGTSASLAI SGLRSBDEAD YYCAAWDDSL NGRVFGGGTK LTVLGQPKAA PSVTLFPSS	240
EELQANKATL VCLISDFYPG AVTVAWKADS SPVKAGVETT TPSKQSNNKY AASSYLSLTP	300
EQWKSHRSYS CQVTHEGSTV EKTVPATECS	330
SEQ ID NO: 153 moltype = AA length = 569	
FEATURE Location/Qualifiers	
source 1..569	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 153	
EVOLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD	60
SRKGRFTISR DNSENTLYLQ MNSLRAEDTA VYYCARDPGV AGWFGQYGMV VWGQGTLVTV	120
SSPLADEVQL LESGGGLVQP GGSLRSLCAA SGFTFSSYAM SWVRQAPGKG LEWVANINQD	180
GSEKNYVDSM RGRFTISRDN SKNTLYLQMN SLRAEDTAVY YCAREFDYWG QGTLVTVTSS	240
ASTKGPSVFP LAPSSKSTSG GTAALGCLVK DYPPEPVTVS WNSGALTSGV HTFPAVLQSS	300
GLYSLSSVVT VPSSSLGTQT YICNVNHNPKS NTKVDKKVEP KSCDKTHTCP PCPAPEAAGA	360
PSVFLFPPK P KDTLMISRTP EVT C VVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN	420
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTI KAKGQPREPQ VYTLPSSRDE	480
LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV LDSDGSFFLY SKLTVDKSRW	540
QQGNVFSCSV MHEALHNHYT QKSLSLSPG	569
SEQ ID NO: 154 moltype = AA length = 335	
FEATURE Location/Qualifiers	
source 1..335	
mol_type = protein	
organism = synthetic construct	
SEQUENCE: 154	
QS VLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI YRSNQRPSGV	60

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PDRFSGSKSG TSASLAISGL RSEDEADYYC SSYAGNNYNLV FGGGTKLTVL PAPNLLGGPQ	120
SVLAQPPSAS CTPGQRTVIS CSGSSSNIGS NVVYWWYQQLP CTAPKLLIYG NNKRPSGVPD	180
RFSGSKSGTS ASLAISGLRS EDEADYYCAA WDDSLNGRVF GGGTKLTVLG QPKAAPSVTL	240
FPPSSEELQA NKATLVCLIS DFYPGAVTVA WKADSSPVKA GVETTPSKQ SNNKYAASSY	300
LSLTPEQWKS HRSYSCQVTH EGSTVEKTV A PTECS	335
 SEQ ID NO: 155 moltype = AA length = 574	
FEATURE Location/Qualifiers	
source 1..574	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 155	
EVQLLESGGG LVQPGGSSLRL SCAASGFTFS DYYMTWIRQA PGKGLEWVSS ISGGSTYYAD	60
SRKGGRFTISR DNSENTLYLQ MNSNRAEDTA VYYCARDPGV AGWFQGYGMD VWGQGTLTV	120
SSPAPNLLGG PEVQLLESQG GLVQPGGSSLR LSCAASGFTF SSYAMSWVRQ APGKGLEWVA	180
NINQDGSEKN YVDSMRGRFT ISRDNDSKNTL YLQMNSLRAE DTAVYYCARE FDYWQGTLV	240
TVTSSASTKG PSVFPLAPSS KSTSGGTAAL GCLVKDVFPE PVTWSWNSGA LTSGVHTFP	300
VLIQSSGLYSL SSVVTPVSSS LGTQTYICNV NHKPSNTKVD KKVEPKSCDK THTCPCPAP	360
EAAGAPSVFL PPPKPKDTLM ISRTPEVTCV VVDVSHEPDE VKFNWYVDDGV EVHNAKT	420
EQQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ PREPOVYTL	480
PSRDELTKNQ VSLTCLVKGF YPSDIAWEWE SNGQPENNYK TPPVVLDSDG SFFLYSKLT	540
DKSRWQQGNV FSCSVMHEAL HNHYTQKSL S LSPG	574
 SEQ ID NO: 156 moltype = AA length = 330	
FEATURE Location/Qualifiers	
source 1..330	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 156	
QSVLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI YRSNQRPSGV	60
PDRFSGSKSG TSASLAISGL RSEDEADYYC SSYAGNNYNLV FGGGTKLTVL PLAPQSVLAQ	120
PPSASGTPQ RVTISCSGSS SNIGSNYVVW YQQLPGTAKP LLIYGNKKRP SGVPDRFSGS	180
KSGTSASLAI SGLRSEDEAD YYCAAWDDSL NGRVFGGGT LTVLGQPKAA PSVTLFPSS	240
EELQANKATL VCLISDFYVG AVTVAWKADS SPVKAGVETT TPSKQSNNKY AASSYLSLTP	300
EQWKSHRSYS CQVTHEGSTV EKTVPATECS	330
 SEQ ID NO: 157 moltype = AA length = 9	
FEATURE Location/Qualifiers	
source 1..9	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 157	
PAPNLLGGP	9
 SEQ ID NO: 158 moltype = AA length = 5	
FEATURE Location/Qualifiers	
source 1..5	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 158	
SYAMS	5
 SEQ ID NO: 159 moltype = AA length = 17	
FEATURE Location/Qualifiers	
source 1..17	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 159	
NINQDGSEKN YVDSMRG	17
 SEQ ID NO: 160 moltype = AA length = 4	
FEATURE Location/Qualifiers	
source 1..4	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 160	
EFDY	4
 SEQ ID NO: 161 moltype = AA length = 13	
FEATURE Location/Qualifiers	
source 1..13	
mol_type = protein	
organism = synthetic construct	
 SEQUENCE: 161	
SGSSSNIGSN YVY	13

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SEQ ID NO: 162	moltype = AA length = 7 Location/Qualifiers source 1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 162	GNNKRPS	7
SEQ ID NO: 163	moltype = AA length = 11 Location/Qualifiers source 1..11 mol_type = protein organism = synthetic construct	
SEQUENCE: 163	AAWDDSLNGR V	11
SEQ ID NO: 164	moltype = AA length = 5 Location/Qualifiers source 1..5 mol_type = protein organism = synthetic construct	
SEQUENCE: 164	SYWMS	5
SEQ ID NO: 165	moltype = AA length = 17 Location/Qualifiers source 1..17 mol_type = protein organism = synthetic construct	
SEQUENCE: 165	NINQDGSEKY YVDSMRG	17
SEQ ID NO: 166	moltype = AA length = 4 Location/Qualifiers source 1..4 mol_type = protein organism = synthetic construct	
SEQUENCE: 166	EYDY	4
SEQ ID NO: 167	moltype = AA length = 17 Location/Qualifiers source 1..17 mol_type = protein organism = synthetic construct	
SEQUENCE: 167	NIKQDGSEKN YVDSMRG	17
SEQ ID NO: 168	moltype = AA length = 4 Location/Qualifiers source 1..4 mol_type = protein organism = synthetic construct	
SEQUENCE: 168	EFDF	4
SEQ ID NO: 169	moltype = AA length = 5 Location/Qualifiers source 1..5 mol_type = protein organism = synthetic construct	
SEQUENCE: 169	DYYMT	5
SEQ ID NO: 170	moltype = AA length = 15 Location/Qualifiers source 1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 170	SISGGSTYYA DSRKG	15
SEQ ID NO: 171	moltype = AA length = 15 Location/Qualifiers source 1..15 mol_type = protein	

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SEQUENCE: 171 DFGVAGWFGQ YGMDV	organism = synthetic construct	
		15
SEQ ID NO: 172 FEATURE source	moltype = AA length = 14 Location/Qualifiers 1..14 mol_type = protein organism = synthetic construct	
SEQUENCE: 172 TGSSSNIGAG YDVH		14
SEQ ID NO: 173 FEATURE source	moltype = AA length = 7 Location/Qualifiers 1..7 mol_type = protein organism = synthetic construct	
SEQUENCE: 173 RSNQRPS		7
SEQ ID NO: 174 FEATURE source	moltype = AA length = 10 Location/Qualifiers 1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 174 SSYAGNYNLV		10
SEQ ID NO: 175 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = synthetic construct	
SEQUENCE: 175 DYYMN		5
SEQ ID NO: 176 FEATURE source	moltype = AA length = 15 Location/Qualifiers 1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 176 SISGGSTYYA DSVKG		15
SEQ ID NO: 177 FEATURE source	moltype = AA length = 15 Location/Qualifiers 1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 177 DFGVAGWFGQ PGMDV		15
SEQ ID NO: 178 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = synthetic construct	
SEQUENCE: 178 SCDKT		5
SEQ ID NO: 179 FEATURE source	moltype = AA length = 15 Location/Qualifiers 1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 179 DFGVAGWFGY YGMDV		15
SEQ ID NO: 180 FEATURE source	moltype = AA length = 113 Location/Qualifiers 1..113 mol_type = protein organism = synthetic construct	
SEQUENCE: 180 EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVAN INQDGSEKNY VDSMRGRFTI SRDNSKNLTY LQMNSLRAED TAVYYCAREF DYWGQGTLVT VSS	60	113

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SEQ ID NO: 181      moltype = AA length = 110
FEATURE
source
1..110
mol_type = protein
organism = synthetic construct
SEQUENCE: 181
QSVLAQPPSA SGTPGQRVTI SCSGSSSNIG SNVYVWYQQL PGTAPKLLIY GNNKRPSGVP 60
DRFSGSKSGT SASLAISGLR SEDEADYYCA AWDDSLNNGRV FGGGTKLTVL 110

SEQ ID NO: 182      moltype = AA length = 113
FEATURE
source
1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 182
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYWMSWVRQA PGKGLEWVAN INQDGSEKYY 60
VDSMRGRFTI SRDNSKNLY LQMNSLRAED TAVYYCAREY DYWGQGTLVT VSS 113

SEQ ID NO: 183      moltype = AA length = 113
FEATURE
source
1..113
mol_type = protein
organism = synthetic construct
SEQUENCE: 183
EVOLLESGGG LVQPGGSLRL SCAASGFTFS SYWMSWVRQA PGKGLEWVAN IKQDGSEKNY 60
VDSMRGRFTI SRDNSKNLY LQMNSLRAED TAVYYCAREY DFWGQGTLVT VSS 113

SEQ ID NO: 184      moltype = AA length = 122
FEATURE
source
1..122
mol_type = protein
organism = synthetic construct
SEQUENCE: 184
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMTWIROA PGKGLEWVSS ISGGSTYYAD 60
SRKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVT 120
SS 122

SEQ ID NO: 185      moltype = AA length = 110
FEATURE
source
1..110
mol_type = protein
organism = synthetic construct
SEQUENCE: 185
QSVLTQPPSA SGTPGQRVTI SCTGSSSNIG AGYDVHWYQQ LPGTAPKLLI YRSNQRPSGV 60
PDRFSGSKSG TSASLAISGL RSEDEADYYC SSYAGNLYNLV FGGGTKLTVL 110

SEQ ID NO: 186      moltype = AA length = 122
FEATURE
source
1..122
mol_type = protein
organism = synthetic construct
SEQUENCE: 186
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMNWIROA PGKGLEWVSS ISGGSTYYAD 60
SVKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVT 120
SS 122

SEQ ID NO: 187      moltype = AA length = 122
FEATURE
source
1..122
mol_type = protein
organism = synthetic construct
SEQUENCE: 187
EVQLLESGGG LVQPGGSLRL SCAASGFTFS DYYMNWIROA PGKGLEWVSS ISGGSTYYAD 60
SVKGRTFISR DNSENTLYLQ MNSLRAEDTA VYYCARDFGV AGWFGQYGMV VWGQGTLVT 120
SS 122

SEQ ID NO: 188      moltype = AA length = 6
FEATURE
source
1..6
mol_type = protein
organism = synthetic construct
SEQUENCE: 188
GGGGSG

SEQ ID NO: 189      moltype = AA length = 5

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FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 189	
GGSGG	5
SEQ ID NO: 190	moltype = AA length = 10
FEATURE	Location/Qualifiers
source	1..10
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 190	
GGGGSGGGGS	10
SEQ ID NO: 191	moltype = AA length = 9
FEATURE	Location/Qualifiers
source	1..9
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 191	
GGSGGGGSG	9
SEQ ID NO: 192	moltype = AA length = 10
FEATURE	Location/Qualifiers
source	1..10
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 192	
GGSGGGGSGS	10
SEQ ID NO: 193	moltype = AA length = 13
FEATURE	Location/Qualifiers
source	1..13
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 193	
GGSGGGGSGG GGS	13
SEQ ID NO: 194	moltype = AA length = 14
FEATURE	Location/Qualifiers
source	1..14
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 194	
GGGGSGGGGS GGG	14
SEQ ID NO: 195	moltype = AA length = 15
FEATURE	Location/Qualifiers
source	1..15
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 195	
GGGGSGGGGS GGGGS	15
SEQ ID NO: 196	moltype = AA length = 27
FEATURE	Location/Qualifiers
source	1..27
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 196	
RADAAAAGGG GSAGGGGGGG GSAGGGGS	27
SEQ ID NO: 197	moltype = AA length = 6
FEATURE	Location/Qualifiers
source	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 197	
ASTKGP	6
SEQ ID NO: 198	moltype = AA length = 13
FEATURE	Location/Qualifiers
source	1..13
	mol_type = protein
	organism = synthetic construct

-continued

SEQUENCE: 198 ASTKGPSVFP LAP		13
SEQ ID NO: 199 FEATURE source	moltype = AA length = 5 Location/Qualifiers 1..5 mol_type = protein organism = synthetic construct	
SEQUENCE: 199 TVAAP		5
SEQ ID NO: 200 FEATURE source	moltype = AA length = 6 Location/Qualifiers 1..6 mol_type = protein organism = synthetic construct	
SEQUENCE: 200 RTVAAP		6
SEQ ID NO: 201 FEATURE source	moltype = AA length = 12 Location/Qualifiers 1..12 mol_type = protein organism = synthetic construct	
SEQUENCE: 201 TVAAPSVIF PP		12
SEQ ID NO: 202 FEATURE source	moltype = AA length = 13 Location/Qualifiers 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 202 RTVAAPSVFI FPP		13
SEQ ID NO: 203 FEATURE source	moltype = AA length = 16 Location/Qualifiers 1..16 mol_type = protein organism = synthetic construct	
SEQUENCE: 203 AKTPPKLEEG EFSEAR		16
SEQ ID NO: 204 FEATURE source	moltype = AA length = 17 Location/Qualifiers 1..17 mol_type = protein organism = synthetic construct	
SEQUENCE: 204 AKTPPKLEEG EFSEARV		17
SEQ ID NO: 205 FEATURE source	moltype = AA length = 9 Location/Qualifiers 1..9 mol_type = protein organism = synthetic construct	
SEQUENCE: 205 AKTPPKLGG		9
SEQ ID NO: 206 FEATURE source	moltype = AA length = 10 Location/Qualifiers 1..10 mol_type = protein organism = synthetic construct	
SEQUENCE: 206 SAKTPKLGG		10
SEQ ID NO: 207 FEATURE source	moltype = AA length = 6 Location/Qualifiers 1..6 mol_type = protein organism = synthetic construct	
SEQUENCE: 207 SAKTTP		6
SEQ ID NO: 208	moltype = AA length = 6	

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FEATURE	Location/Qualifiers
source	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 208	
RADAAP	6
SEQ ID NO: 209	moltype = AA length = 9
FEATURE	Location/Qualifiers
source	1..9
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 209	
RADAAPTVS	9
SEQ ID NO: 210	moltype = AA length = 12
FEATURE	Location/Qualifiers
source	1..12
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 210	
RADAAAAGGP GS	12
SEQ ID NO: 211	moltype = AA length = 18
FEATURE	Location/Qualifiers
source	1..18
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 211	
SAKTTPKLEE GEFSEARV	18
SEQ ID NO: 212	moltype = AA length = 5
FEATURE	Location/Qualifiers
source	1..5
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 212	
ADAAP	5
SEQ ID NO: 213	moltype = AA length = 12
FEATURE	Location/Qualifiers
source	1..12
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 213	
ADAAPTVSIF PP	12
SEQ ID NO: 214	moltype = AA length = 6
FEATURE	Location/Qualifiers
source	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 214	
QPKAAP	6
SEQ ID NO: 215	moltype = AA length = 13
FEATURE	Location/Qualifiers
source	1..13
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 215	
QPKAAPSVTL FPP	13
SEQ ID NO: 216	moltype = AA length = 6
FEATURE	Location/Qualifiers
source	1..6
	mol_type = protein
	organism = synthetic construct
SEQUENCE: 216	
AKTTPP	6
SEQ ID NO: 217	moltype = AA length = 13
FEATURE	Location/Qualifiers
source	1..13
	mol_type = protein
	organism = synthetic construct

-continued

SEQUENCE: 217 AKTTPPSVTP LAP	13
SEQ ID NO: 218 FEATURE source	
moltype = AA length = 6 Location/Qualifiers 1..6 mol_type = protein organism = synthetic construct	
SEQUENCE: 218 AKTTAP	6
SEQ ID NO: 219 FEATURE source	
moltype = AA length = 13 Location/Qualifiers 1..13 mol_type = protein organism = synthetic construct	
SEQUENCE: 219 AKTTAPS VYP LAP	13
SEQ ID NO: 220 FEATURE source	
moltype = AA length = 15 Location/Qualifiers 1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 220 GENKVEYAPA LMALS	15
SEQ ID NO: 221 FEATURE source	
moltype = AA length = 15 Location/Qualifiers 1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 221 GPAKELTPLK EAKVS	15
SEQ ID NO: 222 FEATURE source	
moltype = AA length = 15 Location/Qualifiers 1..15 mol_type = protein organism = synthetic construct	
SEQUENCE: 222 GHEAAAVMQV QYPAS	15
SEQ ID NO: 223 FEATURE source	
moltype = AA length = 6 Location/Qualifiers 1..6 mol_type = protein organism = synthetic construct	
SEQUENCE: 223 KSCDKT	6

1. A multispecific binding protein comprising at least a first polypeptide chain, wherein said first polypeptide chain comprises a first variable heavy chain domain (VH1) linked to a second variable heavy chain domain (VH2) via at least one modified hinge region, wherein:

the VH1 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and the VH2 binds specifically to ALK1; or

the VH1 binds specifically to ALK1 and the VH2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.

2. (canceled)

3. The multispecific binding protein of claim 1, further comprising a second polypeptide chain, wherein said second polypeptide chain comprises a first variable light chain domain (VL1) linked to a second variable light chain domain (VL2), wherein:

the VL1 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and the VL2 binds specifically to a ALK1; or

the VL1 binds specifically to ALK1 and the VL2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.

4. The multispecific binding protein of claim 3, wherein the VL1 is linked to the VL2 via at least one modified hinge region.

5. The multispecific binding protein of claim 1, wherein one or both of VH1 and VH2 is truncated at the C-terminal end.

6. The multispecific binding protein of claim 5, wherein the C-terminal end is truncated by at least one residue.

7. The multispecific binding protein of claim 5, wherein the C-terminal end is truncated by at least two residues.

8. The multispecific binding protein of claim 5, wherein the SS amino acid residues of the C-terminal end are deleted.

9. The multispecific binding protein of claim 1, comprising a first polypeptide chain of VH1-HX1-VH2-C-Fc, wherein:

VH1 is a first heavy chain variable domain;

VH2 is a second heavy chain variable domain;

C is a heavy chain constant domain; HX1 is a modified hinge region linker; and Fc is an Fc region; and a second polypeptide chain of VL1-LX1-VL2-C, wherein:

VL1 is a first light chain variable domain; VL2 is a second light chain variable domain; C is a light chain constant domain; and LX1 is a modified hinge region linker.

10. The multispecific binding protein of claim 1, wherein the modified hinge region comprises;

- i) an upper hinge region of up to 7 amino acids in length or is absent; and
- ii) a lower hinge region.

11. The multispecific binding protein of claim 1, wherein the modified hinge region comprises or consists of an amino acid sequence of PLAP (SEQ ID NO:2) or PAPNLLGGP (SEQ ID NO:157).

12. The multispecific binding protein of claim 1, wherein:

A) the VH binding to ALK1 comprises an HCDR1 amino acid sequence of SYAMS (SEQ ID NO:158), an HCDR2 amino acid sequence of NINQDGSEKNYVDSMRG (SEQ ID NO:159), and an HCDR3 amino acid sequence of EFDY (SEQ ID NO:160); and the VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163); or

B) the VH binding to ALK1 comprises an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NINQDGSEKYYVDSMRG (SEQ ID NO:165), and an HCDR3 amino acid sequence of EYDY (SEQ ID NO:166); and the VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163); or

C) the VH binding to ALK1 comprises an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NIKQDGSEKNYVDSMRG (SEQ ID NO:167), and an HCDR3 amino acid sequence of EFDF (SEQ ID NO:168); and the VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163).

13. The multispecific binding protein of claim 1, wherein:

A) the VH binding to BMPRII comprises an HCDR1 amino acid sequence of DYYMT (SEQ ID NO:169), an HCDR2 amino acid sequence of SISGGSTYY-ADSRKG (SEQ ID NO:170), and an HCDR3 amino acid sequence of DFGVAGWFGQQYGMDV (SEQ ID NO:171); and the VL binding to BMPRII comprises an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174); or

B) the VH binding to BMPRII comprises an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYY-ADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGQFGMDV (SEQ ID NO:177); and the VL binding to BMPRII comprises an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174); or

C) the VH binding to BMPRII comprises an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYY-ADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGYYGMDV (SEQ ID NO:179); and the VL binding to BMPRII comprises an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).

14. The multispecific binding protein of claim 1, wherein:

A) the VH binding to ALK1 comprises an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CAASGFTFSSYAMSWVRQAPGKGLEWVAN-INQDGSEK NYVDSMRGRFTISRDN SKNT-LYLMQNSLRAEDTAVYYCAREFDYWGQGT LVT VSS (SEQ ID NO:180), or an amino acid sequence with at least 90% identity thereto; and the VL binding to ALK1 comprises an amino acid sequence of QSV-LAQPPSASGTPGQ RV TISC SGS SNI G-SNYV VY WY QQLPGTAPKLLI YGNN KRP SGVP DRFGSKSGTSASLAISGLRSEDEADYY-CAA WDDSLNGRVFGGGTKLTVL (SEQ ID NO:181), or an amino acid sequence with at least 90% identity thereto; or

B) the VH binding to ALK1 comprises an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CAASGFTFSSYWMSWVRQAPGKGLEWVAN-INQDGSEK YYVDSMRGRFTISRDN SKNT-LYLMQNSLRAEDTAVYYCAREYDYWGQGT LVT VSS (SEQ ID NO:182), or an amino acid sequence with at least 90% identity thereto; and the VL binding to ALK1 comprises an amino acid sequence of QSV-LAQPPSASGTPGQ RV TISC SGS SNI G-SNYV VY WY QQLPGTAPKLLI YGNN KRP SGVP DRFGSKSGTSASLAISGLRSEDEADYY-CAA WDDSLNGRVFGGGTKLTVL (SEQ ID NO:181), or an amino acid sequence with at least 90% identity thereto; or

C) the VH binding to ALK1 comprises an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CAASGFTFSSYWMSWVRQAPGKGLEWVAN-IKQDGSEK NYVDSMRGRFTISRDN SKNT-LYLMQNSLRAEDTAVYYCAREFD FWGQGT LVT VSS (SEQ ID NO:183), or an amino acid sequence with at least 90% identity thereto; and the VL binding to ALK1 comprises an amino acid sequence of QSV-LAQPPSASGTPGQ RV TISC SGS SNI G-SNYV VY WY QQLPGTAPKLLI YGNN KRP SGVP DRFGSKSGTSASLAISGLRSEDEADYY-CAA WDDSLNGRVFGGGTKLTVL (SEQ ID NO:181), or an amino acid sequence with at least 90% identity thereto.

- 15.** The multispecific binding protein of claim 1, wherein:
- A) the VH binding to BMPRII comprises an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CAASGFTSDYYMTWIRQAPGKGLEWVSSIS-GGSTYYA DSRKGRFTISRDNSENTLYLQMNSL-RAEDTAVYYCARDFGVAGWFGQYGMMDVWGQQ TLTVSS (SEQ ID NO:184), or an amino acid sequence with at least 90% identity thereto; and the VL binding to BMPRII comprises an amino acid sequence of QSVLTQPPP-SASGTPGQRVTISCTGSSSNI-GAGYDVHWYQQLPGTAPKLLIYRSNQRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCSSY-AGNYNLVFGGGTKLTVL (SEQ ID NO:185), or an amino acid sequence with at least 90% identity thereto;
 - B) the VH binding to BMPRII comprises an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CAASGFTSDYYMNWIRQAPGKGLEWVSSIS-GGSTYYA DSVKGRFTISRDNSENTLYLQMNSL-RAEDTAVYYCARDFGVAGWFGQFGMDVWGQGT LTVSS (SEQ ID NO:186), or an amino acid sequence with at least 90% identity thereto; and the VL binding to BMPRII comprises an amino acid sequence of QSVLTQPPSASGTPGQRVTISCTGSSSNI-GAGYDVHWYQQLPGTAPKLLIYRSNQRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCSSY-AGNYNLVFGGGTKLTVL (SEQ ID NO:185), or an amino acid sequence with at least 90% identity thereto;
 - C) the VH binding to BMPRII comprises an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CAASGFTSDYYMNWIRQAPGKGLEWVSSIS-GGSTYYA DSVKGRFTISRDNSENTLYLQMNSL-RAEDTAVYYCARDFGVAGWFGQYGMMDVWGQQ TLTVSS (SEQ ID NO:187), or an amino acid sequence with at least 90% identity thereto; and the VL binding to BMPRII comprises an amino acid sequence of QSVLTQPPSASGTPGQRVTISCTGSSSNI-GAGYDVHWYQQLPGTAPKLLIYRSNQRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCSSY-AGNYNLVFGGGTKLTVL (SEQ ID NO:185), or an amino acid sequence with at least 90% identity thereto.
- 16.** The multispecific binding protein of claim 1, wherein the multispecific binding protein is selected from:
- (a) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 136-142, and the second polypeptide chain comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 143-146;
 - (b) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 137, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146;
 - (c) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 138, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146;
 - (d) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 139, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146;
 - (e) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 140, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146;
 - (f) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 141, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146;
 - (g) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 142, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 146;
 - (h) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 68, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 69;
 - (i) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 70, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 71;
 - (j) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 72, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 73; or
 - (k) a multispecific binding protein wherein the first polypeptide chain comprises an amino acid sequence of SEQ ID NO: 74, and the second polypeptide chain comprises an amino acid sequence of SEQ ID NO: 75.
- 17-26.** (canceled)
- 27.** A multispecific binding protein comprising a first polypeptide chain and a second polypeptide chain, wherein the first polypeptide chain and second polypeptide chain each comprise, from N-terminus to C-terminus, a first single chain variable fragment (scFv) linked to a second scFv, wherein:
- the first scFv binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and the second scFv binds specifically to ALK1; or
 - the first scFv binds specifically to ALK1 and the second scFv binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.
- 28.** The multispecific binding protein of claim 27, wherein the first scFv is linked to the second scFv via at least one modified hinge region.
- 29.** The multispecific binding protein of claim 27, wherein the scFv binding to ALK1 comprises:
- A):
 - a VH domain comprising an HCDR1 amino acid sequence of SYAMS (SEQ ID NO:158), an HCDR2 amino acid sequence of NINQDGSEKNYVDSMRG (SEQ ID NO:159), and an HCDR3 amino acid sequence of EFDY (SEQ ID NO:160); and
 - a VL binding to ALK1 comprises an LCDR1 amino acid sequence of SGSSSNIGSNYVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163); or
 - B):
 - a VH domain comprising an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of

- NINQDGSEKYYVDSMRG (SEQ ID NO:165), and an HCDR3 amino acid sequence of EYDY (SEQ ID NO:166); and
- a VL domain comprising an LCDR1 amino acid sequence of SGSSNIGSNVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163); or
- C):
- a VH domain comprising an HCDR1 amino acid sequence of SYWMS (SEQ ID NO:164), an HCDR2 amino acid sequence of NIKQDGSEKYYVDSMRG (SEQ ID NO:167), and an HCDR3 amino acid sequence of EFDF (SEQ ID NO:168); and
 - a VL domain comprising an LCDR1 amino acid sequence of SGSSNIGSNVY (SEQ ID NO:161), an LCDR2 amino acid sequence of GNNKRPS (SEQ ID NO:162), and an LCDR3 amino acid sequence of AAWDDSLNGRV (SEQ ID NO:163).
- 30.** The multispecific binding protein of claim **27**, wherein the scFv binding to BMPRII comprises:
- A):
- a VH domain comprising an HCDR1 amino acid sequence of DYYMT (SEQ ID NO:169), an HCDR2 amino acid sequence of SISGGSTYYADSRKG (SEQ ID NO:170), and an HCDR3 amino acid sequence of DFGVAGWFGQYGMMDV (SEQ ID NO:171); and
 - a VL domain comprising an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174); or
- B):
- a VH domain comprising an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYYADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGQFGMDV (SEQ ID NO:177); and
 - a VL domain comprising an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174); or
- C):
- a VH domain comprising an HCDR1 amino acid sequence of DYYMN (SEQ ID NO:175), an HCDR2 amino acid sequence of SISGGSTYYADSVKG (SEQ ID NO:176), and an HCDR3 amino acid sequence of DFGVAGWFGYYYGMMDV (SEQ ID NO:179); and
 - a VL domain comprising an LCDR1 amino acid sequence of TGSSSNIGAGYDVH (SEQ ID NO:172), an LCDR2 amino acid sequence of RSNQRPS (SEQ ID NO:173), and an LCDR3 amino acid sequence of SSYAGNYNLV (SEQ ID NO:174).
- 31.** The multispecific binding protein of claim **27**, wherein the scFv binding to ALK1 comprises:
- a VH domain comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CAASGFTFSSYAMSWVRQAPGKGLEWVAN-INQDGSEK NYVDSMRGRFTISRDNSKNT-LYLQMNSLRAEDTAVYYCAREFDYWQGQTLVT VSS(SEQ ID NO:180), or an amino acid sequence with at least 90% identity thereto; and
- a VL domain comprising an amino acid sequence of QSVLAQPPSASGTPGQRTISCTSGSSNI-G-SNYVWYQQLPGTAPKLLIYGNKNKRPSGV DRFSGSKSGTSASLAISGLRSEDEADYY-CAAWDDSLNGRVFGGGTKLTVL (SEQ ID NO:181), or an amino acid sequence with at least 90% identity thereto.
- 32.** The multispecific binding protein of claim **27**, wherein the scFv binding to BMPRII comprises:
- a VH domain comprising an amino acid sequence of EVQLLESGGGLVQPGGSLRLS-CAASGFTFSYYMTWIRQAPGKGLEWVSSIS-GGSTYYA DSRKGRFTISRDNSENTLYLQMNSL-RAEDTAVYYCARDFGVAGWFGQYGMMDVWGQG TLTVSS (SEQ ID NO:184), or an amino acid sequence with at least 90% identity thereto; and
- a VL domain comprising an amino acid sequence of QSVLTQPPSASGTPGQRTISCTGSSSNIT-GAGYDVHWYQQLPGTAPKLLIYRSNQRPSGV PDRFSGSKSGTSASLAISGLRSEDEADYYCSSY-AGNYNLVFGGGTKLTVL (SEQ ID NO:185), or an amino acid sequence with at least 90% identity thereto.
- 33-71.** (canceled)
- 72.** A pharmaceutical composition comprising the multispecific binding protein of claim **1** and a pharmaceutically acceptable carrier.
- 73.** An isolated nucleic acid molecule encoding a multispecific binding protein comprising at least a first polypeptide chain, wherein said first polypeptide chain comprises a first variable heavy chain domain (VH1) linked to a second variable heavy chain domain (VH2) via at least one modified hinge region, wherein:
- the VH1 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and the VH2 binds specifically to ALK1; or
 - the VH1 binds specifically to ALK1 and the VH2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.
- 74.** An expression vector comprising the nucleic acid molecule of claim **73**.
- 75.** A host cell comprising the expression vector of claim **74**.
- 76.** A method for treating a disease or disorder in a subject, comprising administering to a subject in need thereof a multispecific binding protein comprising at least a first polypeptide chain, wherein said first polypeptide chain comprises a first variable heavy chain domain (VH1) linked to a second variable heavy chain domain (VH2) via at least one modified hinge region, wherein:
- the VH1 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB and the VH2 binds specifically to ALK1; or
 - the VH1 binds specifically to ALK1 and the VH2 binds specifically to a target selected from BMPRII, ActRIIA, and ActRIIB.
- 77.** The method of claim **76**, wherein the disease or disorder is a vascular disease or disorder.

78. The method of claim 77, wherein the vascular disease or disorder is hereditary hemorrhagic telangiectasia (HHT).

79. The method of claim 77, wherein the vascular disease or disorder is pulmonary arterial hypertension (PAH).

80. (canceled)

81. A method for inducing signaling between ALK1 and BMPRII, ActRIIA, or ActRIIB in a subject, comprising administering to the subject the multispecific binding protein of claim 1.

82-85. (canceled)

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