

NON-RECEPTOR TYROSINE KINASE COMPOSITIONS FOR TARGETED LYSOSOMAL DEGRADATION AND METHODS OF USE THEREOF

5 Related Application

This application claims priority to U.S. Provisional Application No. 63/529,587, filed July 28, 2023, and U.S. Provisional Application No. 63/550,872, filed February 7, 2024, the entire contents of each of which is hereby incorporated by reference.

BACKGROUND

10 Protein degradation regulates numerous aspects of cellular homeostasis. The endogenous protein degradation machinery has been reprogrammed to eliminate a variety of intracellular substrate through an approach named targeted protein degradation. Targeted protein degradation (TPD) has emerged as a promising therapeutic strategy with advantage over conventional inhibition. Unlike inhibitors, degraders can enable catalytic and durable knockdown of protein
15 levels. Proteolysis-targeting chimeras (PROTACs) consist of two moieties, which bind a target and ubiquitin ligase (E3), separated by a flexible linker. However, PROTACs are limited to targeting intracellular proteins due to their intracellular mechanism of action.

Lysosomal degradation platforms such as cytokine receptor-targeting chimeras (KineTacs) and lysosomal targeting chimera (LYTACs) using E3/USP to eliminate disease-
20 causing proteins has been developed. KineTacs platforms are genetically encoded bispecific antibodies consisting of a cytokine arm that binds its cognate cytokine receptor, and a target-binding moiety for the protein of interest. However, KineTacs are limited to apply to cytokine receptors on the T cells and can degrade the target protein if it is also present on the T cells. LYTACs platform consisting of antibody-glycan conjugates degrades cell surface and
25 extracellular proteins by shuttling the target protein to the lysosome for degradation.

Accordingly, additional approaches for lysosomal degradation platforms are needed in the art.

BRIEF SUMMARY

30 The present disclosure relates to a novel and unique bispecific binding molecule

comprised of fully recombinant bispecific binding domains that utilize a neuropilin-1 (NRP1)-mediated internalization to target various therapeutically relevant target proteins, particularly cell surface receptors such as receptors that are not Receptor Tyrosine Kinases (non-RTKs), for lysosome degradation. Accordingly, the present disclosure provides a bispecific binding molecule-based degrader that degrades a target protein, such as a target protein on a cancer cell. The bispecific binding molecule specifically binds to the target protein of interest and to a neuropilin-1 (NRP1). The present disclosure further relates to methods of using an NRP1-dependent bispecific binding molecule that induces degradation of a target protein through lysosomal degradation pathway. The present disclosure provides methods of using the bispecific binding molecules to inhibit tumor growth, e.g., to enhance the therapeutic efficacy of cancer treatment.

The present disclosure relates to a bispecific binding molecule comprising a target protein binding domain and a neuropilin-1 (NRP1) binding domain, for example an NRP-1 binding domain that is an antibody or NRP-1-binding fragment thereof. In some embodiments of the bispecific binding molecule comprising the target protein binding domain that specifically binds to its cognate protein receptor and the NRP1 binding domain that binds to its cognate receptor. In some embodiments, the target protein and the NRP1 are membrane associated. In some embodiments, the binding of the bispecific binding molecule to the NRP1 results in the internalization of the target protein bound to the bispecific binding molecule. In some embodiments, the binding of the bispecific binding molecule to the NRP1 subsequently induces lysosomal degradation of target proteins.

In certain embodiments, the target protein binding domain of the bispecific molecule binds to a non-Receptor Tyrosine Kinase (non-RTK). Accordingly, in one aspect, the disclosure pertains to a bispecific binding molecule comprising:

- (a) a target protein binding domain that specifically binds to a target protein, wherein the target protein is a non-Receptor Tyrosine Kinase (RTK); and
- (b) a neuropilin-1 (NRP1) binding domain that binds to NRP1 comprising an antibody or NRP-1-binding fragment thereof,

wherein binding of the bispecific binding molecule to the target protein and to NRP1 results in lysosomal degradation of the target protein in a target cell.

In embodiments, the non-RTK protein can be selected from integrins, G-protein

coupled receptors (GPCRs), immune checkpoint receptors, and ion channel receptors.

In an embodiment, the non-RTK protein is an integrin. In embodiments, the non-RTK protein is integrin $\alpha V\beta$ or integrin $\alpha V\beta 3$.

In an embodiment, the non-RTK protein is a GPCR.

5 In an embodiment, the non-RTK protein is an immune checkpoint receptor. In embodiments, the immune checkpoint receptor is PD-L1.

In an embodiment, the non-RTK protein is an ion channel receptor.

In an embodiment, the target cell is a cancer cell. In embodiments, the cancer cell is selected from the group consisting of lung cancer, breast cancer, colon and rectum cancer, head
10 and neck cancer, esophagogastric cancer, liver cancer, glioblastoma, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, kidney cancer, and pancreatic cancer. In an embodiment, the cancer cell is a non-small cell lung cancer (NSCLC) cell.

In embodiments, the target protein binding domain and the NRP1 binding domain are each independently selected from the group consisting of IgG, half antibodies, single-domain
15 antibodies, nanobodies, Fabs, monospecific Fab2, Fc, scFv, minibodies, IgNAR, V-NAR, hcIgG, VHH domain, camelid antibodies, and peptibodies.

In an embodiment, the NRP1 binding domain comprises:

(i) an antibody heavy chain variable (VH) domain comprising CDR1, CDR2 and CDR3 regions (HCDR1, HCDR2 and HCDR3, respectively), wherein HCDR1
20 consists of the sequence shown in SEQ ID NO: 79, HCDR2 consists of the sequence shown in SEQ ID NO: 80, and HCDR3 consists of the sequence shown in any one of SEQ ID NOs: 81-84; and

(ii) an antibody light chain variable (VL) domain comprising CDR1, CDR2 and CDR3 regions (LCDR1, LCDR2 and LCDR3, respectively), wherein LCDR1
25 consists of the sequence shown in any one of SEQ ID NOs: 85-87, LCDR2 consists of the sequence shown in SEQ ID NO: 88, and LCDR3 consists of the sequence shown in SEQ ID NO: 89.

In an embodiment,

(i) HCDR1 consists of the sequence shown in SEQ ID NO: 79, HCDR2
30 consists of the sequence shown in SEQ ID NO: 80, and HCDR3 consists of the sequence shown in any one of SEQ ID NO: 84; and

- (ii) LCDR1 consists of the sequence shown in SEQ ID NO: 85, LCDR2 consists of the sequence shown in SEQ ID NO: 88, and LCDR3 consists of the sequence shown in SEQ ID NO: 89.

In other aspects, the disclosure pertains to a nucleic acid encoding a bispecific binding molecule of the disclosure, an expression vector comprising a nucleic acid of the disclosure, and a cell capable of protein expression comprising a nucleic acid (e.g., expression vector) of the disclosure.

In another aspect, the disclosure pertains to use of the bispecific binding molecule of the disclosure in the manufacture of a medicament for treating cancer in a subject.

In another aspect, the disclosure pertains to a method of inducing lysosomal degradation of a target protein in a cell, the method comprising contacting the cell with the bispecific binding molecule of the disclosure such that lysosomal degradation of the target protein is induced in the cell. In embodiments, the cell comprises one or more mutations in the target protein and/or overexpresses the target protein. In embodiments, the cell is resistant or refractory to responsiveness to an inhibitor of the target protein. In an embodiment, the target protein is an integrin, such as an integrin $\alpha V\beta$ or integrin $\alpha V\beta 3$. In an embodiment, the target protein is a GPCR. In an embodiment, the target protein is an immune checkpoint receptor, such as PD-L1. In an embodiment, the target protein is an ion channel receptor.

In another aspect, the disclosure pertains to a method of inhibiting tumor growth in a subject having a tumor, the method comprising administering to the subject the bispecific binding molecule of the disclosure such that growth of the tumor in the subject is inhibited. In embodiments, the tumor comprises one or more mutations in the target protein and/or overexpresses the target protein. In embodiments, the tumor is resistant or refractory to responsiveness to an inhibitor of the target protein. In an embodiment, the target protein is an integrin, such as an integrin $\alpha V\beta$ or integrin $\alpha V\beta 3$. In an embodiment, the target protein is a GPCR. In an embodiment, the target protein is an immune checkpoint receptor, such as PD-L1. In an embodiment, the target protein is an ion channel receptor.

In embodiments, the bispecific binding molecule is administered intravenously, intraperitoneally, intrathecally, intraventricularly, or intraparenchymally.

The present disclosure relates to a bispecific binding molecule comprising a target protein binding domain that specifically binds to a target protein and a neuropilin-1 (NRP1) binding

domain that binds to the NRP1. In some embodiments, the target protein and the NRP1 are membrane associated. In some embodiments, the target protein cell surface receptor protein. In some embodiments, the target protein is a transmembrane protein.

In some embodiments, the target protein comprises receptors tyrosine kinase (RTKs). In some embodiments, the tyrosine kinase comprises epidermal growth factor receptors (EGFRs), platelet-derived growth factor receptors (PDGFRs), fibroblast growth factor receptors (FGFRs), receptors tyrosine kinase Met (METs), and receptors vascular endothelial growth factors (VEGFRs).

In some embodiments, the receptor tyrosine kinase comprises EGFR/HER1/Erb1, HER2/ErbB2, HER3/ErbB3, HER4/ErbB4, FGFR1, FGFR2, FGFR3, FGFR4, MET, RON, PDGFR, PDGFR α , PDGFR β , CSF-1R, Kit, FLT-3, VEGFR1, VEGFR2, and VEGFR3.

In some embodiments, the target protein comprises the EGFRs. In some embodiments, the EGFR is selected from the group of consisting of EGFR/HER1/Erb1, HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4. In some embodiments, the target protein is EGFR.

In some embodiments, the target protein comprises the FGFRs. In some embodiments, the FGFR1 is selected from the group of consisting of FGFR1, FGFR2, FGFR3, and FGFR4.

In some embodiments, the target protein comprises receptors tyrosine kinase MET. In some embodiments, the receptor tyrosine kinase MET is MET or macrophage-stimulating protein receptor (MST1R/RON).

In some embodiments, the target protein comprises the PDGFRs. In some embodiments, the PDGFR is selected from the group of consisting of PDGFR, PDGFR α , PDGFR β , CSF-1R, Kit, and FLT-3.

In some embodiments, the target protein comprises the VEGFRs. In some embodiments, the VEGFR is selected from the group of consisting of VEGFR1, VEGFR2, and VEGFR3.

In some embodiments, the receptor tyrosine kinase is selected from the group of consisting of EGFR/HER1/Erb1, HER2/ErbB2, HER3/ErbB3, HER4/ErbB4 VEGFR1, VEGFR2, and VEGFR3.

In some embodiments, the target protein comprises receptors serine/threonine kinase (RSTKs), G-protein coupled receptors (GPCRs), immune checkpoint receptors, and ion channel receptors.

In some embodiments, the target protein comprises receptors serine/threonine kinase

(RSTKs). In some embodiments, the RSTK comprises ACVRL1, ACVR1, ACVR1B, ACVR1C, BMPR1A, BMPR1B, TGFBR1, ACVR2A, ACVR2B, AMHR2, BMPR2 and TGFBR2.

In some embodiments, the target protein comprises G-protein coupled receptors (GPCRs). In some embodiments, the GPCR is selected from the group of consisting of CXCR4, CCR5, FFAR2, GLP2R, 5-HT1A receptor, 5-HT2A receptor, 5-HT4 receptor, 5-HT5A receptor, M1 receptor, M2 receptor, A1 receptor, A2A receptor, α 1A-adrenoceptor, α 2A-adrenoceptor, β 1-adrenoceptor, β 3-adrenoceptor, AT1 receptor, BB1 receptor, B1 receptor, CB1 receptor, CB2 receptor, chemerin receptor 1, CCR1, CX3CR1, ACKR3, CCK1 receptor, GPR3, GPR12, GPR17, GPR32 and GPR35.

In some embodiments, the target protein comprises immune checkpoint receptors. In some embodiments, the immune checkpoint receptor is selected from the group of consisting of CD27, CD28, CD40, CD122, CD137, OX40, GITR, ICOS, A2AR, B7-H3, B7-H4, BTLA, CTLA-4, IDO, KIR, LAG3, NOX2, PD-1, TIM-3, VISTA, SIGEC7 and PD-L1.

In some embodiments, the target protein comprises ion channel receptors. In some embodiments, the ion channel receptor is selected from the group of consisting of KCa1.1, KCa2.1, CatSper1, TPC1, CNGA1, HCN1, Kir1.1, Kir3.2, RyR1, TRPA1, TRPC3, TRPM1, TRPP1, TRPV1, K2P1.1, K2P10.1, Cav1.1, Cav2.1, Kv1.1, Kv1.8, Kv11.2, Hv1, Nav1.1 and Nav1.2.

In some embodiments, the target protein comprises a membrane associated target protein, which the target protein binding domain of a bispecific binding molecule binds to a cell surface receptor. In some embodiments, the target protein binding domain of a bispecific binding molecule binds to the extracellular epitope of a membrane-associated target protein. In some embodiments, the target cell comprises a neoplastic cell. In some embodiments, the target cell is a cancer cell. In some embodiments, the cancer cell is selected from the group consisting of lung cancer, breast cancer, colon and rectum cancer, head and neck cancer, esophagogastric cancer, liver cancer, glioblastoma, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, kidney cancer, and pancreatic cancer. In some embodiments, the target cell comprises an immune cell.

In some embodiments, the target protein binding domain and the NRP1 binding domain are each independently selected from the group consisting of IgG, half antibodies, single-domain antibodies, nanobodies, Fabs, monospecific Fab2, Fc, scFv, minibodies, IgNAR, V-NAR, hcIgG,

VHH domain, camelid antibodies, and peptibodies.

In some embodiments, the target protein binding domain and the NRP1 binding domain together form a bispecific binding molecule, a bispecific diabody, a bispecific Fab2, a bispecific camelid antibody, or a bispecific peptibody scFv-Fc, a bispecific IgG, a knob and hole bispecific IgG, a Fc-Fab, and a knob and hole bispecific Fc-Fab, a cytokine-IgG fusion, a cytokine-Fab fusion, and a cytokine-Fc-scFv fusion. In some embodiments, the target protein binding domain comprises an Fc-Fab and the NRP1 binding domain comprises an Fc-fusion. In another embodiment, the bispecific binding molecule is an immunoglobulin G1 (IgG1) or variant thereof. In another embodiment, the IgG1 is a human IgG1 or variant thereof.

In some embodiments, the bispecific binding molecule comprises: two identical heavy chain polypeptides comprising a first heavy chain is fused to a first single chain variable fragment (scFv) by a peptide linker, to create a first heavy chain fusion polypeptide, and a second heavy chain is fused to a second scFv by a peptide linker, to create a second heavy chain fusion polypeptide, wherein the first and second scFv are identical; and two identical light chains comprising a first light chain and a second light chain, wherein each heavy chain fusion polypeptide sequence is any of SEQ ID NOs: 1 to 11 or 39 and the light chain polypeptide sequence is SEQ ID NO: 12. In some embodiments, the heavy chain fusion polypeptide sequence is SEQ ID NO: 11 and the light chain polypeptide is SEQ ID NO: 12. In some embodiments, the peptide linker comprises an amino acid sequence (GGGGS)_n set forth in SEQ ID NO: 13, wherein n is each independently an integer between 1 and 20. In some embodiments, the present disclosure further provides the nucleotide sequences encoding each heavy chain fusion polypeptides set forth in any of SEQ ID NOs: 15 to 24 or 40 and light chain polypeptide set forth in and SEQ ID NO: 25.

In another embodiment, the bispecific binding molecule comprises: (a) two identical heavy chain polypeptides comprising a first heavy chain is fused to a first single chain variable fragment (scFv) by a peptide linker, to create a first heavy chain fusion polypeptide, and a second heavy chain is fused to a second scFv by a peptide linker, to create a second heavy chain fusion polypeptide, wherein the first and second scFv are identical; and (b) two identical light chains comprising a first light chain and a second light chain, wherein (i) a heavy chain fusion polypeptide comprises a variable heavy chain (VH), a constant heavy chain 1 (CH1), CH2, CH3, and a short chain variable fragment (scFv) comprising a NRP1 binding domain that is to the C-

terminal end of the CH3; and (ii) a light chain polypeptide comprises a variable light chain (VL) and a constant light chain (CL), wherein the VL and VH of the heavy chain fusion polypeptides and light chain polypeptides comprise the target protein binding domain that binds to the target protein and the scFv comprising the NRP1 binding domain that binds to the NRP1.

5 In some embodiments, the NRP1 binding domain of the bispecific binding molecule comprises:

(i) an antibody heavy chain variable (VH) domain comprising CDR1, CDR2 and CDR3 regions (HCDR1, HCDR2 and HCDR3, respectively), wherein HCDR1 consists of the sequence shown in SEQ ID NO: 79, HCDR2 consists of
10 the sequence shown in SEQ ID NO: 80, and HCDR3 consists of the sequence shown in any one of SEQ ID NOs: 81-84; and

(ii) an antibody light chain variable (VL) domain comprising CDR1, CDR2 and CDR3 regions (LCDR1, LCDR2 and LCDR3, respectively), wherein LCDR1 consists of the sequence shown in any one of SEQ ID NOs: 85-87, LCDR2
15 consists of the sequence shown in SEQ ID NO: 88, and LCDR3 consists of the sequence shown in SEQ ID NO: 89.

In another embodiment,

(iii) HCDR1 consists of the sequence shown in SEQ ID NO: 79, HCDR2 consists of the sequence shown in SEQ ID NO: 80, and HCDR3 consists
20 of the sequence shown in any one of SEQ ID NO: 84; and

(iv) LCDR1 consists of the sequence shown in SEQ ID NO: 85, LCDR2 consists of the sequence shown in SEQ ID NO: 88, and LCDR3 consists of the sequence shown in SEQ ID NO: 89.

In some embodiments, a binding affinity (K_D) of the bispecific binding molecule for the
25 target protein is < 0.1 nM. In some embodiments, a binding affinity (K_D) of the bispecific binding molecule for the NRP1 ranges between 0.1 nM and 100 nM. In some embodiments, the binding affinity (K_D) of the binding antibody for the target protein is at least 2-, at least 10-, at least 20-, at least 30-, at least 40-, at least 50-, at least 60-, at least 70-, at least 80-, at least 90-, at least 100-, or more than 100-fold greater than the binding affinity (K_D) of the bispecific binding
30 molecule to the NRP1.

In some embodiments, the bispecific binding molecule (bispecific antibody) is part of an

antibody-drug conjugate (ADC), wherein the bispecific binding molecule is conjugated to a drug via a linker. Non-limiting examples of suitable drugs for use in ADC compounds are provided herein.

5 In some embodiments, the EGFRxNRP1 bispecific antibodies inhibit VEGF-mediated VEGFR2 phosphorylation in HUVEC cells. In some embodiments, the binding of the bispecific binding molecule to the target protein and NRP1 induces strong degradation of EGFR^{T790M/L858} *in vitro*. In some embodiments, degradation of the target protein results in the inhibition of the target cell proliferation. In some embodiments, EGFRxNRP1 bispecific antibody reduces *in vitro* cell viability.

10 In some embodiments, the bispecific binding molecule reduces tumor volume in an osimertinib-sensitive xenograft mouse model. In some embodiments, the bispecific binding molecule reduces tumor volume in an osimertinib-resistant or osimertinib-refractor xenograft mouse model. In some embodiments, the treatment with the bispecific binding molecule enhances anti-tumor efficacy.

15 In some embodiments, a nucleic acid encoding bispecific binding molecule disclosed in Table 2. In some embodiments, the nucleic acid is operably linked to a promoter.

Provided is an expression vector comprising the nucleic acid of the bispecific binding molecule. In some embodiments, the vector further comprises a promoter, wherein the promoter is operably linked to the nucleic acid.

20 The present disclosure provides a cell capable of protein expression comprising the nucleic acid of the bispecific binding molecule. In some embodiments, the engineered cell comprises a cancer cell.

In another embodiments, present disclosure provides a method for making a bispecific binding molecule, wherein the method comprises (a) providing a cell capable of protein
25 synthesis, comprising the nucleic acid disclosed herein; and (b) inducing expression of the bispecific binding molecule.

The present disclosure also provides a pharmaceutical composition. In some embodiments, the pharmaceutical composition comprises a bispecific binding molecule, the nucleic acid, the vector, or the engineered cell, and a pharmaceutically acceptable carrier.

30 The present disclosure also provides a use of the bispecific binding molecule in the manufacture of a medicament for treating cancer in a subject.

The present disclosure provides a method of treating a cancer in a subject. In some embodiments, the method comprises administering to a subject in need thereof, a therapeutically effective amount of the bispecific binding molecule, the nucleic acid, the vector, the engineered cell, or the pharmaceutical composition provided herein. In some embodiments, the bispecific
5 binding molecule is administered intraperitoneally.

The present disclosure further provides a method of preventing a cancer in a subject. In some embodiments, provided is a method of inhibiting tumor cell growth.

In some embodiments, a kit comprising one or more unit doses of the pharmaceutical composition and instructions for the one or more unit doses of the pharmaceutical composition to
10 a subject in need thereof.

In some embodiments, the disease comprises a neoplastic disease, an inflammatory disease, a metabolic disease or a neurological disease.

In certain embodiments, the neoplastic disease comprises lung cancer, breast cancer, colon and rectum cancer, head and neck cancer, esophagogastric cancer, liver cancer,
15 glioblastoma, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, kidney cancer, and pancreatic cancer. In one embodiment, the lung cancer is non-small cell lung cancer (NSCLC).

Other features and advantages of the invention will be apparent from the following detailed description and claims.

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BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: A schematic illustration of a bispecific binding molecule that specifically binds to a target protein and neuropilin-1 (NRP1).

FIGS. 2A-2K: The plots displaying binding kinetics of isolated bispecific EGFRxNRP1
25 bispecific antibodies to a recombinant human EGFR (huEGFR). The EGFRxNRP1 antibodies tested for a binding affinity assay herein are as follows: each EGFRxNRP1 bispecific antibody consist of a heavy chain fusion polypeptide and a light chain polypeptide. Construct 1 (SEQ ID NOs: 1 and 12), construct 2 (SEQ ID NOs: 2 and 12), construct 3 (SEQ ID NOs: 3 and 12), construct 4 (SEQ ID NOs: 4 and 12), construct 5 (SEQ ID NOs: 5 and 12), construct 6 (SEQ ID
30 NOs: 6 and 12), construct 7 (SEQ ID NOs: 7 and 12), construct 8 (SEQ ID NOs: 8 and 12), construct 9 (SEQ ID NOs: 9 and 12), construct 10 (SEQ ID NOs: 10 and 12), construct 11 (SEQ

ID NOs: 11 and 12), respectively. Binding affinity to huEGFR was quantitated by Octet Red 96 System (Fortebio). Each line of sensorgram on the graph represents binding kinetics at a specific concentration (going left to right 10, 5, 2.5 nM).

FIGS. 3A-3K: The plots displaying binding kinetics of isolated bispecific EGFRxNRP1 antibodies to a recombinant human NRP1 (huNRP1). The EGFRxNRP1 bispecific antibody constructs tested for a binding affinity assay herein are as follows: each EGFRxNRP1 bispecific antibody consist of a heavy chain fusion polypeptide and a light chain polypeptide. Construct 1 (SEQ ID NOs: 1 and 12), construct 2 (SEQ ID NOs: 2 and 12), construct 3 (SEQ ID NOs: 3 and 12), construct 4 (SEQ ID NOs: 4 and 12), construct 5 (SEQ ID NOs: 5 and 12), construct 6 (SEQ ID NOs: 6 and 12), construct 7 (SEQ ID NOs: 7 and 12), construct 8 (SEQ ID NOs: 8 and 12), construct 9 (SEQ ID NOs: 9 and 12), construct 10 (SEQ ID NOs: 10 and 12), construct 11 (SEQ ID NOs: 11 and 12), respectively. Binding affinity to huNRP1 was quantitated by Octet Red 96 System (Fortebio). Each line of sensorgram on the graph represents binding kinetics at a specific concentration (going left to right 10, 5, 2.5 nM).

FIG. 4: The effect of the EGFRxNRP1 bispecific antibody construct 1 on VEGF-mediated VEGFR2 phosphorylation. The expression levels of total VEGFR and p-VEGFR2 by EGFRxNRP1 bispecific antibody construct 1 (SEQ ID NOs: 1 and 12) was determined. HUVEC cells were preincubated in the presence or absence of construct 1 (1 μ M) for 30 min and treated with VEGF165 (2.2 ng/ml) for an additional 10 min to induce VEGFR2 activation. VEGFR2 signaling activation was detected by western blotting of whole cell lysate using anti-phospho-VEGFR2 (Y1175). Relative p-VEGFR2 expression was quantified by normalizing with total VEGFR2 using Image J software densitometry analysis. The numbers shown below pVEGFR2 blots were the to normalize quantity of pVEGFR2 relative to total VEGFR2.

FIGS. 5A-5B: The effect of the EGFRxNRP1 bispecific antibody construct 2 on VEGF-mediated VEGFR2 phosphorylation. The expression levels of total VEGFR and p-VEGFR2 by EGFRxNRP1 bispecific antibody construct 2 (SEQ ID NOs: 2 and 12) was determined by Western blot using anti-phospho-VEGFR2 (Y1175) (FIG. 5A). HUVEC cells were preincubated with construct 2 (right to left, 6-fold serially diluted concentration from 1 μ M) for 30 min and treated with VEGF165 (2.2ng/ml) for an additional 10 min to induce VEGFR2 activation. (**FIG. 5A**). Inhibition of VEGFR2 phosphorylation by Construct 2 was calculated as % P-VEGFR2 relative to control using Prism9 (**FIG. 5B**). (n=2)

FIGS. 6A-6B: The effect of the EGFRxNRP1 bispecific antibody Construct 3 on VEGF-mediated VEGFR2 phosphorylation. The expression levels of total VEGFR and p-VEGFR2 by EGFRxNRP1 bispecific antibody construct 3 (SEQ ID NOs: 3 and 12) (**FIG. 6A**). Inhibition of VEGFR2 phosphorylation by construct 3 was calculated as % P-VEGFR2 relative to control using Prism9 (**FIG. 6B**). (n=2) Experimental methods and materials are same as described in **FIGS. 5A** and **5B**.

FIGS. 7A-7B: The effect of the EGFRxNRP1 bispecific antibody construct 4 on VEGF-mediated VEGFR2 phosphorylation. The expression levels of total VEGFR and p-VEGFR2 by EGFRxNRP1 bispecific antibody construct 4 (SEQ ID NOs: 4 and 12) (**FIG. 7A**). Inhibition of VEGFR2 phosphorylation by EGFRxNRP1 bispecific antibody construct 4 was calculated as % P-VEGFR2 relative to control using Prism9 (**FIG. 7B**). (n=2)

FIGS. 8A-8B: The effect of the EGFRxNRP1 bispecific antibody Construct 5 on VEGF-mediated VEGFR2 phosphorylation. The expression levels of total VEGFR and p-VEGFR2 by EGFRxNRP1 bispecific antibody construct 5 with the heavy chain fusion polypeptide (SEQ ID NOs: 5 and 12) (**FIG. 8A**). Inhibition of VEGFR2 phosphorylation by EGFRxNRP1 bispecific antibody construct 5 was calculated as % P-VEGFR2 relative to control using Prism9 (**FIG. 8B**). (n=2)

FIGS. 9A-9B: The effect of the EGFRxNRP1 bispecific antibody Construct 6 on VEGF-mediated VEGFR2 phosphorylation. The expression levels of total VEGFR and p-VEGFR2 by EGFRxNRP1 bispecific antibody Construct 6 (SEQ ID NOs: 6 and 12) (**FIG. 9A**). Inhibition of VEGFR2 phosphorylation by EGFRxNRP1 bispecific antibody construct 6 was calculated as % P-VEGFR2 relative to control using Prism9 (**FIG. 9B**). (n=2)

FIGS. 10A-10B: The effect of the EGFRxNRP1 bispecific antibody Construct 7 on VEGF-mediated VEGFR2 phosphorylation. The expression levels of total VEGFR and p-VEGFR2 by EGFRxNRP1 bispecific antibody construct 7 (SEQ ID NOs: 7 and 12) (**FIG. 10A**). Inhibition of VEGFR2 phosphorylation by EGFRxNRP1 bispecific antibody construct 7 was calculated as % P-VEGFR2 relative to control using Prism9 (**FIG. 10B**). (n=2)

FIGS. 11A-11B: The effect of the EGFRxNRP1 bispecific antibody Construct 11 on VEGF-mediated VEGFR2 phosphorylation. The expression levels of total VEGFR and p-VEGFR2 by EGFRxNRP1 bispecific antibody construct 11 (SEQ ID NOs: 11 and 12) (**FIG. 11A**). Inhibition of VEGFR2 phosphorylation by EGFRxNRP1 bispecific antibody construct 11

was calculated as % P-VEGFR2 relative to control using Prism9 (**FIG. 11B**). (n=2).

FIGS. 12A-12B: Effect of the EGFRxNRP1 bispecific antibody on growth rate of H1975 cells. Cells were incubated with EGFRxNRP1 bispecific antibodies at various concentrations for 72 hours and cell growth was evaluated and expressed as (%) growth rate to control. Construct 1 (SEQ ID NOs: 1 and 12) (**FIG. 12A**); and construct 3 (SEQ ID NOs: 3 and 12), construct 7, (SEQ ID NOs: 7 and 12) construct 9 (SEQ ID NOs: 9 and 12), and construct 11 (SEQ ID NOs: 11 and 12) (**FIG. 12B**).

FIGS. 13A-13F: Anti-tumor activity of EGFRxNRP1 bispecific antibodies in a H1975 xenograft mouse model. Mice were treated with various EGFRxNRP1 bispecific antibody constructs, panitumumab, or vehicle (control) with various doses. Construct 1 (SEQ ID NOs: 1 and 12) at 10 mg/kg, i.p., BIW (**FIG. 13A**); construct 1 (SEQ ID NOs: 1 and 12) at 5 mg/kg (**FIG. 13B**); SEQ ID NO: 2 (construct 2) at 6.825 mg/kg (**FIG. 13C**); construct 3 (SEQ ID NOs: 3 and 12) at 5 mg/kg (**FIG. 13D**); construct 7 (SEQ ID NOs: 7 and 12) at 6.85 mg/kg (**FIG. 13E**); and construct 7, construct 9 (SEQ IDs: 9 and 11), and construct 11 (SEQ ID NOs: 11 and 12), respectively at 6.87 mg/kg (**FIG. 13F**) or PBS as a negative control was administered to mice via an intraperitoneal route (i.p.). EGFRxNRP1 bispecific antibody construct 3, 7, 9, and 12 inhibited tumor growth more effectively than construct 1, which has the NRP1 binding domain in CH3 but does not have the scFv.

FIG. 14: EGFRxNRP1 bispecific antibody construct 11 induced strong degradation of EGFR^{T790M/L858R} and NRP1. H1975 cells were incubated with panitumumab, anti-NRP1 mAb, anti-NRP1 mAb plus panitumumab (Pnm), or construct 11 and the isolated whole cell lysate was probed for western blotting to detect EGFR and NRP1 using monoclonal anti-EGFR antibody and anti-NRP1 antibody, respectively. Non-specific protein Actin was used as loading control.

FIG. 15: EGFRxNRP1 bispecific antibody construct 11 induces degradation of EGFR and NRP1 through lysosomal degradation pathway. EGFR and NRP1 degradation by construct 11 is restored by co-treatment with lysosomal protein degradation inhibitor, bafilomycin A1, but not with a proteasome inhibitor, MG132.

FIG. 16: A schematic of the proposed mechanism of EGFRxNRP1 bispecific antibody-mediated degradation of EGFR.

FIG. 17: EGFRxNRP1 bispecific antibody construct 11 (SEQ ID NOs: 11 and 12)-mediated degradation of EGFR^{T790M/L858R} in H1975 cells. H1975 cells treated with construct 11,

panitumumab, or amivantamab at the concentrations between 0.77 nM and 1 μ M (right to left, 6-fold serial dilution of 1 μ M) for 16 hours. Whole cell lysate was used for western blotting to detect EGFR and actin. Actin was used for loading control. Construct 11 treatment induced strong degradation of EGFR^{T790M/L858R} even at the concentration of 0.77 nM in H1975 cells.

FIGS. 18A-18C: Anti-tumor activity of EGFRxNRP1 bispecific antibody construct 11 (SEQ ID NOs: 11 and 12) in various osimertinib xenograft mouse models. Inhibition of tumor growth by construct 1 in osimertinib-sensitive H1975 (**FIG. 18A**), osimertinib-resistant H1975-OR (**FIG. 18B**), and osimertinib-refractory H1975-HGF (**FIG. 18C**) xenograft mouse model was evaluated. Xenograft mice were treated with bs construct 11, osimertinib, panitumumab, amvantamab, or IgG1 isotype control and tumor volume (mm^3) was quantitated at the indicated days post implantation.

FIG. 19A is a graph demonstrating degradation of integrin α V β 3 and NRP1 following treatment with a Int- α V β x NRP1 bispecific antibody construct, as compared to an Int- α V β anti-monoclonal antibody. **FIG. 19B** is a graph demonstrating degradation of integrin α V β 3 and NRP1 following treatment with a Int- α V β 3 x NRP1 bispecific antibody construct, as compared to an Int- α V β 3 anti- monoclonal antibody.

FIGS. 20A-20B: demonstrate that the PD-L1 x NRP1 bispecific antibody induces strong degradation of PD-L1 and NRP1 in a dose-dependent manner. Results shown are Western blots of kidney cancer Renca cell whole cell lysates probed using monoclonal anti-PD-L1 antibody and anti-NRP1 antibody to detect PD-L1 and NRP1, respectively. **FIG. 20A** shows results for Renca cells treated with the indicated concentration of PD-L1 monoclonal antibody. **FIG. 20B** shows results for Renca cells treated with the indicated concentration of PD-L1 x NRP1 bispecific antibody. Non-specific protein Actin was used as loading control.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

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. Accordingly, the following terms are intended to have the following meanings:

The singular form “a”, “an” and “the” includes plural references unless the context

clearly dictates otherwise.

The term “human EGFR” or “EGFR”, as used herein, refers to human epidermal growth factor receptor protein (UniProKB/Swiss-Pro No. P00533) and includes any variants, isoforms and species homologs of EGFR that are naturally expressed by cells, including tumor cells, or are expressed on cells transfected with the EGFR gene or cDNA.

The term “human NRP1” or “NRP1”, as used herein, refers to a human neuropilin-1 protein (UniProKB/Swiss-Pro No. O14786) and includes any variants, isoforms and species homologs of NRP1 that are naturally expressed by cells, including tumor cells, or are expressed on cells transfected with the NRP1 gene or cDNA.

As used herein, the terms “receptors tyrosine kinase” or “Receptor Tyrosine Kinase” or “RTK” refers to proteins that are receptors (i.e., bind a ligand) and that phosphorylate a tyrosine residue(s).

As used herein the terms “non-receptors tyrosine kinase” or “Non-Receptor Tyrosine Kinase” or “non-RTK” refers to proteins that are not RTKs, i.e., proteins that are not receptors and/or do not phosphorylate a tyrosine residue(s).

As used herein, the term “administering or administration” of the disclosed bispecific binding molecule or polypeptide thereof encompasses the delivery to a subject of a polypeptide or composition of the present invention, as described herein, or a prodrug or other pharmaceutically acceptable derivative thereof, using any suitable formulation or route of administration, e.g., as described herein.

The term “and/or,” when used in a list of two or more items, means that any one of the listed items can be employed by itself, or any combination of two or more of the listed items can be employed.

As used herein, “treatment”, “treat”, or “treating”, is used in reference to a disease or condition means that at least an amelioration of the symptoms associated with the condition afflicting a subject is achieved, where amelioration is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, e.g., a symptom, associated with the condition being treated. The term “treatment” or “treating” refers to an approach for obtaining a therapeutic benefit. A therapeutic benefit is determined by whether the tumor shrinks, stays the same size, or an increase in progression free survival time compared to placebo. Thus, treatment includes prevention (i.e., reducing the risk of development of clinical symptoms, including causing the

clinical symptoms not to develop, e.g., preventing disease progression) and inhibition (i.e., arresting the development or further development of clinical symptoms, e.g., mitigating or completely inhibiting an active disease).

5 A “subject,” as used herein, can refer to any animal with a cancer, e.g., a mammal, such as an experimental animal, a farm animal, pet, or the like. In some embodiments, the animal is a primate, preferably a human. As used herein, the terms “subject” and “subject” are used interchangeably. The terms “subject” and “subject” refer to an animal (e.g., a bird such as a chicken, quail or turkey, or a mammal), specifically a “mammal” including a non-primate (e.g., a cow, pig, horse, sheep, rabbit, guinea pig, rat, cat, dog, and mouse) and a primate (e.g., a
10 monkey, chimpanzee, and a human), and more specifically a human. In one embodiment, the subject is a non-human animal such as a farm animal (e.g., a horse, cow, pig or sheep), or a pet (e.g., a dog, cat, guinea pig or rabbit). In a preferred embodiment, the subject is a “human”.

As used herein, the term “fusion” refers to unifying two molecules having the same or different function or structure, and the methods of fusing may include any physical, chemical, or
15 biological method capable of binding the peptide to the protein, the small-molecule drug, the nanoparticle, or the liposome. Preferably, the fusion may be mediated by a linker peptide, and for example, the linker peptide may be fused to the C-terminus of a fragment of an antibody light-chain variable region (Fc). Alternatively, two molecules are fused by the integration of multiple domains within the polypeptide sequence.

20 The term “linker” or “flexible linker” as used herein is a molecule or peptide that links two polypeptide subunits together. A linker peptide sequence may include the amino acid sequence subunit (GGGGS)_n, wherein n defines the number of subunit repeats. The number of subunit repeats defines linker peptide flexibility. A flexible peptide linker allows more flexibility between two binding domains.

25 As used herein, an “effective amount” refers to an amount sufficient to elicit the desired anti-cancer response. In the present invention, the desired biological response is to inhibit cell proliferation. The precise amount of bispecific binding molecule administered to a subject will depend on the mode of administration, the type and severity of the cancer and on the characteristics of the subject, such as general health, age, sex, body weight and tolerance to
30 drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. When co-administered with other anti-cancer agents, e.g., when co-administered

with a chemotherapy, an “effective amount” of the second agent will depend on the type of drug used. Suitable dosages are known for approved agents and can be adjusted by the skilled artisan according to the condition of the subject, the type of cancer being treated, and the amount of a polypeptide herein administered. In cases where no amount is expressly noted, an effective
5 amount should be assumed. For example, bispecific antibodies disclosed herein can be administered to a subject in a dosage range between approximately 0.01 to 100 mg/kg body weight/day at weekly or biweekly intervals.

The terms “polypeptide,” “peptide” and “protein” are used interchangeably herein to refer to a polymer of amino acid residues.

10 The term “variant” as used herein describes a sequence with changes from the wildtype, conventional, or primary sequence. The changes may take the form of deletions, substitutions, or insertions of amino acids or nucleotides. The variant may contain one or more, including a combination of sequence changes.

The term “reduce” or other forms of the word, such as “reducing” or “reduction,”
15 generally refers to the lowering of an event or characteristic (e.g., one or more symptoms, or the binding of one protein to another). It is understood that this is typically in relation to some standard or expected value, in other words it is relative, but that it is not always necessary for the standard or relative value to be referred to.

The term “affinity” as used in the context of “binding affinity” refers to a decrease in the
20 affinity of one molecule to another molecule. For example, in some embodiments, a protein, domain, or motif can specifically bind to a particular target, e.g., a peptide, polypeptide, protein, carbohydrate, saccharide, polysaccharide, glycosaminoglycan, or any epitope thereof, with a given affinity. The term “affinity” refers to the strength of sum total of non-covalent interactions between a single binding domain of a molecule and its binding target or partner (e.g., an
25 antigen). The affinity of a molecule for its target can be represented by the dissociation constant (K_D), which is the ratio of dissociation and association rate constants (k_{off} and k_{on} , respectively). The strength, or affinity of binding interactions can be expressed in terms of the dissociation constant (K_D) of the interaction, wherein a smaller K_D represents a greater affinity. The binding properties (affinity) of selected polypeptides can be quantified using methods well
30 known in the art. One such method entails measuring the rates of antigen-binding domain/antigen complex formation and dissociation, wherein those rates depend on the

concentrations of the complex partners, the affinity of the interaction, and geometric parameters that equally influence the rate in both directions. Thus, both the “on rate constant” (K_{on}) and the “off rate constant” (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation, (See Nature 361:186-87 (1993)).

5 The ratio of K_{off}/K_{on} enables the cancellation of all parameters not related to affinity and is equal to the dissociation constant K_D . (See, generally, Davies et al. (1990) Annual Rev Biochem 59:439-473). In some embodiments, a recombinant polypeptide of the present invention can specifically bind to an epitope when the equilibrium binding constant (K_D) is ≤ 1 μ M. In some embodiments, a recombinant polypeptide of the present invention can specifically
10 bind to an epitope when the equilibrium binding constant (K_D) is ≤ 100 nM. In some embodiments, a recombinant polypeptide of the present invention can specifically bind to an epitope when the equilibrium binding constant (K_D) is ≤ 10 nM. In some embodiments, a recombinant polypeptide of the present invention can specifically bind to an epitope when the equilibrium binding constant (K_D) is ≤ 100 pM to about 1 pM, as measured by assays such as
15 Surface Plasmon Resonance (SPR), Octet assays, or similar assays known to those skilled in the art. In some embodiments, a K_D can be 10^{-5} M or less (e.g., 10^{-6} M or less, 10^{-7} M or less, 10^{-8} M or less, 10^{-8} M or less, 10^{-10} M or less, 10^{-11} M or less, 10^{-12} M or less, 10^{-13} M or less, 10^{-14} M or less, 10^{-15} M or less, or 10^{-16} M or less).

20 Thus, equivalent affinities may comprise different rate constants, as long as the ratio of the rate constants remains the same. Thus, in some embodiments, “reduced binding” refers to a decrease in affinity for the respective interaction. Conversely, “increased binding” refers to an increase in binding affinity for the respective interaction.

As used herein, the term “isotype” refers to the immunoglobulin class (for instance IgG1, IgG2, IgG3, IgG4, IgD, IgA, IgE, or IgM) that is encoded by heavy chain constant region genes.

25 The term “bispecific binding molecule” in the context of the present invention refers to an antibody having two different antigen binding regions defined by different antibody sequences.

A “EGFRxNRP1 bispecific antibody” or “anti-EGFRxNRP1 bispecific antibody” is a bispecific binding molecule, which comprises two different antigen binding domains, one of
30 which binds specifically to the antigen EGFR1 and one of which binds specifically to NRP1.

Similar nomenclature is used throughout for other bispecific binding molecules that bind targets other than EGFR, such as “Integrin x NRP1 bispecific antibody” or “GPCR x NRP1 bispecific antibody” to describe a bispecific binding molecule comprising one antigen binding domain that binds specifically to an integrin or a GPCR, respectively, and the other antigen binding domain that binds specifically to NRP1.

The term “heavy chain” as used herein may be interpreted to include a full-length heavy chain including heavy chain variable region domain (VH), which includes an amino acid sequence having a variable region sequence sufficient to confer antigen-specificity, and three heavy chain constant region domains CH1, CH2 and CH3, or a fragment thereof. Also, the term “light chain” as used herein may be interpreted to include a full-length light chain including a light chain variable region domain (VL), which includes an amino acid sequence having a variable region sequence sufficient to confer antigen-specificity and a light chain constant region domain (CL), a fragment thereof. The term “Fab” as used herein refers to the region that binds the antigen. The Fab consists of one variable heavy and light chain and one constant heavy and light chain.

As used herein, the term “percent identity” between two sequences (e.g., amino acid or nucleotide sequences) refers to the percentage of positions (out of a possible 100%) that when optimally aligned and compared, are identical (with appropriate insertions or deletions for optimal alignment). The percent identity between two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions x 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using mathematical algorithm, as described in the non-limiting examples below. Methods and algorithms for determining the % homology between two protein sequences are well established in the art.

For example, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch ((1970) *J. Mol. Biol.* (48):444-453) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. Furthermore, a protein amino

acid sequence can be used as a “query sequence” to perform a search against public databases to, for example, identify related sequences. Such searches can be performed using the XBLAST programs (version 2.0) of Altschul, et al. (1990) *J. Mol. Biol.* 215:403-10. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to the protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used.

The term “monoclonal antibody” as used herein refers to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope. Accordingly, the term “human monoclonal antibody” refers to antibodies displaying a single binding specificity which have variable and constant regions derived from human germline immunoglobulin sequence.

The term “recombinant host cell” (or simply “host cell”), as used herein, is intended to refer to a cell into which an expression vector has been introduced, *e. g.*, an expression vector encoding an antibody of the invention. Recombinant host cells include, for example, transfectomas, such as CHO, CHO-S, HEK, HEK293, HEK-293F, Expi293F, PER.C6 or NSO cells, and lymphocytic cells.

The term “treatment” refers to the administration of an effective amount of a therapeutically active bispecific binding molecule of the present invention with the purpose of easing, ameliorating, arresting or eradicating (curing) symptoms or disease states.

The term “effective amount” or “therapeutically effective amount” refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result. A therapeutically effective amount of a bispecific binding molecule may vary according to factors such as the disease state, age, sex, and weight of the subject, and the ability of the bispecific binding molecule to elicit a desired response in the subject. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects.

As used herein, the terms “in combination” or “co-administration” can be used interchangeably to refer to the use of more than one therapy (*e.g.*, one or more prophylactic

and/or therapeutic agents). The use of the terms does not restrict the order in which therapies (e.g., prophylactic and/or therapeutic agents) are administered to a subject.

As used herein, the term “synergistic” refers to a combination of a polypeptide of the invention and another therapy (e.g., a prophylactic or therapeutic agent), which is more effective
5 than the additive effects of the therapies.

The term “pharmaceutically acceptable salts” is meant to include salts of the active bispecific antibodies that are prepared with relatively nontoxic acids or bases, depending on the particular substituent found on the bispecific antibodies described herein.

The term “parenteral” as used herein includes, but is not limited to, subcutaneous,
10 intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

The term “carrier” refers to the vehicle used in the formulation of a composition and can be composed of multiple excipients.

The term “excipient” as used herein refers to any pharmacologically inactive, natural, or
15 synthetic, component or substance that is formulated alongside (e.g., concomitantly), or subsequently to, the active ingredient of the present invention. In some embodiments, an excipient can be any additive, adjuvant, binder, bulking agent, carrier, coating, diluent, disintegrant, filler, glidant, lubricant, preservative, vehicle, or combination thereof, with which a recombinant polypeptide of the present invention can be administered, and or which is useful in
20 preparing a composition of the present invention. Excipients, include any such materials known in the art that are nontoxic and do not interact with other components of a composition. In some embodiments, excipients can be formulated alongside a recombinant polypeptide when preparing a composition for the purpose of bulking up compositions (thus often referred to as bulking agents, fillers, or diluents). In other embodiments, an excipient can be used to confer an
25 enhancement on the active ingredient in the final dosage form, such as facilitating absorption and/or solubility. In yet other embodiments, an excipient can be used to provide stability, or prevent contamination (e.g., microbial contamination). In other embodiments, an excipient can be used to confer a physical property to a composition (e.g., a composition that is a dry granular, or dry flowable powder physical form). Reference to an excipient includes both one and more
30 than one such excipients. Suitable pharmaceutical excipients are described in Remington's Pharmaceutical Sciences, by E.W. Martin, the disclosure of which is incorporated herein by

reference in its entirety.

Throughout this specification, unless the context requires otherwise, the word “comprise,” or variations such as “comprises” or “comprising,” will be understood to imply the inclusion of a stated step, element, or integer, or a group of steps, elements, or integers but not the exclusion of any other step, element, or integer or group of elements, steps, or integers.

All patent applications, patents, and printed publications referred to herein are incorporated by reference in their entirety to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety. And, all patent applications, patents, and printed publications cited herein are incorporated herein by reference in their entireties, except for any definitions, subject matter disclaimers, or disavowals, and except to the extent that the incorporated material is inconsistent with the express disclosure herein, in which case the language in this disclosure controls.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims. It is further to be understood that all values are approximate and are provided for description.

Bispecific Antibodies with an EGFR binding domain and a NRP1 binding domain (EGFRxNRP Ab)

As described above, the invention relates to a bispecific binding molecule that specifically binds to a target protein and a neuropilin-1 (NRP1).

Bispecific antibodies have many advantages over monoclonal antibodies. First, a bispecific binding molecule is more efficient to manufacture, since it is one molecule with two efficacious targets. For example, a bispecific binding molecule can target multiple immune cell receptors (CD3, CD16, or CD47) or immune checkpoint proteins (e.g., PD-L1, PD1, LAG-3, or CTLA-4) or both. For example, bispecific antibodies can target a tumor associated essential receptor, such as EGFR, and an immune cell receptor or immune checkpoint regulator, such as neuropilin 1 (NRP1). Bispecific antibodies for anticancer therapy are designed to increase

anticancer potency.

EGFR binding domain

The epidermal growth factor receptor (EGFR) is one of the most frequently altered oncogenes in solid tumors. Increased EGFR signaling drives proliferation and cell survival in many cancer types, including breast, prostate, non-small cell lung cancer (NSCLC), esophagogastric, liver, glioblastoma, cervix, ovary, bladder, kidney, pancreas, colon, and rectum. Increased EGFR signaling can occur from EGFR overexpression, mutations in EGFR or transduction factors within the EGFR signaling pathway resulting in constitutive activation, and/or increased levels of EGFR cognate ligands, such as EGF, tumor necrosis factor- α (TGF- α), amphiregulin (AREG), epigen, β -cellulin, heparin-binding EGF (HB-EGF), and epiregulin. EGFR signaling activates downstream signaling cascades including RAS–RAF–MEK–ERK and PI3K–Akt–mTOR axes that lead to proliferation and cancer cell survival. Unfortunately, anti-EGFR agents, including tyrosine kinase inhibitors, monoclonal antibodies, and radiotherapy, are only effective in a few cancer types, such as metastatic colorectal cancer, non-small cell lung cancer (NSCLC), and advanced head and neck cancers. Moreover, treatment only improves survival in some subjects and the initial response usually ends with drug resistance. Thus, new rational designs are necessary to improve therapeutic efficacy.

Embodiments of the present disclosure further provides a method of treating cancer in a subject, comprising administering to the subject in need a therapeutically effective amount of the bispecific binding molecule. In some embodiments, the present disclosure provides for the use of the disclosed bispecific binding molecule in the manufacture of a medicament for treating cancer.

In certain embodiments of the bispecific binding molecule, the present disclosure provides a method of treating EGFR-overexpressing cancer in a subject in need comprising administering a therapeutically effective amount of a bispecific binding molecule and/or a pharmaceutically acceptable carrier or diluent provided herein. In certain embodiments, the EGFR-overexpressing cancer is non-small cell lung cancer (NSCLC), prostate cancer, breast cancer, colorectal cancer, squamous cell carcinoma of head and neck cancer, gastric junction adenocarcinoma, gastroesophageal junction adenocarcinoma, liver cancer, glioblastoma, cervical cancer, ovarian cancer, bladder cancer, kidney cancer and pancreatic cancer or any other solid tumor tissue that overexpresses of the EGFR or EGFR kinase domain mutations. In some

embodiments of the method treating, the method further comprises administering to the subject an agent that increases cellular EGFR expression.

In certain embodiments of the method of treating, the EGFR-overexpressing cancer is resistant to treatment with anti-EGFR monoclonal antibody. In certain embodiments of the method of treating, the anti-EGFR monoclonal antibody is amivantamab, cetuximab, 5 depatuxizumab, depatuxizumab mafodotin, duligotuzumab, futuximab, GC1118, Imgatuzumab, matuzumab, necitumumab, nimotuzumab, panitumumab, zalutumumab, or HumMR1. In some embodiments of the method treating, the subject is a human. In some embodiments, the EGFR-overexpressing is resistant or refractory to EGFR tyrosine kinase inhibitors. In some 10 embodiments, the EGFR-overexpressing cancer is refractory to osimertinib.

An antibody is a protein that binds to an antigen with high specificity and high affinity, and can neutralize the antigen activity. Anti-EGFR antibodies block ligand activated EGFR signaling and induce receptor endocytosis, leading to EGFR degradation in proteasomes. Subjects can acquire anti-EGFR antibody resistance during the course of treatment when 15 mutations occur at the antibody's EGFR binding domain. Cetuximab, a chimeric mouse/human monoclonal, and panitumumab, a fully humanized monoclonal antibody, have different binding domains on EGFR, and therefore panitumumab is still effective after resistance to cetuximab develops, and vice versa. Thus, subjects who acquire resistance to one anti-EGFR antibody can be administered another anti-EGFR antibody that targets a different EGFR binding domain.

20 Panitumumab is an IgG2 anti-EGFR humanized monoclonal antibody that binds EGFR with an approximately 8-fold greater affinity than cetuximab, an IgG1 anti-EGFR chimeric human/mouse monoclonal antibody (Garcia-Foncillas et al. 2019). Before inducing endocytosis, antibody binding can induce an immune response. Panitumumab binding induces antibody-dependent cell-mediated cytotoxicity (ADCC) and initiates antibody-dependent cellular 25 phagocytosis (ADCP) through activation of neutrophils and monocytes (Schneider-Merk et al. 2010). The IgG1 Fc domain of cetuximab binds to the FcγRIIIA (CD16) receptor on natural killer (NK) cells to induce ADCC. Activated NK cells secrete perforins and granzymes resulting in lysis of the cancer cell and release immunostimulatory molecules, such as interferon-γ (IFN-γ), TNF-α, chemokines, and granulocyte macrophage colony-stimulating factor (GM-CSF). The 30 secretion of cytokines by NK cells stimulates dendritic cells maturation, NK cell cross-talk, and coexpression of CD137. CD137 expression recruits anti-EGFR CD8⁺ T cells leading to

increased killing of EGFR expressing cancer cells. Mature dendritic cells further activate NK cells and present tumor antigen to cytotoxic CD8⁺ T cells. The IgG1 Fc region also binds to Fc receptors on macrophage or plasmacytoid dendritic effector cells or to the first subunit of C1 complement complex (C1q) to initiate antibody-dependent cellular phagocytosis (ADCP) by
5 cells or complement-dependent cytotoxicity (CDC), respectively. Like cetuximab, the anti-EGFR antibodies cetuximab, necitumumab, and nimotuzumab also have an IgG1 Fc region for ADCC induction.

NRP1 binding domain

Cancer cells overexpress pro-angiogenic factors that promote the rapid growth of new
10 blood vessels. The blood vessels surrounding the tumor are abnormal, with capillary constriction that reduces overall blood flow to the tumor. A reduced blood flow rate increases the tumor interstitial fluid pressure and decreases drug flow from blood vessels to the tumor (Milosevic et al., 1999). The paucity of lymphatic vessels in tumor tissue, unlike normal tissue, also contributes to abnormal angiogenesis and high tumor interstitial pressure. The inhibition of angiogenesis by
15 targeting the vascular endothelial cell growth factor-A (VEGF₁₆₅) could normalize blood vessel formation, blood vessel fluid pressure, and increase therapeutic drug accumulation at the tumor site (Marcucci et al. 2013). However, anti-VEGF antibodies, such as bevacizumab, can have adverse side effects and are only effective in a narrow range of exposure (Kamba and McDonald, 2007).

20 Neuropilin-1 (NRP1) and neuropilin-2 (NRP2) receptors are multifunctional single pass transmembrane glycoproteins with important roles in angiogenesis and lymphangiogenesis, respectively. The C-terminal region of each of the VEGF ligand family and Sema3 ligands, which bind to NRP1 and NRP2, binds to the arginine-binding pocket in the b1 domain of NRP1 and NRP2 (Parker et al., 2012). Binding to the arginine-binding pocket occurs by a motif of R/K-
25 x-x-R/K (R = arginine, K = lysine, and x = any amino acids), which is present commonly in the C-terminal region of NRP binding ligands and is known as the "C-end rule" (CendR) (Teesalu et al. 2009). A protein or peptide containing a C-end rule sequence is capable of binding to NRP by the C-terminal arginine (Arg) or lysine (Lys) residue (Zanuy et al, 2013).

Selective targeting of NRP1 is critical for anti-EGFR cancer therapy because silencing
30 NRP2 significantly increases EGFR expression in lung and gastric cancer cells (Rizzolio et al.,

2017). Moreover, NRP1 is overexpressed in many cancer cells, including colon carcinoma, melanoma, astrocytoma, lung, prostate, and pancreatic ductal adenocarcinoma, and plays a critical role in cancer progression (Graziani and Lacal, 2015). In addition to NRP1 being overexpressed in a variety of cancers, NRP1 is also overexpressed in tumor-associated endothelial cells. NRP1 functions as a co-receptor for ligands involved in angiogenesis, such as vascular endothelial growth factor (VEGF₁₆₅), class 3 semaphorin ligands, integrin β 1, TGF- β , HGF, FGF, PDGF, and galectin-1. NRP1 interacts with receptor tyrosine kinases (RTKs) such as VEGFR1 and VEGFR2 and thereby contributes to VEGFR signal transduction leading to increased angiogenesis. NRP1 also binds the secreted class-3 semaphorin ligands (Sema3A, Sema3B, Sema3C, Sema3D, Sema3E, Sema3F, Sema3G), to function as a co-receptor to the plexin family receptors, which also regulate angiogenesis.

Blocking NRP1 ligand binding with the anti-NRP1-specific binding domain reduces the expression of endothelial adhesion molecule VE-cadherin, resulting in increased extravasation of an anti-EGFR antibody from blood vessels. Increased extravasation also reduces tumor interstitial pressure allowing drug to flow more freely from blood vessels to the tumor environment.

The epithelial barrier around solid tumors consists of intercellular space densely filled with interstitial epithelial cells connected by intercellular adhesion factors and prevents a therapeutic agent from penetrating the tumor. E-cadherin overexpression contributes to intercellular adhesion. Since a substance that reduces E-cadherin was found in a virus (adenovirus-3), a case has been reported in which only a portion (JO-1) having an activity of reducing cellular E-cadherin in tight junctions, among proteins constituting the virus, was co-administered with an antibody, thereby increasing the anti-cancer effect of the antibody (Beyer et al. 2011). Targeting NRP1 reduces the expression of the epithelial barrier adhesion molecule E-cadherin and the integrin β 1 subunit, which are overexpressed in many solid tumors and increases extracellular matrix connectivity, resulting in decreased drug penetration. Moreover, the integrin β 1 subunit is involved in activating growth factor receptor mediated cell proliferation.

To summarize, targeting NRP1 can reduce VEGF₁₆₅ binding, and VE-cadherin, E-cadherin, and integrin β 1 expression, which altogether serves to reduce angiogenesis, tumor interstitial pressure, and increase extravasation and tumor penetration of anti-EGFR antibodies.

Cancer cells produce immune checkpoint molecules that inhibit an immune response.

NRP1 is an immune checkpoint molecule, and its expression is increased in tumor associated endothelial cells and cancer cells. NRP1 expression induces immunosuppression by increasing Treg activity and decreasing tumor specific CD8⁺ T cell response (Chuckran et al. 2020). Thus, besides increasing drug extravasation and penetration, the NRP1 binding domain functions as an immune checkpoint inhibitor. In yet another aspect, the disclosure provides a bispecific binding molecule, which targets NRP1 to reduce cancer-mediated checkpoint molecule immunosuppression, permitting natural immunity at the tumor site, and increasing the likelihood of a tumor response.

The anti-NRP1 antibody MNRP1685A, also known as vesencumab, binds competitively with VEGF165 on NRP1, and functions to inhibit VEGF signaling through VEGFR2, thereby affecting angiogenesis, cell survival, migration, adhesion, and invasion (Pan Q et al. 2007). However, subjects treated with vesencumab in phase I trials for advanced solid tumors endured intolerable side effects, including gastrointestinal bleeding, fungemia, duodenal obstruction, thrombocytopenia, proteinuria, alopecia, dysphonia, fatigue, and nausea, which led to aborting further trials (Weekes et al., 2014, Patnaik et al., 2014).

NRP1 is active as a homodimer or heterodimer, and monomeric peptides, such as the cleaved penetrating peptide iRGD, have only a weak ability to regulate NRP1 biological activity (Sugahara et al. 2010). Accordingly, a peptide that selectively binds NRP1 as a homodimer to regulate the biological activity is preferred. Unfortunately, while the Fc heavy-chain fused NRP binding peptide A22p is presented as dual peptides (homodimer), A22p binds both NRP1 and NRP2 (Shin et al. 2014). Thus, identifying an effective homodimer and non-toxic NRP1 selective targeting molecule important.

The NRP1 binding domain comprises an antibody, or an NRP1-binding fragment thereof. For example, all or a portion of an NRP1 antibody known in the art or an anti-NRP1 antibody provided herein can be used. Non-limiting examples of anti-NRP1 mAb heavy chain polypeptide sequences are set forth in SEQ ID NOs: 41-47, which includes an N-terminal NRP1 binding domain. In some embodiments, the monoclonal antibody heavy chain polypeptide comprises the N-terminal NRP1 binding domain including a variable heavy chain (VH) and a constant heavy chain 1 (CH1), and Fc domain comprising a constant heavy chain 2 (CH2) and constant heavy chain 3 (CH3). In some embodiments, the monoclonal antibody comprises a light chain polypeptide sequence as set forth in any of SEQ ID NOs: 48-54. Thus, the heavy chains of SEQ

ID NOs: 41-47 can pair with the light chains of SEQ ID NOs: 48-54, respectively. The polynucleotide sequences that encode the heavy and light chain polypeptides are set forth in SEQ ID NOs: 55-61 and 62-68, respectively.

5 Bispecific antibodies with binding affinity to EGFR and NRP1

The present disclosure provides bispecific antibodies, comprising a heavy chain fusion polypeptide, wherein an N-terminal EGFR binding domain at an N-terminal end and NRP1 binding domain at a C-terminal end of the heavy chain polypeptide. The heavy chain fusion polypeptide of bispecific binding molecule comprises an EGFR binding region at the N-terminal
10 end, which includes a variable heavy chain (VH) and a constant heavy chain 1 (CH1), an Fc domain comprising a constant heavy chain 2 (CH2), constant heavy chain 3 (CH3), and a short chain variable fragment (scFv) comprising a NRP1 binding region that is fused to the C-terminal end of CH3. The scFv comprising the NRP1 binding domain consists of a variable heavy chain (VH) and a variable light chain (VL) fused by a flexible peptide linker.

15 A schematic diagram of a representative bispecific antibody structure of the disclosure is shown in **FIG. 1**.

Exemplary bsAb heavy chain polypeptide sequences are set forth in SEQ ID NO: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 39, and the polynucleotide sequences encoding the bispecific antibody's heavy chain antibody polypeptide sequence are set forth in SEQ ID NO: 14, 15, 16,
20 17, 18, 19, 20, 21, 22, 23, 24, and 40, respectively. In some aspects, the bispecific antibody further comprises a light chain polypeptide sequence comprising a variable light chain and a constant light chain, that pairs with the heavy chain polypeptide and is set forth in SEQ ID NO: 12. The polynucleotide sequence that encodes the light chain polypeptide of SEQ ID NO: 12 is set forth in SEQ ID NO: 25. In some aspects, the disclosure provides the polynucleotide
25 sequence used to encode the GGGGS subunit, and these sequences are set forth in SEQ ID NOS: 26-38. Table 1 lists the polypeptide sequences of the bispecific antibody, and Table 2 lists the polynucleotide sequence that encodes the polypeptides. Example 1 describes the method of bispecific antibody production.

In some aspects, the bispecific antibody comprises an anti-EGFR binding arm comprising
30 (or consisting of) a VH amino acid sequence as shown in SEQ ID NO: 69 and a VL amino acid sequence as shown in SEQ ID NO: 70. In some aspects, the bispecific antibody comprises an

anti-EGFR binding arm comprising heavy chain CDR1, CDR2 and CDR3 regions comprising (or consisting of) the amino acid sequences shown in SEQ ID NOs: 71, 72 and 73, respectively. In some aspects, the bispecific antibody comprises an anti-EGFR binding arm comprising a heavy chain CDR3 region comprising (or consisting of) the amino acid sequences shown in SEQ ID NO: 73. In some aspects, the bispecific antibody comprises an anti-EGFR binding arm comprising light chain CDR1, CDR2 and CDR3 regions comprising (or consisting of) the amino acid sequences shown in SEQ ID NOs: 74, 75 and 76, respectively. In some aspects, the bispecific antibody comprises an anti-EGFR binding arm comprising a light chain CDR3 region comprising (or consisting of) the amino acid sequences shown in SEQ ID NO: 76. In some embodiments, an anti-EGFR binding arm comprises (or consisting of) one or more sequences at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or 99.8% identical to any of the aforementioned VH, VL, HCDR or LCDR sequences.

In some aspects, the bispecific antibody comprises an anti-NRP1 binding arm comprising (or consisting of) a VH amino acid sequence as shown in SEQ ID NO: 77 and a VL amino acid sequence as shown in SEQ ID NO: 78. In some aspects, the bispecific antibody comprises an anti-NRP1 binding arm comprising heavy chain CDR1, CDR2 and CDR3 regions comprising (or consisting of) the amino acid sequences shown in SEQ ID NOs: 79, 80 and 81, respectively. In some aspects, the bispecific antibody comprises an anti-NRP1 binding arm comprising a heavy chain CDR3 region comprising (or consisting of) the amino acid sequences shown in SEQ ID NO: 81. In some aspects, the bispecific antibody comprises an anti-NRP1 binding arm comprising light chain CDR1, CDR2 and CDR3 regions comprising (or consisting of) the amino acid sequences shown in SEQ ID NOs: 82, 83 and 84, respectively. In some aspects, the bispecific antibody comprises an anti-NRP1 binding arm comprising a light chain CDR3 region comprising (or consisting of) the amino acid sequences shown in SEQ ID NO: 84. In some embodiments, an anti-NRP1 binding arm comprises (or consisting of) one or more sequences at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or 99.8% identical to any of the aforementioned VH, VL, HCDR or LCDR sequences.

Thus, in embodiments, the invention relates to a composition comprising a bispecific binding molecule comprising:

(a) two identical heavy chain polypeptides and a first heavy chain polypeptide is fused to a first scFv by a peptide linker, to create a first heavy fusion polypeptide, the second heavy

chain is fused to a second scFv by a peptide linker, to create a second heavy fusion polypeptide, wherein the first and second scFv are identical and bind to NRP1; and

- (b) two identical light chains comprising a first light chain and a second light chain, wherein the VL and VH of the heavy fusion and light chain polypeptides comprises the target protein binding domain that binds to the target protein and the scFv comprising the NRP1 binding domain that binds to the NRP1.

In some embodiments of the bispecific binding molecule, a heavy chain fusion polypeptide pairs with a light chain polypeptide. In some embodiments, the heavy chain polypeptides comprise (a) two identical heavy chain polypeptides and a first heavy chain polypeptide is fused to a first scFv by a peptide linker, to create a first heavy fusion polypeptide, the second heavy chain is fused to a second scFv by a peptide linker, to create a second heavy fusion polypeptide, wherein the first and second scFv are identical and bind to NRP1; and (b) two identical light chains comprising a first light chain and a second light chain, wherein the VL and VH of the heavy fusion and light chain polypeptides comprises the target protein binding domain that binds to the target protein and the scFv comprising the NRP1 binding domain that binds to the NRP1.

Hereby bispecific antibodies with varying binding affinities for EGFR and NRP1 are provided. In one embodiment it is preferred that the binding affinity for NRP1 is lower than it is for the EGFR. In some embodiments,

Thus, the invention relates to a comprising a bispecific binding molecule comprising:

- (a) two identical heavy chain polypeptides and a first heavy chain polypeptide is fused to a first scFv by a peptide linker, to create a first heavy fusion polypeptide, the second heavy chain is fused to a second scFv by a peptide linker, to create a second heavy fusion polypeptide, wherein the first and second scFv are identical and bind to NRP1; and

- (b) two identical light chains comprising a first light chain and a second light chain, wherein the VL and VH of the heavy fusion and light chain polypeptides comprises the target protein binding domain that binds to the target protein and the scFv comprising the NRP1 binding domain that binds to the NRP1.

In some embodiments of the bispecific binding molecule, a heavy chain fusion polypeptide pairs with a light chain polypeptide. In some embodiments, the heavy chain polypeptides comprise (a) two identical heavy chain polypeptides and a first heavy chain

polypeptide is fused to a first scFv by a peptide linker, to create a first heavy fusion polypeptide, the second heavy chain is fused to a second scFv by a peptide linker, to create a second heavy fusion polypeptide, wherein the first and second scFv are identical and bind to NRP1; and (b) two identical light chains comprising a first light chain and a second light chain, wherein the VL and VH of the heavy fusion and light chain polypeptides comprises the target protein binding domain that binds to the target protein and the scFv comprising the NRP1 binding domain that binds to the NRP1.

In some embodiments, the present disclosure provides the polynucleotide sequences used to encode the GGGGS subunit, and these sequences are set forth in SEQ ID NOs: 26-38. Table 1 lists the polypeptide sequences of the bispecific binding molecule, and Table 2 lists the polynucleotide sequence that encodes the polypeptides. Example 1 describes the method of bispecific binding molecule production is described in Example 1.

In some embodiments, the EGFR binding domain of the bispecific binding molecule has EGFR affinity (K_D) in the sub-nanomolar range (<0.1 nM). In some embodiments, the NRP1 binding domain of the bispecific binding molecule has NRP1 affinity (K_D) ranging from 70 nM for the bispecific binding molecule construct with polypeptide sequence with SEQ ID NO: 1 to subnanomolar ranges for bispecific antibodies with polypeptide sequences set forth in SEQ ID NOs: 2, 3, 5, 7, 10, and 11. Thus, in one aspect, the disclosure provides bispecific antibodies having an EGFR binding domain with affinity for EGFR in the subnanomolar range and an NRP1 binding domain with affinity for NRP1 in the subnanomolar range, as shown in Table 2 of Example 2. **FIGS. 2A-2K** show bispecific binding molecule binding affinity curves to immobilized huEGFR. In some embodiments, binding affinity of the bispecific binding molecule for EGFR is <0.1 nM. In some embodiments, binding affinity of the bispecific binding molecule for EGFR is <0.01 nM. **FIGS. 3A-3K** show bispecific binding molecule binding affinity curves to immobilized huNRP1. In some embodiments, binding affinity of the bispecific binding molecule for NRP1 ranges between 0.01 nM and 1000 nM. In some embodiments, binding affinity of the bispecific binding molecule for NRP1 ranges between 0.1nM and 100 nM.

One aspect of the disclosure provides bispecific antibodies with asymmetric binding affinity for EGFR and NRP1, see Table 2. In some embodiments, the K_D of EGFR binding domain for EGFR is at least 2, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 100, or more than 100-fold greater than the NRP1 binding

domain KD for NRP1. The asymmetric affinities provide for better homing to EGFR expressing cancer cells while reducing NRP1-targeting cytotoxicity.

Blocking VEGF binding to NRP1 with the NRP1 binding domain of a bispecific binding molecule may inhibit the activation of VEGFR2, as measured by VEGFR2 phosphorylation.

5 However, the bispecific antibody with heavy chain of SEQ ID NO: 1 has an NRP1 K_D of 69.7 nM, but does not inhibit VEGFR phosphorylation (**FIG. 4**). In some embodiments, the bispecific binding molecule inhibits VEGFR2 phosphorylation to prevent angiogenesis, see Table 3 and **FIGS. 5A-5B** and **FIGS. 11A-11B**. In some embodiments, the inventors discovered that the dissociation constants (K_D) of the NRP1 binding domain does not reflect the bispecific binding
10 molecule's ability to inhibit VEGFR2 phosphorylation. For example, the bispecific binding molecule with heavy chain SEQ ID NO: 6 inhibits 50% VEGFR2 phosphorylation at 10,130 nM (IC_{50}), but the NRP1 K_D is 3.76 nM, whereas the bispecific binding molecule with heavy chain SEQ ID NO: 4 inhibits 50% VEGFR2 phosphorylation at 410 nM (IC_{50}), but the NRP1 K_D is 8.8 nM. Thus, in some embodiments, the disclosure provides bispecific antibodies wherein the
15 NRP1 binding domain affinity and biological function are disproportionate in regards to inhibiting VEGFR2 phosphorylation.

In some embodiments, the bispecific antibodies inhibit cancer cell growth. In some embodiments, the bispecific binding molecule Fc domain, comprising constant heavy chains 2 and 3 (CH2 and CH3), are of the IgG1 or IgG2 subclass. In some embodiments, the disclosure
20 provides a bispecific binding molecule with an EGFR binding domain and NRP1 binding domain of scFv robustly inhibit cell proliferation in the cancer cell line H1975, Table 4 and **FIGS. 12A-12B**. This result demonstrates that scFv is critical for function of the bispecific binding molecule as a degrader. NRP1 Example 4 describes methods used to measure the bispecific binding molecule IC_{50} for cell growth inhibition in the H1975 cancer cell line.

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Additional Bispecific Antibodies with Binding Affinity for NRP1 and non-Receptor Tyrosine Kinases (Non-RTKs)

In embodiments the disclosure provides bispecific antibody constructs having binding affinity for NRP1 and a non-receptor tyrosine kinase (non-RTK). Non-limiting examples
30 include the following representative constructs.

Integrin $\alpha V\beta$ xNRP1 Bispecific Constructs

In one embodiment, the target protein binding domain binds an integrin $\alpha V\beta$. Receptor degradation mediated by an Int- $\alpha V\beta$ xNRP1 bispecific antibody construct is described in detail in Example 8.

5 In embodiments, an Int- $\alpha V\beta$ x NRP1 bispecific antibody comprises an anti-NRP1 binding arm comprising heavy chain CDR1, CDR2 and CDR3 regions comprising (or consisting of) the amino acid sequences shown in SEQ ID NOs: 79, 80 and 81, respectively. In an embodiment, the bispecific antibody comprises an anti-NRP1 binding arm comprising a heavy chain CDR3 region comprising (or consisting of) the amino acid sequences shown in SEQ ID
10 NO: 81. In embodiments, the bispecific antibody comprises an anti-NRP1 binding arm comprising light chain CDR1, CDR2 and CDR3 regions comprising (or consisting of) the amino acid sequences shown in SEQ ID NOs: 82, 83 and 84, respectively. In an embodiment, the bispecific antibody comprises an anti-NRP1 binding arm comprising a light chain CDR3 region comprising (or consisting of) the amino acid sequences shown in SEQ ID NO: 84.

15 In embodiments, the Int- $\alpha V\beta$ binding arm comprises sequences of an anti-Int- $\alpha V\beta$ monoclonal antibody (mAb) known and available in the art, e.g., the heavy and light chain CDRs (1-3) of the mAb or the VH/VL polypeptides of the mAb. In an embodiment, the anti-Int- $\alpha V\beta$ mAb is intetumumab, which is an anti-pan Int- $\alpha V\beta$ mAb.

20 Integrin $\alpha V\beta 3$ xNRP1 Bispecific Constructs

In one embodiment, the target protein binding domain binds an integrin $\alpha V\beta 3$. Receptor degradation mediated by an Int- $\alpha V\beta 3$ xNRP1 bispecific antibody construct is described in detail in Example 9.

In embodiments, an Int- $\alpha V\beta 3$ x NRP1 bispecific antibody comprises an anti-NRP1
25 binding arm comprising heavy chain CDR1, CDR2 and CDR3 regions comprising (or consisting of) the amino acid sequences shown in SEQ ID NOs: 79, 80 and 81, respectively. In an embodiment, the bispecific antibody comprises an anti-NRP1 binding arm comprising a heavy chain CDR3 region comprising (or consisting of) the amino acid sequences shown in SEQ ID NO: 81. In embodiments, the bispecific antibody comprises an anti-NRP1 binding arm
30 comprising light chain CDR1, CDR2 and CDR3 regions comprising (or consisting of) the amino

acid sequences shown in SEQ ID NOs: 82, 83 and 84, respectively. In an embodiment, the bispecific antibody comprises an anti-NRP1 binding arm comprising a light chain CDR3 region comprising (or consisting of) the amino acid sequences shown in SEQ ID NO: 84.

In embodiments, the Int- α V β 3 binding arm comprises sequences of an anti-Int- α V β 3 monoclonal antibody (mAb) known and available in the art, e.g., the heavy and light chain CDRs (1-3) of the mAb or the VH/VL polypeptides of the mAb. In an embodiment, the anti-Int- α V β 3 mAb is etaracizumab.

PD-L1 x NRP1 Bispecific Constructs

10 In one embodiment, the target protein binding domain binds PD-L1. Receptor degradation mediated by a PD-L1 x NRP1 bispecific antibody construct is described in detail in Example 10.

In embodiments, a PD-L1 x NRP1 bispecific antibody comprises an anti-NRP1 binding arm comprising heavy chain CDR1, CDR2 and CDR3 regions comprising (or consisting of) the amino acid sequences shown in SEQ ID NOs: 79, 80 and 81, respectively. In an embodiment, the bispecific antibody comprises an anti-NRP1 binding arm comprising a heavy chain CDR3 region comprising (or consisting of) the amino acid sequences shown in SEQ ID NO: 81. In embodiments, the bispecific antibody comprises an anti-NRP1 binding arm comprising light chain CDR1, CDR2 and CDR3 regions comprising (or consisting of) the amino acid sequences shown in SEQ ID NOs: 82, 83 and 84, respectively. In an embodiment, the bispecific antibody comprises an anti-NRP1 binding arm comprising a light chain CDR3 region comprising (or consisting of) the amino acid sequences shown in SEQ ID NO: 84.

In embodiments, the PD-L1 binding arm comprises sequences of an anti-PD-L1 monoclonal antibody (mAb) known and available in the art, e.g., the heavy and light chain CDRs (CDR1-3) of the mAb or the VH/VL polypeptides of the mAb. Non-limiting examples of anti-PD-L1 antibodies known in the art include Atezolizumab, Avelumab and Durvalumab.

Bispecific binding molecule tumor growth inhibition in xenograft mouse model

In some aspects of the disclosure, treatment with the bispecific antibodies decreases tumor growth. In some embodiments, the bispecific binding molecule with heavy chain SEQ ID NO: 11 and light chain SEQ ID NO: 12 significantly reduces tumor growth rate. In some aspects,

the addition of the scFv comprising a NRP1 binding domain significantly increases efficacy of tumor growth inhibition. Example 5 describes the methods and results of treating H1975 xenograft mouse models with bispecific antibodies for tumor growth inhibition. Table 5 shows the percent tumor growth inhibited and **FIGS. 13A-13F** show the tumor growth over days post-implantation.

Biological effects of bispecific binding molecule

In summary, the disclosure provides bispecific antibodies that combine an EGFR binding domain with an NRP1 binding domain to facilitate homing to high EGFR expression tumors by increased EGFR affinity. The bispecific binding molecule will have multiple biological effects that combine to reduce cancer cell proliferation and survival, including reducing abnormal angiogenesis, increasing extravasation and penetration by reducing VE-cadherin, E-cadherin, and integrin $\beta 1$ expression. NRP1 targeting further decreases EGFR surface pooling to enhance EGFR downregulation and inhibit NRP1 checkpoint immunosuppression. The combination of these features provides for a bispecific binding molecule with potent ability to reduce EGFR-mediated cancer cell proliferation and survival.

FcRn binding for transcytosis recycling

The antibody size of ~150 kD ensures a long serum half-life and therefore a long-lasting therapeutic effect. In addition, antibody IgG Fc portions consisting of heavy chain constant regions 2 and 3 (CH2 and CH3) binds to the neonatal Fc receptor (FcRn) and Fc gamma receptors (Fc γ Rs) at the cell surface is endocytosed and recycled back to the serum through transcytosis, which further increases antibody serum half-life. Cancers with low FcRn or Fc γ R expression are associated with poor prognosis (Pyzik et al., 2019) and thus, the FcRn- or Fc γ R-mediated recycling plays an important role in sustaining antibody serum concentrations. IgG1 antibodies have a more efficient FcRn and Fc γ R recycling process than IgG2 antibodies. Thus, having an IgG1 Fc domain in therapeutic antibodies helps maintain drug therapeutic levels and reduce the frequency of administration, while half-life reduction would be ideal for diagnostic tests or toxicity control.

In some embodiments, the polypeptides of the present invention comprise an immunoglobulin domain, which includes a polypeptide comprising an immunoglobulin domain that comprises an Fc domain selected from the IgG1 subclass.

Expression Construct

The term "vector" or "expression vector" as used herein refers to means for expressing a target gene in a host cell. For example, the vector may include plasmid vector, cosmid vector, bacteriophage vector, and virus vectors such as adenovirus vector, retrovirus vector, and adeno-associated virus vector. The recombinant vector may be produced by operating plasmid (for example, pSC101, pGV1106, pACYC177, ColEI, pKT230, pME290, pBR322, pUC8/9, pUC6, pBD9, pHC79, pIJ61, pLAFR1, pHV14, pGEX series, pET series and pUC19, etc.), phages (for example, Agt4AB, A-Charon, AAZ1 and M13, etc.), or virus (for example, CMV, SV40, etc.) commonly used in the pertinent art. In some embodiments, an expression vector comprises the nucleic acids of encoding a heavy chain fusion polypeptide and a light chain polypeptide of a bispecific binding molecule, wherein the sequence of the nucleic acid encoding heavy chain fusion polypeptide is any one of SEQ ID NOs: 15 to 24 and the sequence of the nucleic acid encoding light chain polypeptide is SEQ ID NO: 25.

In another aspect, the disclosure provides isolated polynucleotides encoding the bispecific binding molecule heavy and light chain amino acid sequence. A polynucleotide encoding an in the recombinant vector may be operatively linked to a promoter. The term "operatively linked" as used herein refers a functional linkage between a nucleotide expression control sequence (such as a promoter sequence) and a second nucleotide sequence. Accordingly, the regulation sequence may control the transcription and/or translation of the second nucleotide sequence. The recombinant vector may be generally constructed as a vector for cloning or a vector for expression. As the vector for expression, vectors generally used for expressing foreign protein from plants, animals or microorganisms in the pertinent art may be used. The recombinant vector may be constructed by various methods known in the pertinent art. The recombinant vector may be constructed using a eukaryotic cell as a host with an fl replication origin, an SV40 replication origin, a pMB1 replication origin, an adeno replication origin, an AAV replication origin, a CMV replication origin and a BBV replication origin, etc., but is not limited thereto.

In addition, a promoter derived from a genome of a mammal cell (for example, a metal thionine promoter) or a promoter derived from a virus of a mammal cell (for example, an adenovirus anaphase promoter, a vaccinia virus 7.5K promoter, a SV40 promoter, a cytomegalovirus (CMV) promoter, or a thymidine kinase (TK) promoter of herpes simplex virus

(HSV) may be used, and the promoter generally has a polyadenylated sequence as a transcription termination sequence. The vector may express not only the peptide domain that binds specifically to NRP1 according to the present disclosure, but also an antibody having the peptide fused thereto, as well as a linker peptide. In the case of an antibody having the peptide fused thereto, the vector may use both a vector system that expresses a peptide and an antibody or a fragment thereof in one vector, and a vector system that expresses the peptide and the antibody or the fragment thereof in separate vectors. For the latter, the two vectors may be introduced into the host cell through co-transformation and targeted transformation. Thus, in another aspect, the disclosure includes a vector containing the nucleic acids disclosed in SEQ ID NO: 14-38.

10 Example 1 describes vector properties that may be utilized to produce the bispecific antibodies.

Another aspect of the present disclosure provides a host cell transformed with the recombinant vector. Any kind of host cell known in the pertinent art may be used as a host cell. Examples of a prokaryotic cell comprise strains such as *E. coli* JM109, *E. coli* BL21, *E. coli* RR1, *E. coli* LE392, *E. coli* B, *E. coli* X 1776, *E. coli* W3110, or strains belonging to the genus *Bacillus* such as *Bacillus subtilis* and *Bacillus thuringiensis*, *Salmonella typhimurium*, *Serratia marcescens* and intestinal flora and strains such as various *Pseudomonas* Spp., etc. Prokaryote cell transformation is useful for cloning plasmids at high scale. Prokaryote host cells may be deficient in the required post-translational modifications required for antibody assembly and structure, and thus, a preferred embodiment is vector transformation in eukaryotic host cells, such as yeast (*Saccharomyces cerevisiae*), an insect cell, a plant cell, a mammalian cell, for example, SP2/0, CHO (Chinese hamster ovary) K1, CHO DG44, CHO-S, PER.C6, W138, BHK, COS-7, 293, HepG2, Huh7, 3T3, RN, and MDCK cell line, etc. In some embodiments, a host cell comprises an expression vector the nucleic acids encoding a heavy chain fusion polypeptide and a light chain polypeptide of a bispecific binding molecule, wherein the sequence of the nucleic acid encoding heavy chain fusion polypeptide is any one of SEQ ID NOs: 15-24 and the sequence of the nucleic acid encoding light chain polypeptide is SEQ ID NO: 25.

Another aspect of the present disclosure provides a method for preparing a peptide that binds specifically to NRP1, comprising culturing the above-described host cell. The polynucleotide and a recombinant vector including the polynucleotide may be inserted into a host cell using an insertion method well known in the pertinent art. For example, when a host cell is a prokaryotic cell, the transfer may be carried out according to CaCl_2 method or an electroporation

method, etc., and when a host cell is an eukaryotic cell, the vector may be transferred into a host cell by various methods including a microscope injection, calcium phosphate precipitation, electroporation, a liposome-mediated transformation, and a gene bombardment, etc., but the transferring method is not limited thereto. The method for selecting the transformed host cell
5 may be readily carried out according to a method well known in the pertinent art using a phenotype expressed by a selected label. For example, when the selected label is a specific antibiotic resistance gene, the transformant may be readily selected by culturing the transformant in a medium containing the antibiotic, acceptable salt thereof and a pharmaceutically acceptable carrier, diluent, adjuvant, or vehicle. Pharmaceutically acceptable carriers include, for example,
10 pharmaceutical diluents, excipients, or carriers suitably selected with respect to the intended form of administration, and consistent with conventional pharmaceutical practices.

Antibody-Drug Conjugates

In another aspect, the disclosure provides antibody-drug conjugates (ADCs) comprising a
15 bispecific antibody (protein degrader) of the disclosure conjugated to a drug or other functional compound, also referred to as a payload. ADC technology is established in the art (reviewed in, for example, Strohl and Strohl (eds) "Ch. 15: Antibody-Drug Conjugates" in *Therapeutic Antibody Engineering* (2012); Tumey (2020) *Methods Mol. Biol.* 2078:1-22), with numerous ADC therapies approved by the FDA.

20 In the ADC, the payload is conjugated to the bispecific antibody, such as via a linker and/or by using site-specific conjugation chemistry established in the art.

Use of linkers in ADCs is reviewed in, for example, Nareshkumar et al. (2015) *Pharm. Res.* 32:3526-3540. In one embodiment, the linker is a cleavable linker. In another embodiment, the linker is a non-cleavable linker. Suitable linkers, based on chemical motifs including
25 disulfides, hydrazones, peptides and thioethers, are available in the art.

Use of various site-specific conjugation chemistries in ADCs is reviewed in, for example, Zhou et al. (2017) *Biomedicines* 5:64. These methods couple a payload to specifically defined sites in the antibody portion of the ADC (i.e., a bispecific antibody of the disclosure) including cysteine, glutamine, unnatural amino acids, short peptide tags and glycans.

30 In one embodiment, the payload used in the ADC is toxic to cells (i.e., exhibits cytotoxicity). In another embodiment, the payload used in the ADC is non-toxic to cells (i.e.,

does not exhibit cytotoxicity).

In embodiments, the payload used in the ADC functions as a cytotoxic or cytolytic agent. In embodiments, the payload used in the ADC functions to enhance one or more pharmacokinetic properties of the molecule, such as serum half life. In embodiments, the payload used in the ADC functions to target the molecule to a microenvironment of interest (e.g., a target cell type or tissue). In embodiments, the payload used in the ADC imparts one or more immunomodulatory properties onto the molecule. In embodiments, the payload used in the ADC imparts one or more enzymatic properties onto the molecule.

In embodiments, the payload used in the ADC is a cytotoxic or cytolytic agent, non-limiting examples of which include small molecule drugs (e.g., chemotherapeutic agents), protein toxins, bacterial toxins, cytolytic proteins/peptides and radionuclides.

In embodiments, the payload that is conjugated to the bispecific antibody functions by a mechanism selected from the group consisting of targeting the folate receptor, inhibiting microtubules, cleaving DNA and inhibiting TOP1.

In embodiments, the payload that is conjugated to the bispecific antibody belongs to a class of payload selected from the group consisting of maytansinoids (e.g., maytansinoid DM4), MMAE/auristatins and camptothecins.

In embodiments, the payload that is conjugated to the bispecific antibody is selected from the group consisting of vedotin, emtansine, govitecan, talirine, ozogamicin, pasudotox, deruxtecan, mafodotin, soravtansine and tesinine.

In embodiments, the payload that is conjugated to the bispecific molecule is a radionuclide, non-limiting examples of which include ^{90}Y and ^{111}In .

In embodiments, the payload that is conjugated to the bispecific molecule is a protein toxin, such as *Pseudomonas* endotoxin or *Diphtheria* toxin.

In embodiments, the payload that is conjugated to the bispecific molecule is an immunomodulatory peptide, such as Fas ligand (FasL).

In embodiments, the payload that is conjugated to the bispecific molecule is a biologically active peptide, such as to extend the pharmacological half-life (e.g., GLP1) or to target to particular cells. For example, calcitonin has been used to target an ADC to osteoclasts (Newa et al. (2011) *Pharm. Res.* 28:1131-1143).

In embodiments, the payload that is conjugated to the bispecific molecule is an enzyme.

In embodiments, the payload that is conjugated to the bispecific molecule is an oligonucleotide.

5 **Pharmaceutical Composition**

Aspects of the present disclosure further include compositions. According to some embodiments, a composition of the present disclosure includes a bispecific binding molecule of the present disclosure. For example, the bispecific binding molecule may be any of the bispecific binding molecules described in the bispecific antibodies section hereinabove, which descriptions are incorporated but not reiterated herein for purposes of brevity.

The polypeptides described herein can be formulated into pharmaceutical compositions that further comprise a pharmaceutically acceptable carrier, diluent, adjuvant, or vehicle. In one embodiment, the present disclosure provides a pharmaceutical composition comprising the disclosed polypeptides, and a pharmaceutically acceptable carrier, diluent, adjuvant, or vehicle.

15 In one embodiment, the present invention is a pharmaceutical composition comprising an effective amount of the disclosed bispecific antibodies or a pharmaceutically.

A pharmaceutically acceptable carrier or excipient may contain inert ingredients that do not unduly inhibit the biological activity of the polypeptides. The pharmaceutically acceptable carriers should be biocompatible, e.g., non-toxic, non-inflammatory, non- immunogenic or

20 devoid of other undesired reactions or side-effects upon the administration to a subject. Standard pharmaceutical formulation techniques can be employed.

The pharmaceutically acceptable carrier, adjuvant, or vehicle, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders,

25 lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the polypeptides described herein, such as by producing any

30 undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be

within the scope of this invention. As used herein, the phrase “side effects” encompasses unwanted and adverse effects of the therapy.

Materials which can serve as pharmaceutically acceptable carriers for antibodies increase conformation stability, reduce protein dynamics, inhibit aggregation, and protect protein adsorbing to liquid air interface, and include but are not limited to cyclodextrin hydrogels, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins (such as human serum albumin), buffer substances (such as twin 80, phosphates, glycine, sorbic acid, or potassium sorbate), partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes (such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, or zinc salts), colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, methylcellulose, hydroxypropyl methylcellulose, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such a propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

In some embodiments, a composition of the present invention comprises a pharmaceutically acceptable salt. When polypeptides of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such polypeptides with sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When polypeptides of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such polypeptides with a sufficient amount of the desired acid,

either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived
5 from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, oxalic, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge et al., "Pharmaceutical Salts", *Journal of Pharmaceutical Science*,
10 1977, 66, 1-19). Certain specific polypeptides of the disclosure contain both basic and acidic functionalities that allow the polypeptides to be converted into either base or acid addition salts.

Thus, the disclosed polypeptides may exist as salts, such as with pharmaceutically acceptable acids. The present invention includes such salts. Non-limiting examples of such salts include hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, nitrates,
15 maleates, acetates, citrates, fumarates, proprionates, tartrates (e.g., (+)-tartrates, (-)-tartrates, or mixtures thereof including racemic mixtures), succinates, benzoates, and salts with amino acids such as glutamic acid, and quaternary ammonium salts (e.g., methyl iodide, ethyl iodide, and the like). These salts may be prepared by methods known to those skilled in the art.

The neutral forms of the polypeptides are preferably regenerated by contacting the salt
20 with a base or acid and isolating the parent polypeptides in the conventional manner. The parent form of the polypeptide may differ from the various salt forms in certain physical properties, such as solubility in polar solvents.

Certain polypeptides of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to
25 unsolvated forms and are encompassed within the scope of the present invention. Certain polypeptides of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

In some embodiments, subcutaneous formulations may contain recombinant human PH20
30 hyaluronidase (rHuPH20) to facilitate dispersion of the antibody from the injection site.

In some embodiments of the bispecific binding molecule, a pharmaceutical composition

comprising a therapeutically effective amount of the bispecific binding molecule and a pharmaceutically acceptable carrier. In some embodiments of the bispecific binding molecule, a pharmaceutical composition further comprising a therapeutically effective amount of the bispecific binding molecule and one or more therapeutic agents for chemotherapy.

- 5 In some embodiments, the kit comprises one or more unit doses of the pharmaceutical composition comprising the bispecific binding molecule herein and a pharmaceutically effective carrier and instructions for the one or more unit doses of the pharmaceutical composition to a subject in need thereof.

Administration Methods

- 10 The compositions of the present invention may be administered to a subject in need of cancer treatment. The terms “administration” or “administering” refer to the act of providing a composition of the present invention, e.g., a polypeptide or pharmaceutically acceptable salt thereof, to a subject in need of cancer treatment.

- As used herein, “intermittent administration” includes the administration of an agent for a
15 period of time (which can be considered a “first period of administration”), followed by a time during which the composition is not taken or is taken at a lower maintenance dose (which can be considered “off-period”) followed by a period during which the composition is administered again (which can be considered a “second period of administration”). Generally, during the second phase of administration, the dosage level of the agent will match that administered during
20 the first period of administration but can be increased or decreased as medically necessary.

- In some embodiments, the compositions of the present invention can be administered by oral administration, as a suppository, topical contact, intravenous, parenteral, intraperitoneal, intramuscular, intralesional, intrathecal, intranasal or subcutaneous administration, or the implantation of a slow-release device, e.g., a mini-osmotic pump, to a subject. Accordingly,
25 administration can be by any route, including parenteral and transmucosal (e.g., buccal, sublingual, palatal, gingival, nasal, vaginal, rectal, or transdermal). Parenteral administration includes, e.g., intravenous, intramuscular, intra-arteriole, intradermal, subcutaneous, intraperitoneal, intraventricular, and. Other modes of delivery include, but are not limited to, the use of liposomal formulations, intravenous infusion, or via an implanted reservoir, etc.
30 Specifically, the compositions are administered orally, intraperitoneally or intravenously.

 In some embodiments, the bispecific binding molecule composition is administered by

systemic intravenous (IV) or by oral route for intestinal cancers, such as gastric or intestinal cancer (Tashima et al., 2021). Formulations for delivery can be optimized by routine, conventional methods that are well-known in the art. Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active polypeptides, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

In some embodiments, the bispecific binding molecule composition is administered by subcutaneous injection. Injectable bispecific binding molecule formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents dispersed in sterile water or other sterile injectable medium prior to use. In order to prolong the effect of a polypeptide described herein, it is often desirable to slow the absorption of the polypeptide from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the polypeptide then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered polypeptide form is accomplished by dissolving or suspending the polypeptide in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the polypeptide in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of polypeptide to polymer and the nature of the particular polymer employed, the rate of polypeptide release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the polypeptide in liposomes or microemulsions that are compatible with body tissues.

Sterile injectable forms of the compositions described herein may be aqueous or

oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable
5 vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically acceptable oils, such as olive oil or
10 castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers
15 which are commonly used in the manufacture of pharmaceutically acceptable dosage forms may also be used for the purposes of formulation.

In some embodiments, the formulation includes agents, such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and preferably zinc. The formulation can also include an excipient or agent for polypeptide stabilization, such as a buffer, a reducing agent, a
20 bulk protein, or a carbohydrate. Bulk proteins useful in formulating at least one polypeptide compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating at least one polypeptide include sucrose, mannitol, lactose, trehalose, glucose, or the like. The bispecific binding molecule formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the at least one polypeptide caused by atomization of
25 the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbital fatty acid esters. Amounts will generally range between about 0.001 and 4% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan mono-oleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for
30 formulation of a polypeptide, such as antibody protein, can also be included in the formulation.

Target Protein of Interest

The genomic studies have revealed the presence of various types of alterations in the genes encoding receptors tyrosine kinase (RTKs) such as EGFR, HER2/Erb2, and MET, amongst many others have been known to be associated with many human diseases, especially in cancer. For instance, EGFR mutation in non-small cell lung cancer (NSCLC), MET exon 14 skipping mutation in NSCLC, RET mutation in medullary thyroid carcinoma, ALK translocation and ROS1 translocation in NSCLC, and amplification or overexpression of HER2 in breast cancer have been reported.

The present invention provides a bispecific binding molecule that binds to EGFR and subsequently degrading EGFR by lysosomal degradation pathway. Twenty receptors tyrosine kinase including EGFR family, FGFR family, PDGFR family, MET family, and VEGFR family have been known to be co-receptors of NRP1 (see Critchley et al., Cells (2018) 7(3):22).

In some embodiments, a target protein of the bispecific binding molecule herein includes but is not limited to, oncogenic receptors such as receptors tyrosine kinases (RTKs) and receptors serine/threonine kinases (RSTKs), fibroblast growth factor receptor (FGFR) family, platelet-derived growth factor receptor (PDGFR) family, tyrosine kinase MET family, and vascular endothelial growth factor (VEGFR) family.

In some embodiments, the receptors tyrosine kinase receptors include HER1/ErbB1, HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4, FGFR1, FGFR2, FGFR3, and FGFR4, Met and Ron, PDGFR family PDGFRalpha, PDGFRbeta, CSF-1R, Kit, and FLT-3, and VEGFR1, VEGFR2, and VEGFR3.

In some embodiments, the target protein of the bispecific binding molecule herein includes but is not limited to, the receptors serine/threonine kinase, G-protein coupled receptors, immune checkpoint receptors, and ion channel receptors.

In some embodiments, receptors serine/threonine kinase is ACVR1/ALK1, ACVR2/ALK2, ACVR1B /ALK4, ACVR1C /ALK7, ACVRL1, BMPR1A, BMPR1B, TGFBR1, ActR2, ActR2B, MISR2, BMPR2, TGFBR2, and TGFBR3. In some embodiments, G-protein couple receptors (GPCR) are CXCR4, EBI2, CCR7, ADRB2, BAI2, FZD6, CD97, GPR153, FZD4, FZD2, F2R, ADORA2B, CD97, OPN3, GPR125, GPR126, GABBR1, CNR2, GPR92, PAR1, LPAR1, SSTR1, GPRC5B, GPRC5B, GPCR68, OXTR, LPHN2, FZD7, GABBR1, GPR125, and EDG3.

In some embodiments, G-protein coupled receptor is selected from the group consisting of GPCR, CCR and CXCR.

In some embodiments, the immune checkpoint receptors is selected from the group consisting of CTLA4, PD-L1, PD-1, and integrins. In embodiments, the immune checkpoint
5 receptor is PD-L1.

In some embodiments, the ion channel receptors are voltage-gated receptors.

In some embodiments of the bispecific binding molecule, target protein of interest, herein includes but is not limited to, disease-associated proteins.

10 **Kit**

Aspects of the present disclosure further include kits. In certain embodiments, the kits find use in practicing the methods of the present disclosure, e.g., methods comprising administering a pharmaceutical composition of the present disclosure to a subject to enhance anti-tumor immunity in the subject, administering a pharmaceutical composition of the present
15 disclosure to a subject to enhance or suppress an immune response in a subject, or the like.

Accordingly, in certain embodiments, a kit of the present disclosure comprises one or more unit doses of the pharmaceutical composition of the present disclosure, and instructions for administering the pharmaceutical composition to a subject in need thereof. The pharmaceutical composition included in the kit may include any of the bispecific antibodies of the present
20 disclosure, e.g., any of the bispecific binding molecule described hereinabove, which are not reiterated herein for purposes of brevity.

The kits of the present disclosure may include a quantity of the compositions, present in unit doses, e.g., ampoules, or a multi-dosage format. As such, in certain embodiments, the kits may include one or more (e.g., two or more) units dose (e.g., ampoules) of a composition that
25 includes bispecific binding molecule of the present disclosure. The term "unit doses", as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of the composition calculated in an amount sufficient to produce the desired effect. The amount of the unit doses depends on various factors, such as the particular bispecific binding molecule employed, the effect to be achieved,
30 and the pharmacodynamics associated with the bispecific binding molecule, in the individual. In yet other embodiments, the kits may include a single multi dosage amount of the composition. In

certain embodiments, a kit of the present disclosure includes instructions for administering the one or more units dose of the pharmaceutical composition to a subject in need of enhancement of anti-tumor immunity. According to some embodiments, a kit of the present disclosure includes instructions for administering the one or more units dose of the pharmaceutical composition to a
5 subject in need of enhancement or suppression of an immune response.

Combination Therapy

In some embodiments, an effective amount of bispecific antibodies can be achieved in the method or pharmaceutical composition of the invention employing the polypeptide or a
10 pharmaceutically acceptable salt or solvate (e.g., hydrate) thereof alone or in combination with an additional suitable chemotherapeutic agent, for example, oxaliplatin, irinotecan, or FOLFOX. When “combination therapy” is employed, an effective amount can be achieved using a first amount of the polypeptide, or a pharmaceutically acceptable salt or solvate (e.g., hydrate) thereof, and a second amount of an additional suitable chemotherapeutic agent.

15 Co-administration encompasses administration of the first and second amounts of the polypeptides and chemotherapeutic agent in an essentially simultaneous manner, such as in a single pharmaceutical composition, for example, a capsule having a fixed ratio of first and second amounts, or in multiple, separate capsules for each. In addition, such co-administration also encompasses use of each polypeptide in a sequential manner in either order.

20 When co-administration involves the separate administration of the first amount of the polypeptide and a second amount of an additional therapeutic agent, the polypeptides are administered sufficiently close in time to have the desired therapeutic effect. For example, the period of time between each administration which can result in the desired therapeutic effect, can range from minutes to hours and can be determined taking into account the properties of each
25 agent such as potency, solubility, bioavailability, plasma half-life and kinetic profile. For example, the polypeptide and the second therapeutic agent can be administered in any order within about 24 hours of each other, within about 16 hours of each other, within about 8 hours of each other, within about 4 hours of each other, within about 1 hour of each other or within about 30 minutes of each other.

30 More, specifically bispecific binding molecule of the invention can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12

hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second anticancer agent to a subject.

It is understood that the method of co-administration of a first amount of the bispecific binding molecule and a second amount of an additional therapeutic agent can result in an enhanced or synergistic therapeutic effect, wherein the combined effect is greater than the additive effect that would result from separate administration of the first amount of the polypeptide and the second amount of the additional therapeutic agent.

A synergistic effect of a combination of therapies (e.g., a combination of prophylactic or therapeutic agents) can permit the use of lower dosages of one or more of the therapies and/or less frequent administration of said therapies to a subject. The ability to utilize lower dosages of a therapy (e.g., a prophylactic or therapeutic agent) and/or to administer said therapy less frequently can reduce the toxicity associated with the administration of said therapy to a subject without reducing the efficacy of said therapy in the treatment of cancer. In addition, a synergistic effect can result in improved efficacy of agents in the prevention, management or treatment of a disorder. Finally, a synergistic effect of a combination of therapies (e.g., a combination of prophylactic or therapeutic agents) may avoid or reduce adverse or unwanted side effects associated with the use of either therapy alone.

When the combination therapy using the bispecific binding molecule of the present invention is in combination with another anti-cancer agent, both therapeutic agents can be administered so that the period of time between each administration can be longer (e.g., days, weeks or months).

The presence of a synergistic effect can be determined using suitable methods for assessing drug interaction. Suitable methods include, for example, the Sigmoid-Emax equation (Holford, N.H.G. and Scheiner, L.B., Clin. Pharmacokinet. 6: 429-453 (1981)), the equation of Loewe additivity (Loewe, S. and Muischnek, H., Arch. Exp. Pathol Pharmacol. 114: 313-326 (1926)) and the median-effect equation (Chou, T.C. and Talalay, P., Adv. Enzyme Regul. 22: 27-55 (1984)). Each equation referred to above can be applied with experimental data to generate a corresponding graph to aid in assessing the effects of the drug combination. The corresponding

graphs associated with the equations referred to above are the concentration-effect curve, isobologram curve and combination index curve, respectively.

5 **Methods**

Aspects of the present disclosure include methods of using the bispecific antibodies of the present disclosure. The methods are useful in a variety of contexts, including in vitro and/or in vivo research and/or clinical applications.

10 In certain aspects, provided are methods of enhancing anti-tumor immunity in a subject in need thereof. Such methods comprise administering an effective amount of a pharmaceutical composition of the present disclosure to the individual, e.g., a pharmaceutical composition comprising a bispecific binding molecule of the present disclosure comprising a target protein binding domain and a NRPI binding domain. In certain embodiments, the methods are for enhancing antibody-dependent lysosomal degradation of the target protein and/or cytotoxicity to
15 a cancer cell in the individual.

In certain aspects, provided are methods of inhibiting or suppressing tumor cell growth in a subject in need thereof. Such methods comprise administering an effective amount of a pharmaceutical composition of the present disclosure to the individual, e.g., a pharmaceutical composition comprising a bispecific binding molecule of the present disclosure comprising a
20 target protein binding domain and a NRPI binding domain.

The subject in need thereof may have a cell proliferative disorder. By “cell proliferative disorder” is meant a disorder wherein unwanted cell proliferation of one or more subset(s) of cells in a multicellular organism occurs, resulting in harm, for example, pain or decreased life expectancy to the organism. Cell proliferative disorders include, but are not limited to, cancer,
25 pre-cancer, benign tumors, blood vessel proliferative disorders (e.g., arthritis, restenosis, and the like), fibrotic disorders (e.g., hepatic cirrhosis, atherosclerosis, and the like), psoriasis, epidermic and dermoid cysts, lipomas, adenomas, capillary and cutaneous hemangiomas, lymphangiomas, nevi lesions, teratomas, nephromas, myofibromatosis, osteoplastic tumors, dysplastic masses, mesangial cell proliferative disorders, and the like.

30 In some embodiments, the subject has cancer. The subject methods may be employed for the treatment of a large variety of cancers. “Tumor”, as used herein, refers to all neoplastic cell

growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues. The terms “cancer” and “cancerous” refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth/proliferation. Examples of cancers that may be treated using the subject methods include, but are not limited to, carcinoma, lymphoma, blastoma, and sarcoma. More particular examples of such cancers include squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bile duct cancer, bladder cancer, hepatoma, breast cancer, colon cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, various types of head and neck cancer, and the like. In certain embodiments, the subject has a cancer selected from a solid tumor, recurrent glioblastoma multiforme (GBM), non-small cell lung cancer, metastatic melanoma, melanoma, peritoneal cancer, epithelial ovarian cancer, glioblastoma multiforme (GBM), metastatic colorectal cancer, colorectal cancer, pancreatic ductal adenocarcinoma, squamous cell carcinoma, esophageal cancer, gastric cancer, neuroblastoma, fallopian tube cancer, bladder cancer, metastatic breast cancer, pancreatic cancer, soft tissue sarcoma, recurrent head and neck cancer, squamous cell carcinoma, head and neck cancer, anaplastic astrocytoma, malignant pleural mesothelioma, breast cancer, squamous non-small cell lung cancer, rhabdomyosarcoma, metastatic renal cell carcinoma, basal cell carcinoma (basal cell epithelioma), and gliosarcoma. In certain aspects, the subject has a cancer selected from melanoma, Hodgkin lymphoma, renal cell carcinoma (RCC), bladder cancer, non-small cell lung cancer (NSCLC), and head and neck squamous cell carcinoma (HNSCC).

The bispecific antibodies of the present disclosure may be administered via a route of administration selected from oral (e.g., in tablet form, capsule form, liquid form, or the like), parenteral (e.g., by intravenous, intra-arterial, subcutaneous, intramuscular, or epidural injection), topical, intra-nasal, or intra-tumoral administration.

The bispecific antibodies of the present disclosure may be administered in a pharmaceutical composition in a therapeutically effective amount. By “therapeutically effective amount” is meant a dosage sufficient to produce a desired result, e.g., an amount sufficient to effect beneficial or desired therapeutic (including preventative) results, such as a reduction in a

symptom of a cancer and/or immune disorder, as compared to a control. With respect to cancer, in some embodiments, the therapeutically effective amount is sufficient to slow the growth of a tumor, reduce the size of a tumor, and/or the like. An effective amount can be administered in one or more administrations.

5 Aspects of the present disclosure include methods for treating a cancer and/or immune disorder of an individual. By treatment is meant at least an amelioration of one or more symptoms associated with the cancer and/or immune disorder of the individual, where amelioration is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, e.g., symptom, associated with the cancer and/or immune disorder being treated. As
10 such, treatment also includes situations where the cancer and/or immune disorder, or at least one or more symptoms associated therewith, are completely inhibited, e.g., prevented from happening, or stopped, e.g., terminated, such that the subject no longer suffers from the cancer and/or immune disorder, or at least the symptoms that characterize the cancer and/or immune disorder.

15 The present invention is further illustrated by the following examples, which should not be construed as further limiting. The contents of figures and all references, patents and published patent applications cited throughout this application are expressly incorporated herein by reference.

20 EXAMPLES

The Examples in this specification are not intended to, and should not be used to, limit the invention; they are provided only to illustrate the invention.

25 **Example 1. Production of Bispecific Antibodies**

The designed proteins were generated by codon-optimized gene synthesis and inserted into pcDNA3.4 as expression vector using Not I and Hind III restriction enzyme. Table 1 shows the sequences of the heavy chain polypeptide set forth in SEQ ID NO: 1 and the heavy chain fusion polypeptide of the bispecific binding molecule used herein in SEQ ID NOs: 2, 3, 4, 5, 6, 7,
30 8, 9, 10, 11 and 39, which combines with the sequence of the light chain polypeptide set forth in SEQ ID NO: 12. Table 2 shows the sequence of polynucleotide encoding the heavy chain

polypeptide set forth in SEQ ID NO: 14 and the polynucleotide nucleotide sequences encoding the heavy chain polypeptide of the bispecific antibodies set forth in SEQ ID NOs: 15, 16, 17, 18, 19, 20, 21, 22, 23, 24 and 40. The sequence of a polynucleotide encoding the light chain polypeptide that combines with the heavy chain polypeptide of the bispecific antibodies is set forth in SEQ ID NO: 25. Sequences set forth in SEQ ID NOs: 26-38 disclose the polynucleotide sequence used to encode the GGGGS subunit of a peptide linker. The constructed expression vectors include signal peptides for optimized transcription a Kozak sequence may be included in the 5' untranslated region.

To obtain the amount of the plasmid constructs for transfection, the plasmid construct was transformed into One Shot™ Top10 E. coli competent cells followed by culturing overnight. The construct plasmids were obtained by PureLink™ HiPure Expi plasmid Megaprep kit.

Fusion proteins were transiently expressed in the CHO-S system (Thermo Fisher Scientific Inc.). The proteins were expressed individually as per the manufacturer's instructions. Briefly, a total of 0.8 µg of plasmid DNA at a ratio of 1:1 light to heavy chain per mL of CHO-S culture was prepared with OPTIPRO™ SFM and ExpiFectamine™. The mixture was added to CHO-S cells at a viable cell density of 6×10⁶ cells/mL and greater than 98% viability. The cell culture was incubated overnight at 37° C., 80% humidity, 8% CO₂ in a Nalgene™ Single-Use PETG Erlenmeyer Flasks shaking at 125 RPM with a 19-mm orbit. The next day the culture was enhanced (ExpiCHO™ enhancer; Thermo Fisher Scientific Inc.) and fed (ExpiCHO™ feed; Thermo Fisher Scientific Inc.) and transferred to 32° C., 80% humidity, 5% CO₂ shaking at 125 RPM with a 19-mm orbit. The second feed was performed on day 5 and the culture returned to 32° C. until harvest on day 12. Harvesting was accomplished via centrifugation at 4000×g for 20 minutes. The clarified supernatant was sterilized using an asymmetrical polyethersulfone (PES) 0.22-µm filter assembly (Nalgene). The filtrate was stored at 4° C. until purification the next day. All of the antibody sterilized supernatants were purified using MabSelect prismA™ resin (GE Healthcare Life Sciences) on an ÄKTApure (GE Healthcare Life Sciences). A 50 mM sodium phosphate, 150 mM NaCl, pH 7.0 buffer was used to equilibrate the resin. The antibody supernatant was then loaded into the column. The resin was washed with 50 mM sodium phosphate, 150 mM NaCl, pH 7.0 buffer until the chromatographic baseline returned to column equilibration levels. Elution was then performed using 100 mM sodium acetate, 20% glycerol,

pH 3.0, and fractions are collected. The fractions were immediately neutralized with 1 M Tris, pH 9. The fractions containing predominant absorbance at wavelength 280 nm were pooled into an Amicon 10-kDa ultrafiltration device for buffer exchange. The storage buffer (Phosphate Buffered Saline) was used to remove the elution buffer by centrifugation with half dilution, 5 seven times in the Amicon concentrator. The material was submitted for SEC and then stored at 4° C.

Cationic exchange chromatography was used to purify the antibodies. The cationic exchange chromatography column (Capto S ImpAct) was sanitized with 1 M NaOH and rinsed with MQ. Equilibration was done with 50 mM NaAc pH 5.5 (starting buffer) and 50 mM NaAc 10 pH5.5, 1M NaCl (elution buffer). The protein A purified antibody was loaded with a concentration of 1-2 g antibody/mL resin. The column was then washed with 50 mM NaAc pH 5.5. The antibody product was then eluted using a gradient of 5%-60% elution buffer in 25 column volumes. Each peak in CEX purification was collected separately and concentrated via centrifugation at 4000xg using Amicon® Ultra-15 Centrifugal Filter Units followed by buffer 15 change into PBS.

Size exclusion chromatography (SEC) analysis was performed on an Agilent Infinity 1260 II Quaternary Pump high performance liquid chromatographic (HPLC) system with diode array UV detector WR. Twenty (20) µg of antibody material was injected on an XBridge Protein BEH SEC Column, 200 Å, 2.5 µm, 4.6 mm X 150 mm column. The mobile phase was 100 mM 20 Phosphate, 300 mM Sodium Chloride pH7.0 at 50°C and, and the flowrate was 0.3 mL/min. The antibody material was detected at wavelength 220, 280 and 330 nm at 1 Hz sampling rate during a 10-minute acquisition.

Table 1. Amino acid sequences of the bispecific binding molecule

Bispecific binding molecule Components	Amino Acid Sequence
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SEQ ID NO: 1	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYYSGNTNYPNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYCVDRDVTGAF DIWGQGTMTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPS NTKVDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQD WLNKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSHT PGNSKPTRTPRR
SEQ ID NO: 2	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYYSGNTNYPNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYCVDRDVTGAF DIWGQGTMTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPS NTKVDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQD WLNKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEV QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVSQIS PAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPY YRMSKVMQVWGQGLTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVITICRASQYFSSYLAWYQQKPGKAPKLLIYGASSRASGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQYLGSPPTFGQGTKVEIK
SEQ ID NO: 3	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYYSGNTNYPNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYCVDRDVTGAF DIWGQGTMTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPS NTKVDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQD WLNKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEV QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKLEWVSQIS PAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPY FRMSKVMQVWGQGLTVTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVITICRASQFLSSYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQQYLASPATFGQGTKVEIK

SEQ ID NO: 4	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYSGNTNYPNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVGTAF DIWGQGTMTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPS NTKVDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQD WLNKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEV QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQIS PAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPY YQMSKVMVWGQGTLLTVSSGGGGSGGGGSGGGGSDIQTQSPSSLSA SVGDRVTITCRASQYFSSYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGS GSGDFTLTISLQPEDFATYYCQQLASPATFGQGTKEIK
SEQ ID NO: 5	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYSGNTNYPNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVGTAF DIWGQGTMTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPS NTKVDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQD WLNKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEV QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQIS PAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPFF RMSQVMDVWGQGTLLTVSSGGGGSGGGGSGGGGSDIQTQSPSSLSAS VGDRVTITCRASQFLSSYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGSG SGDFTLTISLQPEDFATYYCQQLASPATFGQGTKEIK
SEQ ID NO: 6	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYSGNTNYPNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVGTAF DIWGQGTMTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPS NTKVDKTVERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVV VDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVSVLTVVHQD WLNKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEV QLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQIS PAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPY FRMSKVMVWGQGTLLTVSSGGGGSGGGGSGGGGSDIQTQSPSSLSA SVGDRVTITCRASQFLSSYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGS GSGDFTLTISLQPEDFATYYCQQLASPATFGQGTKEIK

SEQ ID NO: 7	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYYSGNTNYPNLSKRLTISIDTSKTQFSLKLSSVTAADTAIYCVDRDVTGAF DIWGQGTMTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEV QLVEGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQIS PAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPY FRMSKVMQVWGQGTLLTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSA SVGDRVTITCRASQFLSSYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGS GSGTDFLTISLQPEDFATYYCQQLASPATFGQGTKEIK
SEQ ID NO: 8	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYYSGNTNYPNLSKRLTISIDTSKTQFSLKLSSVTAADTAIYCVDRDVTGAF DIWGQGTMTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEV QLVEGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQIS PAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPY FRMSKVMQVWGQGTLLTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGD RVTITCRASQFLSSYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGSGTDF LTISLQPEDFATYYCQQLASPATFGQGTKEIK
SEQ ID NO: 9	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYYSGNTNYPNLSKRLTISIDTSKTQFSLKLSSVTAADTAIYCVDRDVTGAF DIWGQGTMTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEV QLVEGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQIS PAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPY FRMSKVMQVWGQGTLLTVSSGGGGSGGGGSGGGGSGGGGSDIQMTQS PSSLSASVGDRTITCRASQFLSSYLAWYQQKPGKAPKLLIYGASARASGVPS RFSGSGSGTDFLTISLQPEDFATYYCQQLASPATFGQGTKEIK

SEQ ID NO: 10	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYSGNTNYPNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAF DIWGQGTMTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSDI QMTQSPSSLSASVGRVTITCRASQFLSSYLAWYQQKPGKAPKLLIYGASAR ASGVPSRFSGSGSGTDFLTITSLQPEDFATYYCQOYLASPATFGQGTKVEIK GGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMS WVRQAPGKGLEWVSQISPAAGGYTNYADSVKGRFTISADTSKNTAYLQMNS LRAEDTAVYYCARGELPYFRMSKVMMDVWGQGTLLTVSS
SEQ ID NO: 11	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIG HIYSGNTNYPNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAF DIWGQGTMTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQ DWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQV SLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSR WQQGNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEV QLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQIS PAGGYTNYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGELPYF RMSKVMMDVWGQGTLLTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSP GERATLS CRASQFLSSYLAWYQQKPGQAPRLLIYGASARASGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYCQOYLASPATFGQGTKVEIK
SEQ ID NO: 39	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGH IYSGNTNYPNPSLKSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDI WGQGTMTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVS WNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTK VDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWL NGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCL VKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQISPAAGGYT NYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGELPYHRMSKV MDVWGQGTLLTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSPGERATLS CRASQFLSSYLAWYQQKPGQAPRLLIYGASARASGIPDRFSGSGSGTDFLTIS RLEPEDFAVYYCQOYLASPATFGQGTKVEIK

SEQ ID NO: 12	DIQMTQSPSSLSASVGDRTITCQASQDISNYLNWYQQKPGKAPKLLIYDAS NLETGVPSRFSGSGSGTDFTFTISSLPEDIATYFCQHFHDLPLAFGGGKTKEI KRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSG NSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN RGEC
SEQ ID NO: 13	GGGGS

Table 2. Nucleotide sequences encoding bispecific binding molecule polypeptides

Bispecific binding molecule Components	Polynucleotide Sequence
SEQ ID NO: 14 Encodes polypeptide SEQ ID NO: 1	CAAGTGCAGCTGCAGGAATCCGGCCCCGGGCTTGTGAAGCCTAGCGAA ACACTCTCGCTCACCTGTACTGTCAGCGGTGGATCAGTGTCTCCGGCGA TTACTACTGGACCTGGATTTCGGCAGAGCCCTGAAAGGGACTGGAGTG GATCGGACACATCTACTACTCCGGGAACATACTACAACCCGTCGTTGA AGTCCAGACTGACGATCAGTATCGATACCTCCAAGACCCAGTTCAGCCTG AAGCTGAGCTCAGTGACAGCCGCCGACACTGCAATCTACTACTGCGTGC GGGACAGAGTGACCGGAGCCTTCGACATCTGGGGCCAGGGAACCATGG TCACTGTGTCGTCTGCGTCAACCAAGGGTCCGTCCGTGTTTCCCTGGCC CCGTGCTCGCGGAGCACCTCCGAGTCCACTGCCGCCTTGGGCTGCCTGG TCAAAGACTACTTCCCTGAACCCGTGACTGTCAGCTGGAATCCGGAGCT CTGACCTCGGGAGTGACACCTTCCCGGCCGTGCTGCAATCGAGCGGCC TCTACTCCCTGTCTCCGTGACCGTGCCATCATCAAATTCGGAACCC AAACTTATACGTGCAACGTGACACCAAGCCCTCAATACCAAAGTCGAC AAGACCGTGGAGAGGAAATGCTGCGTGGAGTGTCGCGCTTCCCCCGCG CCGCCGTGGCCGGACCTAGCGTGTTCTGTTCCCGCCGAAGCCAAAGG ACACTCTCATGATCTCCCGCACCCCTGAAGTCACTTGCGTCTGGTGGAC GTTTCCACGAGGATCCCGAAGTGCAGTTCATTGGTACGTGGACGGGG TGGAAGTACATAACGCCAAGACCAAGCCAGGGAAGAAGTTAACTC CACCTTCCGGGTGGTGTGCGTGTCACTGTGGTGCATCAGGATTGGCTC AATGGAAGGAGTACAAGTGCAAAGTGTGAACAAGGGTCTGCCCCGT CCTATTGAAAAGACCATTTCAAAACCAAGGGACAGCCAGAGAGCCTC AGGTCTACACCTGCCTCCGAGCCGCGAGGAAATGACCAAGAACCAAGT GTCTCTGACTTGCCTCGTGAAGGGATTCTACCCCTCCGATATCGCGGTGG AGTGGGAGAGCAACGGGCAGCCAGAGAACAATAAGACCACCCCGC CTATGCTGGACTCCGATGGCTCCTTCTTGTACTCGAAGCTGACCGTG GACAAGTCCCGCTGGCAACAGGGAACGTGTTCAAGCTGTAGCGTGATGC ACGAAGCCCTGCACAACCACTACACCCAGAAGTCCCTGTCGCTTTCCCC GGGAAGGGCGGTGGCGGATCCGGCGGCGGGGGCAGCGGGGCGGCG GTTCCCATACCCCGGGAACCAAAGCCACCCGGAAGTCCACGGCGC
SEQ ID NO: 15 Encodes polypeptide SEQ ID NO: 2	CAGGTTCAAGTGCAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAA CACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTGCTCTGGCGAT TACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGGCCTGGAATGGA TCGGCCACATCTACTACTCCGGCAACCAACTACAACCCAGCCTGAAG TCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAA

	GCTGTCTCTGTGACCGCCGCTGATACCGCCATCTACTATTGCGTGCGGG ACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCAC CGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTT GCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGTCTGGTCAAG GACTACTTCCCTGAGCCTGTGACCGTGCCTGGAATTCTGGCGCTGTGAC ATCTGGCGTGACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACT CTCTGTCTCCGTGCGTGACCGTGCCCTTCTCTAACTTTGGCACCAGACCT ACACCTGTAATGTGGACCACAAGCCATCCAACACCAAGGTGGACAAGAC CGTGAACGGAAGTGCTGCGTGAATGCCCTCCTTGTCTGCTCCTCCTG TGGCTGGCCCTTCCGTGTTTCTGTTCCCTCCAAAGCCTAAGGACACCCTG ATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTC ACGAGGATCCCGAGGTGCAGTTCAATTGGTACGTGGACGCGGTGGAAG TGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCACCTT CAGAGTGGTGTCCGTGCTGACCGTGGTGCATCAGGATTGGCTGAACGG CAAAGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCCTGCTCCTATC GAAAAGACCATCTCTAAGACCAAGGGGCAGCCCCGGAACCTCAGGTTT ACACACTGCCTCCAAGCCGGAAGAGATGACCAAGAACCAGGTGTCCCT GACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGG GAGTCTAATGGCCAGCCTGAGAACAACTACAAGACCACACCTCCTATGC TGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAGTGGACAAG TCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGG CCCTGCACAATCACTACACCCAGAAGTCCCTGTCTCTGTCCCTGGAAAA GGCGGCGGAGGATCTGGCGGAGGCGGTAGCGGTGGTGGCGGATCTGA AGTTCACTGGTTGAATCTGGCGGCGGACTGGTTCAACCAGGCGGATCT CTGAGACTGTCTTGTGCCGCTCCGGCTTCACTTCTCCTTACGCTATG TCCTGGGTCCGACAGGCCCCAGGCAAGGATTGGAGTGGGTGTCCAG ATCTCTCCCGCTGGCGGCTACACCAATTACGCGACTCTGTGAAGGGCA GATTCACCATCTCTGCCGACACCTCCAAGAACACCGCTACCTGCAGATG AACTCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGCGG AGCTGCCCTACTACCGGATGTCCAAAGTGATGGACGTGTGGGGACAGG GAACCTCGTGACAGTTTCTAGCGGTGGCGGAGGTAGCGGAGGCGGTG GAAGCGGCGGAGGCGGAAGTGATATTCAGATGACCCAGTCTCCTTCCAG CCTGTCCGCTTCTGTGGGCGATAGAGTGACCATCACCTGTCCGGCCTCTC AGTACTTCTCCTCCTACCTGGCTTGGTATCAGCAGAAGCCTGGCAAGGCC CCTAAGCTGCTGATCTACGGCGCCTCCTCTAGAGCTAGCGGCGTGCCCTC TAGATTCTCCGGATCTGGCTCTGGCACCGACTTTACCCTGACAATCTCCA GCCTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCAGTACCTGGG CTCTCCTCCAACCTTTGGCCAGGGAACAAAGGTGAGATCAAGCGCTGA
SEQ ID NO: 16 Encodes polypeptide SEQ ID NO: 3	CAGGTTCACTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAA CACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTCTCTTGCGAT TACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGGCCTGGAATGGA TCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAG TCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAA GCTGTCTCTGTGACCGCCGCTGATACCGCATCTACTATTGCGTGCGGG ACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCAC CGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTT GCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGTCTGGTCAAG GACTACTTCCCTGAGCCTGTGACCGTGTCTGGAATTCTGGCGCTGTGAC ATCTGGCGTGACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACT

	CTCTGTCTCCGTGCTGACCGTGCCTTCCTCTAACTTTGGCACCCAGACCT ACACCTGTAATGTGGACCACAAGCCATCCAACACCAAGGTGGACAAGAC CGTGGAACGGAAGTGCTGCGTGGAATGCCCTCCTTGTCCTGCTCCTCCTG TGGCTGGCCCTTCCGTGTTTCTGTTCCCTCCAAAGCCTAAGGACACCCCTG ATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTC ACGAGGATCCCGAGGTGCAGTTCAATTGGTACGTGGACGGCGTGGAAG TGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCACCTT CAGAGTGGTGTCCGTGCTGACCGTGGTGCATCAGGATTGGCTGAACGG CAAAGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTGCTCCTATC GAAAAGACCATCTCTAAGACCAAGGGGCAGCCCCGGAACCTCAGGTTT ACACACTGCCTCCAAGCCGGAAGAGATGACCAAGAACCAGGTGTCCCT GACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGG GAGTCTAATGGCCAGCCTGAGAACAACTACAAGACCACACCTCCTATGC TGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAGTGGACAAG TCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGG CCCTGCACAATCACTACACCAGAAGTCCCTGTCTGTGCCCTGGAAAA GGCGGGCGAGGATCTGGCGGAGGCGGTAGCGGTGGTGGCGGATCTGA AGTTCAGCTGGTTGAATCTGGCGGCGGACTGGTTCAACCAGGCGGATCT CTGAGACTGTCTTGCGCCCTCCGGCTTACCTTCTCCTTACGCTATG TCCTGGGTCCGACAGGCCCCAGGCAAAGGATTGGAGTGGGTGTCCCAG ATCTCTCCCGCTGGCGGCTACACCAATTACGCCGACTCTGTGAAGGGCA GATTCACCATCTCTGCCGACACCTCCAAGAACACCGCTACCTGCAGATG AACTCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGGCG AGCTGCCCTACTCCGGATGTCCAAAGTGATGGACGTGTGGGGACAGG GAACCCTCGTGACAGTTTCTAGCGGTGGCGGAGGTAGCGGAGGCGGTG GAAGCGGCGGAGGCGGAAGTGATATTCAGATGACCCAGTCTCCTTCCAG CCTGTCCGCTTCTGTGGGCGATAGAGTGACCATCACCTGTCCGGCCTCTC AGTTCCTGTCTCCTACCTGGCTTGGTATCAGCAGAAGCCTGGCAAGGCC CCTAAGCTGCTGATCTACGGCGCTTCTGCTAGAGCTTCCGGCGTGCCCTC CAGATTTTCTGGCTCTGGATCTGGCACCGACTTTACCCTGACAATCTCCA GCCTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCAGTACCTGGCC TCTCCTGCCACATTTGGCCAGGGAACAAAGGTCGAGATCAAGCGCTGA
SEQ ID NO: 17 Encodes polypeptide SEQ ID NO: 4	CAGGTTCACTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAA CACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTGTCTCTGGCGAT TACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGGCTGGAATGGA TCGGCCACATCTACTACTCCGGCAACCAACTACAACCCAGCCTGAAG TCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAA GCTGTCTCTGTGACCGCCGCTGATACCGCATCTACTATTGCGTGCGGG ACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATTGGTCAC CGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCTCTGGCTCCTT GCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGTCTGGTCAAG GACTACTTCCCTGAGCCTGTGACCGTGTCTGGAATTCTGGCGCTCTGAC ATCTGGCGTGACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACT CTGTCTCCTCCGTGCTGACCGTGCCTTCCTCTAACTTTGGCACCCAGACCT ACACCTGTAATGTGGACCACAAGCCATCCAACACCAAGGTGGACAAGAC

	CGTGGAACGGAAGTGCTGCGTGGAATGCCCTCCTTGTCTGCTCCTCCTG TGGCTGGCCCTTCGGTGTTCCTGTTCCCTCCAAAGCCTAAGGACACCCCTG ATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTC ACGAGGATCCCGAGGTGCAGTTCAATTGGTACGTGGACGGCGTGGAAG TGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCACCTT CAGAGTGGTGTCCGTGCTGACCGTGGTGCATCAGGATTGGCTGAACGG CAAAGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTGCTCCTATC GAAAAGACCATCTCTAAGACCAAGGGGCAGCCCCGGAACCTCAGGTTT ACACACTGCCTCAAGCCGGAAGAGATGACCAAGAACCAGGTGTCCCT GACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGG GAGTCTAATGGCCAGCCTGAGAACAACCTACAAGACCACACCTCCTATGC TGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAGTGGACAAG TCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGG CCCTGCACAATCACTACACCCAGAAGTCCCTGTCTGTGCCCTGGAAAA GGCGGCGGAGGATCTGGCGGAGGCGGTAGCGGTGGTGGCGGATCTGA AGTTCAGCTGGTTGAATCTGGCGGCGGACTGGTTCAACCAGGCGGATCT CTGAGACTGTCTTGTCGCCCTCCGGCTTACCTTCTCCTTACGCTATG TCCTGGGTCCGACAGGCCCCAGGCAAAGGATTGGAGTGGGTGTCCAG ATCTCTCCCGCTGGCGGCTACACCAATTACGCCGACTCTGTGAAGGGCA GATTCACCATCTCTGCCGACACCTCCAAGAACACCGCTACCTGCAGATG AACTCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGGCG AGCTGCCCTACTACCAGATGTCCAAAGTGATGGACGTGTGGGACAGG GAACCCCTCGTGACAGTTTCTAGCGGTGGCGGAGGTAGCGGAGGCGGTG GAAGCGGCGGAGGCGGAAGTGATATTCAGATGACCCAGTCTCCTTCCAG CCTGTCCGCTTCTGTGGGCGATAGAGTGACCATCACCTGTCCGGCCTCTC AGTACTTCTCTTCTATCTGGCATGGTATCAGCAGAAGCCTGGCAAGGCC CCTAAGCTGCTGATCTACGGCGCTTCTGCTAGAGCTTCCGGCGTGCCCTC CAGATTTTCTGGCTCTGGATCTGGCACCGACTTTACCCTGACAATCTCCA GCCTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCAGTACCTGGCC TCTCCTGCCACATTTGGCCAGGGAACAAAGGTCGAGATCAAGCGCTGA
SEQ ID NO: 18 Encodes polypeptide SEQ ID NO: 5	CAGGTTCACTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAA CACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTCTCCTTGGCGAT TACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGGCCCTGGAATGGA TCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAG TCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAA GCTGTCTCTGTGACCGCCGCTGATACCGCCATCTACTATTGCGTGCGGG ACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCAC CGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCTCTGGCTCCTT GCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGTCTGGTCAAG GACTACTTCCCTGAGCCTGTGACCGTGTCTGGAATTCTGGCGCTCTGAC ATCTGGCGTGCACACCTTCCAGCTGTGCTGCAGTCTAGCGGCCCTGTACT CTCTGTCTCCGTCTGTGACCGTGCCTTCTCTAATTTGGCACCCAGACCT ACACCTGTAATGTGGACCACAAGCCATCCAACACCAAGGTGGACAAGAC CGTGGAACGGAAGTGCTGCGTGGAATGCCCTCCTTGTCTGCTCCTCCTG TGGCTGGCCCTTCGGTGTTCCTGTTCCCTCCAAAGCCTAAGGACACCCCTG

	ATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTC ACGAGGATCCCGAGGTGCAGTTCAATTGGTACGTGGACGGCGTGGAAG TGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCACCTT CAGAGTGGTGTCCGTGCTGACCGTGGTGCATCAGGATTGGCTGAACGG CAAAGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCGTGCTCCTATC GAAAAGACCATCTCTAAGACCAAGGGGCAGCCCCGGAACCTCAGGTTT ACACACTGCCTCCAAGCCGGGAAGAGATGACCAAGAACCAGGTGTCCCT GACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGG GAGTCTAATGGCCAGCCTGAGAACAACCTACAAGACCACACCTCCTATGC TGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAGTGGACAAG TCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGG CCCTGCACAATCACTACACCCAGAAGTCCCTGTCTGTGCCCTGGAAAA GGCGGCGGAGGATCTGGCGGAGCGGGTAGCGGTGGTGGCGGATCTGA AGTTCAGCTGGTTGAATCTGGCGGCGGACTGGTTCAACCAGGCGGATCT CTGAGACTGTCTTGTCGCCCTCCGGCTTACCTTCTCCTTTACGCTATG TCCTGGGTCCGACAGGCCCCAGGCAAAGGATTGGAGTGGGTGTCCCAG ATCTCTCCCGCTGGCGGCTACACCAATTACGCCGACTCTGTGAAGGGCA GATTCACCATCTCTGCCGACACCTCCAAGAACACCGCTACCTGCAGATG AACTCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGGCG AGCTGCCATTCTCCGGATGTCCCAAGTGATGGACGTGTGGGGACAGGG AACCCTCGTGACAGTTTCTAGCGGTGGCGGAGGTAGCGGAGGCGGTGG AAGCGGCGGAGGCGGAAGTGATATTCAGATGACCCAGTCTCCTTCCAGC CTGTCCGCTTCTGTGGGCGATAGAGTGACCATCACCTGTGGGCCCTCTCA GTTCTGTCTAGTTATCTGGCATGGTATCAGCAGAAGCCCCGGCAAGGCT CCCAAGCTGTTGATCTACGGCGCCTCTGCTAGAGCTTCCGGCGTGCCATC TAGATTCTCCGGCTCTGGCTCTGGCACCGACTTTACCTGACAATCTCCA GCCTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCAGTACCTGGCC TCTCCTGCCACATTTGGCCAGGGAACAAAGGTCGAGATCAAGCGCTGA
SEQ ID NO: 19 Encodes polypeptide SEQ ID NO: 6	CAGGTTCACTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAA CACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTCTCCTTGGCGAT TACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGGCTGGAATGGA TCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAG TCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAA GCTGTCTCTGTGACCGCCGCTGATACCGCCATCTACTATTGCGTGCGGG ACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCAC CGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTT GCTCCAGATCCACCTCCGAGTCTACAGCTGCTCTGGGCTGTCTGGTCAAG GACTACTTCCCTGAGCCTGTGACCGTGTCTGGAATTCTGGCGCTCTGAC ATCTGGCGTGCACACCTTTCAGCTGTGCTGCAGTCTAGCGGCCCTGTACT CTCTGTCTCCGTGCTGACCGTGCTTCCCTAACTTTGGCACCCAGACCT ACACCTGTAATGTGGACCACAAGCCATCCAACACCAAGGTGGACAAGAC CGTGAACGGAAGTGCTGCGTGGAATGCCCTCCTTGTCTGCTCCTCTG TGGCTGGCCCTTCCGTGTTTCTGTTCCCTCCAAGCCTAAGGACACCCTG ATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTC ACGAGGATCCCGAGGTGCAGTTCAATTGGTACGTGGACGGCGTGGAAG

	TGCACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCACCTT CAGAGTGGTGCCGTGCTGACCGTGGTGCATCAGGATTGGCTGAACGG CAAAGAGTACAAGTGCAAGGTGTCCAACAAGGGCCTGCCTGCTCCTATC GAAAAGACCATCTCTAAGACCAAGGGGCAGCCCCGGAACCTCAGGTTT ACACACTGCCTCCAAGCCGGAAGAGATGACCAAGAACCAGGTGTCCCT GACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGG GAGTCTAATGGCCAGCCTGAGAACAACACAAGACCACACCTCCTATGC TGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAGTGGACAAG TCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGG CCCTGCACAATCACTACACCAGAAGTCCCTGTCTGTGCCCTGGAAAA GGCGGCGGAGGATCTGGCGGAGCGGTAGCGGTGGTGGCGGATCTGA AGTTCAGCTGGTTGAATCTGGCGGCGGACTGGTTCAACCAGGCGGATCT CTGAGACTGTCTTGCCGCTCCGGCTTACCTTCTCCTCTTACGCTATG TCCTGGGTCCGACAGCCCCAGGCAAAGGATTGGAGTGGGTGTCCCAG ATCTCTCCCGCTGGCGGCTACACCAATTACGCCGACTCTGTGAAGGGCA GATTCACCATCTCTGCCGACACCTCCAAGAACACCGCTACCTGCAGATG AACTCCCTGAGAGCCGAGGACACCGCGTGTACTATTGTGCTAGAGGCG AGCTGCCCTACTTCCAGATGTCCAAAGTGATGGACGTGTGGGGACAGGG AACCCTCGTGACAGTTTCTAGCGGTGGCGGAGGTAGCGGAGGCGGTGG AAGCGGCGGAGGCGGAAGTGATATTCAGATGACCCAGTCTCCTTCCAGC CTGTCCGCTTCTGTGGGCGATAGAGTGACCATCACCTGTGGGCTCTCA GTACTTCTACTCCTATCTGGCTTGGTATCAGCAGAAGCCTGGCAAGGCCC CTAAGCTGTGATCTACGGCGCTTCTGCTAGAGCTTCCGGCGTGCCCTCC AGATTTTCTGGCTCTGGATCTGGCACCGACTTTACCTGACAATCTCCAG CCTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCAGTACCTGGCCT CTCCTGCCACATTTGGCCAGGGAACAAAGGTGAGATCAAGCGCTGA
SEQ ID NO: 20 Encodes polypeptide SEQ ID NO: 7	CAGGTTGAGCTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAA CACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTCTCCTTGCGGAT TACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGGCCTGGAATGGA TCGGCCACATCTACTACTCCGGCAACCAACTACAACCCAGCCTGAAG TCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAA GCTGTCTCTGTGACCGCCGCTGATACCGCCATCTACTATTGCGTGCGGG ACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCAC CGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCTCTGGCTCCTT CCAGCAAGTCTACCTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAA GGACTACTTCCCTGAGCCTGTGACCGTGTCTGGAATTCTGGCGCTCTGA CATCTGGCGTGCACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTAC TCTCTGTCTCCGTGCGTACCGTGCCTTCTAGCTCTCTGGGCACCCAGAC CTACATCTGCAATGTGAACCACAAGCCATCCAACACCAAGGTGGACAAG AAGGTGGAACCAAGTCTGCGACAAGACCCACACCTGTCTCCTCATGTC CTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCTGTTTCTCCAAAG CCTAAGGACACCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGG TGGTGGATGTGTCTCACGAGGATCCCGAAGTGAAGTTCAATTGGTACGT GGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCTAGAGAGGAACA GTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGTGCACCAAG

	GATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCC CTGCCTGCTCCTATCGAAAAGACCATCAGCAAGGCTAAGGGCCAGCCTC GGGAACCCAGGTTTACACATTGCCTCCATCTCGGGACGAGCTGACCAA GAACCAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATA TCGCCGTGGAATGGGAGTCCAATGGCCAGCCTGAGAACAACCTACAAGA CAACCCCTCCTGTGCTGGACTCCGACGGCTCATTCTTCTGTACTCCAAG CTGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCT CCGTGATGCACGAGGCCCTGCACAATCACTACCCAGAAGTCCCTGTCT CTGTCCCCTGAAAAGGCGGCGGAGGATCTGGCGGAGGTGGAAGCGG AGGCGGTGGATCTGAAGTGCAGCTGGTTGAAAGTGGCGGCGGATTGGT TCAGCCTGGCGGATCTCTGAGACTGTCTTGTCGCCCTCCGGCTTTACCT TCTCCTCTACGCTATGTCTGGGTCCGACAGGCTCCCGAAAAGGACTT GAATGGGTGTCCAGATCTCCCTGCTGGCGGCTACACCAATTACGCCG ACTCTGTGAAGGGCAGATTACCATCTCTGCCGACACCTCCAAGAACC GCCTACCTGCAGATGAACCTCCTGAGAGCCGAGGACACCGCCGTGTACT ATTGTGCTAGAGGCGAGCTGCCCTACTCCGGATGTCAAAGTGATGGA CGTGTGGGACAGGGAACCCTCGTGACAGTTTCTAGTGGTGGCGGAGG AAGCGGCGGAGGCGGTTCTGGCGGTGGTGGATCTGATATCCAGATGAC CCAGTCTCCTAGCAGCCTGTCTGCCTCTGTGGGCGATAGAGTGACCATCA CCTGTCCGGCCTCTCAGTTCCTGTCCAGCTACCTGGCTTGGTATCAGCAG AAGCCTGGCAAGGCCCTAAGCTGCTGATCTACGGCGCTTCTGCTAGAG CTTCCGGCGTGCCCTCCAGATTTTCTGGCTCTGGATCTGGCACCGACTTT ACCCTGACAATCTCCAGCCTGCAGCCTGAGGACTTCGCCACCTACTACTG CCAGCAGTACCTGGCCTCTCCTGCCACATTTGCCAGGGAACAAAGGTC GAGATCAAGCGCTGA
SEQ ID NO: 21 Encodes polypeptide SEQ ID NO: 8	CAGGTTGAGCTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAA CACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTCTCCTTGGCGAT TACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGGCCTGGAATGGA TCGGCCACATCTACTACTCCGGCAACCAACTACAACCCAGCCTGAAG TCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAA GCTGTCTCTGTGACCGCCGCTGATACCGCCATCTACTATTGCGTGCGGG ACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCAC CGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCTCTGGCTCCTT CCAGCAAGTCTACCTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAA GGACTACTTCCCTGAGCCTGTGACCGTGTCTGGAATTCTGGCGCTCTGA CATCTGGCGTGCACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTAC TCTCTGTCTCCGTCTGACCGTGCTTCTAGCTCTCTGGGCACCCAGAC CTACATCTGCAATGTGAACCACAAGCCATCCAACCAAGGTGGACAAG AAGGTGGAACCAAGTCTGCGACAAGACCCACACCTGTCCTCCATGTC CTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCTGTTTCTCCAAAG CCTAAGGACACCCGTATGATCTCTCGGACCCCTGAAGTGACCTGCGTGG TGGTGGATGTGTCTACGAGGATCCCGAAGTGAAGTTCAATTGGTACGT GGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCTAGAGAGGAACA GTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGTGCACCAG GATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCC

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SEQ ID NO: 22 Encodes polypeptide SEQ ID NO: 9	CAGGTTCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAA CACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTCTCCTTGGCGAT TACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGCCTGGAATGGA TCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAG TCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAA GCTGTCTCTGTGACCGCGCTGATACCGCCATCTACTATTGCGTGCGGG ACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCAC CGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCTCTGGCTCCTT CCAGCAAGTCTACCTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAA GGACTACTTCCCTGAGCCTGTGACCGTGTCTGGAATTCTGGCGCTCTGA CATCTGGCGTGCACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCTGTAC TCTCTGTCTCCGTCTGTGACCGTGCCTTCTAGCTCTCTGGGCAACAGAC CTACATCTGCAATGTGAACCACAAGCCATCCAACACCAAGGTGGACAAG AAGGTGGAACCCAAGTCTGCGACAAGACCCACACCTGTCTCCATGTC CTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCTGTTCTCCAAAG CCTAAGGACACCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGG TGGTGGATGTGTCTCACGAGGATCCCGAAGTGAAGTTCAATTGGTACGT GGACGGCGTGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACA GTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGTGCACCAG GATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCC CTGCCTGCTCCTATCGAAAAGACCATCAGCAAGGCTAAGGGCCAGCCTC GGGAACCCCAGGTTTACACATTGCCTCCATCTCGGGACGAGCTGACCAA

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SEQ ID NO: 23 Encodes polypeptide SEQ ID NO: 10	CAGGTTCACTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTCCGAAA CACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTCTCCTGGCGAT TACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGCCCTGGAATGGA TCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAG TCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAA GCTGTCTCTGTGACCGCCGCTGATACCGCCATCTACTATTGCGTGCGGG ACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCAC CGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCTCTGGCTCCTT CCAGCAAGTCTACCTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAA GGACTACTTCCCTGAGCCTGTGACCGTGTCTGGAATTCTGGCGCTCTGA CATCTGGCGTGCACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTAC TCTCTGTCTCCGTCTGTGACCGTGCCTTCTAGCTCTCTGGGCAACCCAGAC CTACATCTGCAATGTGAACCACAAGCCATCCAACACCAAGGTGGACAAG AAGGTGGAACCAAGTCTGCGACAAGACCCACACCTGTCTCTCATGTC CTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCTGTTTCTCCAAAG CCTAAGGACACCCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGG TGGTGGATGTGTCTCACGAGGATCCCGAAGTGAAGTTCAATTGGTACGT GGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACA GTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGTGCACACG GATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCC CTGCCGTGCTCTATCGAAAAGACCATCAGCAAGGCTAAGGGCCAGCCTC GGGAACCCAGGTTTACACATTGCCTCCATCTCGGGACGAGCTGACCAA GAACCAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATA

	TCGCCGTGGAATGGGAGTCCAATGGCCAGCCTGAGAACAACCTACAAGA CAACCCCTCCTGTGCTGGACTCCGACGGCTCATTCTTCTGTACTCCAAG CTGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCT CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCT CTGTCCCTTGAAAAGGCGGCGGAGGATCTGGCGGAGGTGGAAGCGG AGGCGGTGGATCTGATATCCAGATGACCCAGTCTCCTAGCAGCCTGTCT GCCTCTGTGGCGATAGAGTGACCATCACCTGTCGGGCCTCTCAGTTCT GTCCAGCTACCTGGCTTGGTATCAGCAGAAGCCTGGCAAGGCCCTAAG CTGCTGATCTACGGCGCTTCTGCTAGAGCTTCCGGCGTGCCCTCCAGATT TTCTGGCTCTGGATCTGGCACCGACTTTACCCTGACAATCTCCAGCCTGC AGCCTGAGGACTTCGCCACCTACTACTGCCAGCAGTACCTGGCCTCTCCT GCCACATTTGGCCAGGGAACAAAGGTGGAATCAAAGGTGGCGGCGGT AGTGGTGGCGGAGGAAGCGGCGGAGGCGGCTCTGAAGTTCAGCTTGTT GAATCTGGCGGCGGACTGGTTCAGCCTGGCGGATCTCTGAGACTGTCTT GTGCCGCCAGCGGCTTACCTTCTCCTTTACGCTATGTCTGGGTCCGA CAGGCCCCAGGCAAAGGATTGGAGTGGGTGTCCAGATCTCTCCTGCTG GCGGCTACACCAATTACGCCGACTCTGTGAAGGGCAGATTACCATCTCT GCCGACACCTCCAAGAACACCGCCTACCTGCAGATGAACCTCCTGAGAG CCGAGGACACCGCGTGTACTATTGTGCTAGAGGCGAGCTGCCCTACTT CCGGATGTCAAAGTGATGGACGTGTGGGGACAGGGAACCTCGTGAC AGTGTCTCTTGA
SEQ ID NO: 24 Encodes polypeptide SEQ ID NO: 11	CAGGTTGAGCTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCGAAA CACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTCTCCTTGCGCAT TACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGGCTGGAATGGA TCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAG TCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAA GCTGTCTCTGTGACCGCGCTGATACCGCATCTACTATTGCGTGCGGG ACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCAC CGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCTCTGGCTCCTT CCAGCAAGTCTACCTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAA GGACTACTTCCCTGAGCCTGTGACCGTGTCTGGAATTCTGGCGCTCTGA CATCTGGCGTGCACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTAC TCTCTGTCTCCGTCTGTGACCGTGCCTTCTAGCTCTCTGGGACCCAGAC CTACATCTGCAATGTGAACCACAAGCCATCCAACACCAAGGTGGACAAG AAGGTGGAACCCAAGTCTGCGACAAGACCCACACCTGTCTCCTCATGTC CTGCTCCAGAAGTCTGCTCGGCGGACCTTCCGTGTTCTGTTTCTCCAAAG CCTAAGGACACCCGTATGATCTCTCGGACCCCTGAAGTGACCTGCGTGG TGGTGGATGTGTCTCACGAGGATCCCGAAGTGAAGTTCAATTGGTACGT GGACGGCGTGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGGAACA GTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGTGCACCAG GATTGGCTGAACGGCAAAGAGTACAAGTGCAAGGTGTCCAACAAGGCC CTGCCGTGCTCTATCGAAAAGACCATCAGCAAGGCTAAGGGCCAGCCTC GGGAACCCAGGTTTACACATTGCCTCCATCTCGGGACGAGCTGACCAA GAACCAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTACCCCTCCGATA TCGCCGTGGAATGGGAGTCCAATGGCCAGCCTGAGAACAACCTACAAGA

	CAACCCCTCCTGTGCTGGACTCCGACGGCTCATTCTTCTGTACTCCAAG CTGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCT CCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCT CTGTCCCCTGGAAAAGGCGGCGGAGGATCTGGCGGAGGTGGAAGCGG AGGCGGTGGATCTGAAGTGCAGCTGTTGGAAAGTGGCGGCGGATTGGT TCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCCCTCCGGCTTTACCT TCTCCTCCTACGCTATGTCTGGGTCCGACAGGCTCCCGGAAAAGGACTT GAATGGGTGTCCAGATCTCCCTGCTGGCGGCTACACCAATTACGCCG ACTCTGTGAAGGGCAGATTCACCATCTCTCGGGACAACCTCAAAGAACAC CCTGTACCTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTAC TATTGTGCTAGAGGCGAGCTGCCCTACTTCCGGATGTCCAAAGTGATGG ACGTGTGGGGACAGGGAACCCCTCGTGACAGTTTCTAGTGGTGGCGGAG GAAGCGGCGGAGGCGGTTCTGGCGGTGGCGGATCTGAAATTGTGCTGA CCCAGTCTCCAGGCACACTCAGTTTGAGCCCTGGCGAGAGAGCTACCCT GAGCTGTAGAGCCTCTCAGTTCCTGTCCAGCTACCTGGCTTGGTATCAGC AGAAGCCAGGACAGGCCCTCGGCTGTTGATCTATGGCGCTTCTGCTAG AGCCAGCGGCATCCCTGATAGATTCTCCGGCTCTGGCTCTGGCACCGACT TCACCCTGACAATCTCCCGCTGGAACCTGAGGACTTCGCTGTGTACTAC TGCCAGCAGTACCTGGCCTCTCCTGCCACATTTGCCAGGGAACAAAGG TCGAGATCAAGTGA
SEQ ID NO: 40 Encodes polypeptide SEQ ID NO: 39	CAGGTTCACTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAACA CTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTGCTCTGGCGATTACT ACTGGACCTGGATCCGGCAGTCTCCTGGCAAAGGCCTGGAATGGATCGGC CACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGGC TGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCTC TGTGACCGCCGCTGATACCGCCATCTACTATTGCGTGCGGGACAGAGTGAC CGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCACCGTGTCCAGTGC TTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTACC TCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAG CCTGTGACCGTGTCTGGAATTCTGGCGCTCTGACATCTGGCGTGACACCT TTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACTCTCTGTCTCCGTCGTGAC CGTGCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACCAC AAGCCATCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCTGCGA CAAGACCCACACCTGTCTCCATGTCTGCTCCAGAACTGCTCGGCGGACCT TCCGTGTTCTGTTTCTCCAAAGCCTAAGGACACCTGATGATCTCTCGGA CCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTACGAGGATCCCGAA GTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGACAAACGCCAAGAC CAAGCCTAGAGAGGAACAGTACAACCTCCACCTACAGAGTGGTGTCCGTGCT GACCGTGCTGCACAGGATTGGCTGAACGGCAAAGAGTACAAGTGCAAGG TGTCCAACAAGGCCCTGCCTGCTCCTATCGAAAAGACCATCAGCAAGGCTA AGGGCCAGCCTCGGGAACCCAGGTTTACACATTGCCTCCATCTCGGACG AGCTGACCAAGAACCAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTACC CCTCCGATATCGCCGTGGAATGGGAGTCCAATGGCCAGCCTGAGAACAAC ACAAGACAACCCCTCTGTGCTGGACTCCGACGGCTCATTCTTCTGTACTC CAAGCTGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCT GCTCCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGT

	CTCTGTCCCCTGGAAAAGGCGGCGGAGGATCTGGCGGAGGTGGAAGCGG AGGCGGTGGATCTGAAGTGCAGCTGTTGGAAAGTGGCGGCGGATTGGTTC AGCCTGGCGGATCTCTGAGACTGTCTTGCCGCCTCCGGCTTTACCTTCTC CTCCTACGCTATGTCTGGGTCCGACAGGCTCCCGGAAAAGGACTTGAATG GGTGTCCCAGATCTCCCCTGCTGGCGGCTACACCAATTACGCCGACTCTGT GAAGGGCAGATTACCATCTCTCGGGACAACCTCAAGAACACCCTGTACCT GCAGATGAATCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAG AGGCGAGCTGCCCTACCACCGGATGTCCAAAGTGATGGATGTGTGGGGAC AGGGAACCCCTCGTGACAGTCTCTAGTGGTGGCGGAGGAAGCGGCGGAGG CGGTTCTGGCGGTGGCGGATCTGAAATTGTGCTGACCCAGTCTCCAGGCAC ACTCAGTTTGAGCCCTGGCGAGAGAGCTACCCTGAGCTGTAGAGCCTCTCA GTTCTGTCCAGCTACCTGGCTTGGTATCAGCAGAAGCCAGGACAGGCCCC TCGGCTGTTGATCTATGGCGCTTCTGCTAGAGCCAGCGGCATCCCTGATAG ATTCTCCGGCTCTGGCTCTGGCACCGACTTCACCCTGACAATCTCCCGGCTG GAACCTGAGGACTTCGCTGTGTACTACTGCCAGCAGTACCTGGCCTCTCT GCCACATTTGGCCAGGGAACAAAGGTCGAGATCAAG
SEQ ID NO: 25 Encodes polypeptide SEQ ID NO: 12	GACATCCAGATGACCCAGTCTCCATCATCCCTGTCGGCCTCAGTGGGCGA CAGAGTGACCATCACTTGTCAAGCCTCCCAAGACATTAGCAACTACCTGA ACTGGTACCAGCAGAAGCCCGAAAGGCCCGAAGCTGCTCATCTATGA CGCTTCCAACCTTGAGACTGGAGTGCCTTCGCGCTTCTCCGGCTCCGGGA GCGGTACCGATTTACCTTCACCATCTCCTCCCTGCAACCCGAGGACATT GCGACTTACTTCTGCCAACATTTGATCACCTCCCTCTCGGTTCCGGCGG CGGAATAAGGTCGAGATTAAGCGGACCGTGGCTGCCCGTCCGTGTTT ATCTTCCCGCCGTCCGATGAACAGCTGAAGTCCGGTACCGCATCAGTCGT GTGCTTGCTGAACAACCTTCTACCCCGGGAAGCCAAGTCCAGTGGA GTGGACAATGCGCTCGAGTCGGGAACTCGCAGGAATCCGTGACCGAA CAGGATTCGAAGGACAGCACATACAGCCTGTATCCACCCTCACGCTGTC GAAGGCCGACTACGAGAAGCACAAAGTGTACGCCTGCGAAGTGACCCA CCAAGGGCTTAGCAGCCCTGTGACCAAGTCCTCAACCGCGGAGAGTGC
SEQ ID NO: 26 Encodes polypeptide SEQ ID NO: 13	GGCGGCGGGGGCAGC
SEQ ID NO: 27 Encodes polypeptide SEQ ID NO: 13	GGGGGCGGCGGTTCC
SEQ ID NO: 28 Encodes polypeptide SEQ ID NO: 13	GGCGGCGGAGGATCT
SEQ ID NO: 29 Encodes polypeptide SEQ ID NO: 13	GGCGGAGGCGGTTAGC
SEQ ID NO: 30 Encodes polypeptide SEQ ID NO: 13	GGTGGTGGCGGATCT

SEQ ID NO: 31 Encodes polypeptide SEQ ID NO: 13	GGCGGCGGAGGATCT
SEQ ID NO: 32 Encodes polypeptide SEQ ID NO: 13	GGCGGAGGTGGAAGC
SEQ ID NO: 33 Encodes polypeptide SEQ ID NO: 13	GGAGGCGGTGGATCT
SEQ ID NO: 34 Encodes polypeptide SEQ ID NO: 13	GGTGGCGGAGGAAGC
SEQ ID NO: 35 Encodes polypeptide SEQ ID NO: 13	GGCGGAGGCGGTTCT
SEQ ID NO: 36 Encodes polypeptide SEQ ID NO: 13	GGCGGTGGCGGATCT
SEQ ID NO: 37 Encodes polypeptide SEQ ID NO: 13	GGCGGTGGCGGATCC
SEQ ID NO: 38 Encodes polypeptide SEQ ID NO: 13	GGCGGCGGGGGCAGC

Example 2. Bispecific binding molecule binding affinity to EGFR and NRP1

BLI binding studies using the Octet red 96 system were conducted to assess the binding of the bispecific antibodies to recombinant hu EGFR and huNRP1. Briefly, commercially sourced biotinylated huEGFR and huNRP1 were immobilized on Streptavidin (Sa) biosensors and interrogated with the produced constructs for binding and characterization. Using BLI technology, the binding to the constructs was evaluated for both kinetics and binding affinity (equilibrium binding constant, KD) and were assessed in the bivalent format. These studies were performed to determine if tumor associated essential receptor targeting antibodies (TAER-TAB) bind cancer targets (EGFR and NRP1) with and to assess their affinity for the targets. The constructs binding huEGFR and huNRP1 as well as the KD determination were performed using the Octet Red 96 system.

huEGFR and huNRP1 (in their respective immobilization columns) were immobilized at a concentration of 0.2 µg/ml (load signal range if 0.2-0.4 nanometers) in 2X Kinetic buffer onto Sa biosensors with a loading time of 180 seconds for each. Baseline post- loading was performed

for 60 seconds. Association of the constructs starting at 100nM (10nM for high affinity binding) followed by 2 1:1 serial dilution and then a fourth well with only buffer (blank). Dissociation of the constructs followed in the baseline wells. Reference sensors were generated by applying the constructs over a blank AMC biosensors or streptavidin biosensors surface. The association and dissociation steps were 600 seconds each. The data were analyzed using the Octet analysis software with 1:1 and 2:1 model fit applied which reports a dissociation constant K_D (M).

All EGFRxNRP1 bispecific antibody constructs, including construct 1 (SEQ ID NOs: 1 and 12) and construct 11 (SEQ ID NOs: 11 and 12), have binding affinity with double digit picomolar for EGFR. see Table 3. For NRP1 binding, EGFRxNRP1 bispecific antibody constructs 2, 3, 5, 7, 9, 10, and 11 exhibited sub-nanomolar affinity, while the construct 1 binds to NRP1 at double digit nanomolar. **FIGS. 2A-2K** show binding affinity curves to immobilized huEGFR for bispecific antibodies. **FIGS. 3A-3K** show binding affinity curves of EGFRxNRP1 antibodies for immobilized huNRP1.

Table 3. Binding Affinity of EGFRxNRP1 Antibodies for EGFR and NRP1

Construct No.	Bispecific binding antibody (heavy and light chains)	Binding affinity (K_D)	
		EGFR (nM)	NRP1 (nM)
Construct 1	SEQ ID NO: 1 and 12	0.05	69.7
Construct 2	SEQ ID NO: 2 and 12	<0.1	0.19
Construct 3	SEQ ID NO: 3 and 12	<0.1	0.53
Construct 4	SEQ ID NO: 4 and 12	<0.1	8.8
Construct 5	SEQ ID NO: 5 and 12	<0.1	0.72
Construct 6	SEQ ID NO: 6 and 12	<0.1	3.76
Construct 7	SEQ ID NO: 7 and 12	<0.1	0.28
Construct 8	SEQ ID NO: 8 and 12	<0.1	2
Construct 9	SEQ ID NO: 9 and 12	<0.1	0.88
Construct 10	SEQ ID NO: 10 and 12	<0.1	0.25
Construct 11	SEQ ID NO: 11 and 12	<0.1	0.25

Example 3. VEGFR2 signaling inhibition in HUVEC cells

Inhibition of VEGFR2 signaling by EGFRxNRP1 bispecific antibody was tested in HUVEC cells by probing electrophoresed cell lysates with anti-phospho-VEGFR2 on western blots. The HUVEC cells were grown in 6 well plates in EBM-2 medium supplemented with EGM-2 SingleQuots overnight. Next day, cells were incubated with 2 ml of F-12K medium with

0.1 mg/ml heparin, endothelial cell growth supplement and 10% FBS for 4 hours. To see the dose dependent response to EGFRxNRP1 antibodies, cells were treated with EGFRxNRP1 bispecific antibody serially diluted by sixfold from the highest concentration of 1 μ M to lowest concentration 0.005 μ M with serum free media for 30 minutes, followed by 2.2 ng/ml of VEGF165 or control for 10 minutes. Cell lysates were prepared by collecting cells with a cell scraper and incubating with 100 μ l of NP-40 lysis buffer with protease/phosphatase inhibitors for 20 minutes on ice. Supernatant lysate was collected after centrifugation at 13,000 rpm for 10 minutes into a new tube, measured for protein quantification using BCA protein assay, and denatured at 70°C for 10 minutes after mixing with NuPAGE LDS sample buffer and LDS sample reducing buffer.

The cell lysates equal to 10 μ g were loaded with 4 μ l of PageRuler Plus prestained protein ladder into 4-12% Bis-Tris Gel and run at 200 V for 45 minutes. Gels were washed with distilled water and transferred to membranes using IBlot2 Drying Blotting System. Membranes were blocked with 5% milk in 1x TBST at room temperature for an hour and incubated with Anti-phospho-VEGFR2 (Y1175) in 5% milk in 1xTBST at 4C overnight. Next day, membranes were washed with TBST for 10 minutes three times and incubated with a secondary antibody in 5% milk at room temperature for an hour. Membranes were washed with 1xTBST for 10 minutes three times. Then, membranes were incubated with SuperSignal Femto Chemiluminescent substrate for 1-2 minutes and imaged with Amersham ImageQuant 800. Blots were then stripped with Restore Plus western Blot stripping buffer for 15 minutes on rocker at room temperature followed by 1x TBST washing three times and the procedure was repeated from milk blocking followed by incubation of primary Anti-VEGFR2 antibody.

Intensity of western blot band of phosphorylated-VEGFR2 (Y1175) and VEGFR2 was analysed using ImageJ software. Obtained band density of phosphorylated-VEGFR2 (Y1175) were normalized by the VEGFR2 and inhibition of VEGFR2 phosphorylation by EGFRxNRP1 bispecific antibody construct 11 was calculated by ratio against VEGF165 control cell lysate (positive control). IC50 of VEGFR2 phosphorylation by EGFRxNRP1 bispecific antibody was determined using Prism9 software. see **FIGS. 11A-11B**. The western blot in **FIG. 3** shows that incubating HUVEC cells with the bispecific binding molecule of EGFRxNRP1 bispecific antibody construct 1 (SEQ ID NOs: 1 and 12) did not inhibit VEGF165-mediated VEGFR phosphorylation. **FIGS. 5-11** show western blots and IC50 plots of VEGFR2 phosphorylation

inhibition after incubation with bispecific antibodies. The IC50 of bispecific antibodies are shown in Table 4.

5

Table 4. VEGFR signaling inhibition by EGFRxNRP1 antibodies

EGFRxNRP1 BsA Construct	SEQ ID NOs (Heavy and light chains)	FIG.	VEGF inhibition (nM)
Construct 1	SEQ ID NO: 1, 12	3	n/a (below 5% inhibition in the 1μM)
Construct 2	SEQ ID NO: 2, 12	4	12.9
Construct 3	SEQ ID NO: 3, 12	5	3.3
Construct 4	SEQ ID NO: 4, 12	6	410
Construct 5	SEQ ID NO: 5, 12	7	61
Construct 6	SEQ ID NO: 6, 12	8	10130
Construct 7	SEQ ID NO: 7, 12	9	1.74
Construct 11	SEQ ID NO: 11, 12	10	20

10 **Example 4: Effect of EGFRxNRP1 bispecific antibody on cell viability**

The inhibition of cell viability by bispecific antibodies was tested in the H1975 lung cancer cell line. Briefly, H1975 lung cancer cells were grown in RPMI1640 supplemented with 1% Penicillin/Streptomycin, and 10% FBS. Cells were trypsinized and plated into 96 well 3D culture plate with round bottom (3,000 cells/120μl/well) and incubate for 3-4 hours until they aggregated to form 3D spheroids. A stock master plate of 6-fold serially diluted EGFRxNRP1 bispecific antibody was prepared from 5 μM to 0.6 pM. H1975 cells were treated with 30 μl of EGFRxNRP1 bispecific antibody and incubated for 72 hours (duplicate). Subsequently, CellTiter-Glo 3D reagent plus 25 μl of serum-free media was added into each well, wrapped with foil, and incubated on a rocker for 7 minutes. Plates were read with Varioskan Lux

15

20 Multimode Plate Reader and analyzed with Prism9 software.

Table 5 shows the IC50s for EGFRxNRP1 antibodies. The EGFRxNRP1 bispecific

antibody construct (SEQ ID NOs: 1 and 12) having an NRP1 binding domain at a C-terminal end without being fused to an scFv has a high IC50 value (1.96 μ M), as shown in **FIG. 12A** compared to the other EGFRxNRP1 antibodies constructs. see **FIG. 12B**. The IC50 value data indicate that a short chain variable fragment (scFv) comprising the NRP1 binding domain of
5 EGFRxNRP1 antibodies is critical for the function of EGFRxNRP1 antibodies in inhibiting tumor cell growth.

Table 5. Cell growth inhibition by EGFRxNRP1 antibodies

Cell line	IC50 (μ M)					
	SEQ ID NOs: 1, 12	SEQ ID NOs: 11, 12	SEQ ID NOs: 9, 12	SEQ ID NOs: 10, 12	SEQ ID NOs: 7, 12	SEQ ID NOs: 3, 12
H1975	1.96	0.001362	0.005693	0.002074	0.001652	0.001727

Example 5: Tumor growth inhibition in H1975 xenograft mouse model cell line

10 The ability of EGFRxNRP1 antibodies to inhibit tumor growth was tested in a H1975 cell line xenograft mouse model. All cell lines were acquired from the American Type Culture Collection (Manassas, VA, USA). The cells were maintained at 37°C in a 5% CO2 incubator in RPMI 1640 (Gibco, Carlsbad, CA, USA) containing 10% fetal bovine serum (HyClone, Logan, UT, USA) and 2 mmol/L Glutamine (HyClone, Logan, UT, USA).

15 Xenograft models

The experiments and procedures involving mice were performed according to the U.S. Department of Agriculture, Department of Health and Human Services, and NIH policies regarding the humane care and use of laboratory animals. Six- to eight-week-old female athymic (nu/nu) mice from Charles River Laboratories (Wilmington, MA, USA) were housed under
20 pathogen-free conditions with laboratory chow and water ad libitum. Prior to tumor cell line implantation, all cell lines were screened for infectious agents (mycoplasma, etc.). Xenografts were established by injecting 100 μ l subcutaneous into the right flanks containing 1×10^7 (NCI-H1975) cells per mouse mixed 1:1 in Matrigel (Corning, Corning, NY, USA). For efficacy studies, tumors were allowed to reach 150 to 300 mm³ (7 to 10 mice per group) prior to
25 randomization and start of treatment.

Treatments and tumor measurements

Antibodies were diluted in sterile phosphate-buffered saline (Corning, Corning, NY, USA) and administered via injecting i.p. with a total volume of 100μl per mouse per treatment at indicated dose levels on the day of randomization, and then twice weekly.

Digital caliper measurements were used to measure tumor sizes and tumor volumes were calculated using the formula $V = (W^2 \times L)/2$, where W is tumor width, and L is tumor length.

Statistical analysis

The GraphPad Prism 7 software (La Jolla, CA, USA) was used for statistical analysis. Results are shown as mean. The data between control and experimental groups at individual time points or at endpoint were compared using Student t test. For growth curve analysis, involving longitudinal data with repeated measures, a type II ANOVA was used. Statistical differences at $p < 0.05$ were considered significant. TGI% was calculated according to the formula, $TGI (\%) = (V_{C1} - V_{t1}) / (V_{C0} - V_{t0}) \times 100$, where V_{C1} and V_{t1} is the mean tumor volume in the control and treatment group at the study end point and V_{C0} and V_{t0} are the mean tumor volumes in the control and treatment group at the beginning of the experiment, respectively. Table 6 shows tumor growth inhibition by EGFRxNRP1 antibodies and treatment-to-control percent tumor volume in the xenograph mouse model. The curves in **FIGS. 13A-13F** show the mean tumor volume over days post implantation in mice treated with EGFRxNRP1 antibodies. The EGFRxNRP1 bispecific antibody construct 11 with the scFv NRP1 binding domain have the highest tumor growth inhibition, e.g., treatment with the EGFRxNRP1 bispecific antibody construct 11 (SEQ ID NOs: 11 and 12) resulted in 100% tumor growth inhibition.

Table 6. Tumor growth inhibition and treatment-to-control percent tumor volume

Bispecific binding molecule polypeptides	TGI% mean	T/C%
SEQ ID NOs: 1, 12	39.94	74.58%
SEQ ID NOs: 2, 12	23.94	81.91%
SEQ ID NOs: 3, 12	71.13	37.15%
SEQ ID NOs: 7, 12	81.09%	28.08%
SEQ ID NOs: 9, 12	94.96%	18.86%

SEQ ID NOs: 11, 12	102.56%	12.54%
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Example 6. Degradation of EGFR^{T790M/L858R} by construct 11 in H1975 cells

EGFR tyrosine kinase inhibitors (TKIs) have been widely used to treat cancer with constitutively active EGFR mutations by binding the catalytic site of EGFR and blocking its kinase activity. However, they may also induce acquired resistance and. The first-generation EGFR TKIs gefitinib induces T790M mutation in most patients after treatment. The second-generation EGFR TKI afatinib irreversibly binds to EGFR but it lacks selectivity for EGFR WT and EGFR^{T790M} and provokes adverse reactions. The third-generation EGFR TKI osimertinib is effective to tumor with EGFR^{T790M} mutation but certain patients develop acquired resistance such as a C797S mutation. Moreover, NSCLC with EGFR WT do not respond to TKIs. Therefore, targeting EGFR by inducing degradation could be a more effective approach to repress EGFR in cancer treatment regardless of EGFR mutational status.

Anti-EGFR antibodies block ligand-mediated activation of EGFR signaling and induce receptor endocytosis, but EGFR receptors are mostly recycled. Ability to degrade double-mutated EGFR^{T790M/L858R} by EGFRxNRP1 bispecific antibody construct 11 was assessed in cancer cells in order to validate the association between the anticancer activity of construct 11 and the EGFR protein levels. H1975 cells harboring EGFR^{T790M/L858R} mutation were grown in tissue culture plate in RPMI1640 media with 10% fetal bovine serum. The cells were incubated with construct 11 with fixed (150 nM) or serially diluted by sixfold from the highest concentration of 1 μM to lowest concentration 0.77 nM for 16 hours. Proteasome inhibitor MG132 (10 μM) or lysosomal protein degradation inhibitor bafilomycin A1 (Baf A1, 200 nM) were used together with EGFRxNRP1 bispecific antibody treatment to define mechanism of action of the EGFRxNRP1 antibodies. Cell lysates were prepared by collecting cells with a cell scraper and incubating with NP40 lysis buffer with protease/phosphate inhibitors for 20 minutes on ice. Supernatant lysate was collected after centrifugation at 13,000 rpm for 10 minutes into a new tube, measured protein quantification using BCA protein assay, and denatured at 70°C for 10 minutes after mixing with NuPAGE LDS sample buffer and LDS sample reducing buffer. The cell lysate equal to 20 μg were loaded with 4 μl of PageRuler Plus prestained ladder into 4-12% Bis-Tris Gel and run at 200V for 45 minutes. Gels were washed with distilled water and transferred to membranes using IBlot2 Drying Blotting System. Membranes were blocked with 5% milk in 1x TBST at

room temperature for an hour and incubated with Anti-EGFR, anti-NRP1, and anti-beta actin at in 5% milk in 1xTBST at 4°C overnight. Next day, membranes were washed with TBST for 10 minutes three times and incubated with a secondary antibody in 5% milk at room temperature for an hour. Membranes were washed with 1xTBST for 10 minutes three times. Then, membranes
 5 were incubated with SuperSignal Femto Chemiluminescent substrate for 5 minutes and imaged with BioRad ChemiDoc Touch Imaging system.

Human NSCLC H1975 cells (EGFR^{T790/L858R}) were treated with anti-NRP1 antibody (anti-NRP1 mAb), panitumumab (Pnm, anti-EGFR antibody), anti-NRP1 plus panitumumab, and EGFRxNRP1 bispecific antibody construct 11 (SEQ ID NOs: 11 and 12) (150 nM) for 16 hours.
 10 EGFR, NRP1, and actin protein levels were measured by Western blot.

The levels of both total EGFR (tEGFR) and NRP1 in cells treated with construct 11 were very low. In contrast, the levels of EGFR in cells treated with anti-NRP1 mAb, panitumumab (Pnm), or anti-NRP1 mAb plus panitumumab are similar to that in untreated cells (**FIG. 14**). This result suggests that degradation of EGFR and NRP1 is only achieved by EGFRxNRP1
 15 antibodies construct 11, which bind to EGFR^{T790/L858R} and NRP1, simultaneously.

Degradation of EGFR^{T790/L858R} and NRP1 by EGFRxNRP1 bispecific antibody in H1975 cells was restored by co-treatment with the lysosomal protein degradation inhibitor, bafilomycin A1 (Baf A1, 200nM), but not by co-treatment with the proteasome inhibitor MG132 (10 μM) (**FIG. 15**). Similar experiments using the Baf A1 and MG132 inhibitors were performed to
 20 examine degradation of various EGFR forms (WT or mutant) by construct 11 in other NSCLC cell lines. Degradation was examined for: EGFR^{del19} in PC9 cells, EGFR^{WT} in H1299 (NRAS^{Q61K}) cells, EGFR^{WT} in HCC44 (KRAS^{G12C}) cells, EGFR^{del19}/NRP1 in HCC827 cells and EGFR^{WT}/NRP1 in H358 (KRAS^{G12C}) cells (data not shown). For all EGFR forms and cell lines examined, the results confirmed that receptor degradation by construct 11 was restored by co-
 25 treatment with the Baf A1 lysosomal protein degradation inhibitor but not by co-treatment with the MG132 proteasome inhibitor.

Taking this data together, EGFRxNRP1 antibodies construct 11 induces degradation of EGFR and NRP1 via lysosomal protein degradation pathway. The diagram depicts that the simultaneous binding of the EGFRxNRP1 bispecific antibody to EGFR and NRP1 results in
 30 degradation of EGFR through lysosomal degradation pathway and its binding to NRP1 is essential for the degradation of EGFR. (**FIG. 16**) The effects of EGFR antibody panitumumab,

amivantamab, and CONSTRUCT-11 on degradation of EGFR^{T790/L858R} in H1975 cells was assessed. Construct 11 treatment significantly reduced EGFR^{T790/L858R} (tEGFR) protein level even at the low concentration of 0.77 nM, whereas there is no distinct degradation of tEGFR in both cellpanitumumab-treated and amivantamab-treated cells (**FIG. 16**). Construct 11 can be used for the treatment of tumors with EGFR mutations as a novel and unique antibody-based EGFR receptor degrader. Furthermore, EGFRxNRP1 bispecific antibody construct 11 degraded EGFR with mutations, including single mutation (Del 19), double mutations (T790M/L858R), triple mutation (T790M/C797S/L858R), and insertion (InsEx20) (data not shown).

Thus, in summary, EGFRxNRP1 bispecific antibody construct 11 has been shown to degrade both wild-type and mutant forms of EGFR in a wide panel of NSCLC cell lines by a lysosomally-mediated degradation pathway.

Example 7. Effect of EGFRxNRP1 bispecific antibody on anti-tumor activity in Osimertinib-resistant xenograft mouse model

Osimertinib is a third-generation irreversible EGFR TKI targeting activating mutations (L858R and chromosome 19 deletions) and T790M mutations. The resistance to osimertinib has become a major obstacle to the treatment of EGFR mutated NSCLC. Recent study showed that osimertinib-resistant patients treated with lazertinib plus amivantamab had 36% of overall response rate (ORR). Preclinical study in H1975-HGF xenograft mouse model found great efficacy of lazertinib plus amivantamab.

To determine the effect of EGFRxNRP1 bispecific antibody construct 11 on tumor with resistance to osimertinib, osimertinib-sensitive, osimertinib-resistant, or osimertinib-refractory xenograft mice were treated with osimertinib (1 mg/kg, i.p., QD), panitumumab (5 mg/kg, i.p., BIW), CONSTRUCT-11 (6.87 mg/kg, i.p. BIW), amivantamab (5.05 mg/kg, i.p., BIW) and IgG1 isotype as control (5 mg/kg, i.p., BIW). Osimertinib was formulated for i.p. administration by dissolution of the dry power in a small amount (10% of final volume) of dimethyl sulfoxide. Osimertinib and antibodies were diluted in sterile phosphate-buffered saline and administered starting at the day of randomization as indicated above by injecting with total volume of 100µl per mouse per treatment. Digital caliper measurements were used to calculate tumor volume using the formula $V = (W^2 \times L)/2$, where W is tumor width, and L is tumor length. The GraphPad Prism 7 software (La Jolla, CA, USA) was used for statistical analysis. Results are shown as mean $\pm$ SEM.

The data between control and experimental groups at individual time points or at end point were compared using Student t test. In osimertinib-sensitive xenograft mice (H1975), construct 11 was highly effective in inhibiting tumor growth in mice, compared to mice treated with amivantamab. Construct 11 treatment continued to suppress tumor growth up to 42 days post implantation, while tumor did not effectively respond to osimertinib, panitumumab, and amivantamab (FIG. 18A). Osimertinib-resistant H1975-OR cell line was developed by growing H1975 cells in media with increasing concentration of Osimertinib up to 4μM. In an osimertinib-resistant xenograft mice (H1975-OR), CONSTRUCT-11 treatment group also showed stronger inhibition of tumor growth compared amivantamab treatment group (FIG. 18B). Osimertinib-refractory H1975-HGF cell line was developed by overexpressing hepatocyte growth factor (HGF) in H1975 cells to activate cMET signaling to reduce H1975 cell line’s dependency on EGFR signaling for its growth. In osimertinib-refractory xenograft mice (H1975-HGF), EGFRxNRP1 bispecific antibody construct 11 treatment exhibited similar inhibition efficacy on tumor growth to amivantamab treatment (FIG. 18C). These results demonstrate that EGFRxNRP1 bispecific antibody construct 11 induced strong degradation of EGFR^{T790M/L858R} and had anti-tumor activity in osimertinib-sensitive H1975. Efficacy of EGFRxNRP1 bispecific antibody construct 11 in various EGFR^{T790M/L858R} xenograft mouse models is summarized in Table 7 as below. EGFRxNRP1 bispecific antibody construct 11 can be applicable to other receptor tyrosine kinase inhibitor (RTK)-resistant tumors.

Table 7. Preclinical Proof-of-Concept in various xenograft mouse models of EGFR^{T790M/L858R}

	osimertinib-sensitive	osimertinib-refractory	osimertinib-resistant	osimertinib-refractory
	H1975	H1975-TAER OE	H1975-OR	H1975-HGF
Osimertinib	O	Δ	X	Δ
Pantimumab	O	X	X	X
Amivantamab	O	O	X	O
CONSTRUCT-11	O	O	O	O

O: great efficacy with low dose in sensitized mode
Δ: no efficacy with low dose and good efficacy at high dose
X: no efficacy even with high dose

We demonstrated that EGFRxNRP1 bispecific antibody inhibits tumor cell growth and

reduces cell viability. Also, EGFRxNRP1 bispecific antibody treatment degrades EGFR through lysosomal degradation pathway, which was validated by the Experiment 6 using the lysosomal protein degradation inhibitor or proteasome inhibitor (**FIG. 15**). Importantly, the degradation of EGFR was detected only when EGFRxNRP1 bispecific antibody bound to both EGFR and NRP1.

5 The presence of NRP1 is essential for the degradation of a target protein, i.e., functionality of bispecific binding molecule.

The present disclosure provides a novel antibody-based receptor degrader (ApReptor) platform, which has several advantages over other degraders: (i) no need of E3/ubiquitin specific protein (USP), (ii) no need of a linker and catalytic enzyme, (iii) preclinical PoC validation, (iv) preclinical validation in drug resistant model, and (v) wide range of applications to disease-associated extracellular receptors.

This antibody-based receptor degraders (ApReptors) platform provides modular, selective, and simple genetically encoded strategy for inducing lysosomal delivery of extracellular and surface target receptors with broad or tissue specific distribution. The AbReptor platform holds tremendous promise for personalized medicine that can be customized on the genetic background of the patient.

Example 8. Degradation of Integrin α V β Receptor by Integrin α V β x NRP1 Bispecific Antibody Construct

20 In this example, a bispecific antibody (BsA) construct similar to construct 11 was prepared in which the anti-NRP1 antibody binding arm of the BsA was maintained but an anti-integrin α V β antibody was used as the other binding arm of the BsA (instead of anti-EGFR as in construct 11). The K_D for NRP1 binding of the integrin α V β x NRP1 bispecific antibody construct was 2.38×10^{-10} M. The K_D for integrin α V β binding of the integrin α V β x NRP1 bispecific antibody construct was <0.1 nM, which was comparable to the K_D for integrin α V β binding of the anti- integrin α V β mAb alone.

Degradation of NRP1 and integrin α V β by the integrin α V β x NRP1 BsA construct was examined, the results of which are shown in **FIG. 19A**. Cells were either untreated (control), treated with anti-integrin α V β antibody alone or treated with the integrin α V β x NRP1 BsA construct. The results demonstrated that the bispecific antibody construct effectively degraded both NRP1 and integrin α V β . These results confirmed the ability of the BsA construct

comprising anti-integrin $\alpha V\beta 3$ to degrade integrin $\alpha V\beta 3$ in integrin $\alpha V\beta 3$ -expressing cells.

Example 9. Degradation of Integrin $\alpha V\beta 3$ Receptor by Integrin $\alpha V\beta 3$ x NRP1 Bispecific Antibody Construct

5 In this example, a bispecific antibody (BsA) construct similar to construct 11 was prepared in which the anti-NRP1 antibody binding arm of the BsA was maintained but an anti-integrin $\alpha V\beta 3$ antibody was used as the other binding arm of the BsA (instead of anti-EGFR as in construct 11). The K_D for NRP1 binding of the integrin $\alpha V\beta 3$ x NRP1 bispecific antibody construct was 1.07×10^{-10} M. The K_D for integrin $\alpha V\beta 3$ binding of the integrin $\alpha V\beta 3$ x NRP1
10 bispecific antibody construct was <0.1 nM, which was comparable to the K_D for integrin $\alpha V\beta 3$ binding of the anti- integrin $\alpha V\beta 3$ mAb alone.

Degradation of NRP1 and integrin $\alpha V\beta 3$ by the integrin $\alpha V\beta 3$ x NRP1 BsA construct was examined, the results of which are shown in **FIG. 19B**. Cells were either untreated (control), treated with anti-integrin $\alpha V\beta 3$ antibody alone or treated with the integrin $\alpha V\beta 3$ x NRP1 BsA
15 construct. The results demonstrated that the bispecific antibody construct effectively degraded both NRP1 and integrin $\alpha V\beta 3$. These results confirmed the ability of the BsA construct comprising anti-integrin $\alpha V\beta 3$ to degrade integrin $\alpha V\beta 3$ in integrin $\alpha V\beta 3$ -expressing cells.

Example 10. Degradation of PD-L1 and NRP1 by PD-L1 x NRP1 Bispecific Antibody Construct

20 In this example, a bispecific antibody (BsA) construct similar to construct 11 was prepared in which the anti-NRP1 antibody binding arm of the BsA was maintained but an anti-PD-L1 antibody was used as the other binding arm of the BsA (instead of anti-EGFR as in construct 11). The K_D for NRP1 binding of the PD-L1 x NRP1 bispecific antibody construct was 8.22×10^{-9} M. The K_D for PD-L1 binding of the PD-L1 x NRP1 bispecific antibody
25 construct was 1.00×10^{-10} M.

Degradation of PD-L1 and NRP1 by the PD-L1 x NRP1 BsA construct was examined, the results of which are shown in **FIGS. 20A-20B**. Kidney cancer Renca cells were incubated with increasing concentrations of either an anti-PD-L1 monoclonal antibody alone or the PD-L1
30 x NRP1 BsA construct. Whole cell lysates were isolated and probed for standard western

blotting analysis with a monoclonal anti-PD-L1 antibody or an anti-NRP1 antibody to detect PD-L1 or NRP1 expression, respectively. The non-specific protein actin was used as a loading control.

The results for cells treated with the anti-PD-L1 monoclonal antibody alone are shown in **FIG. 20A**. The results for cells treated with the PD-L1 x NRP1 BsA construct are shown in **FIG. 20B**. The results demonstrated that, while the anti-PD-L1 mAb treatment led to minimal degradation of PD-L1 at higher concentrations and, as expected, no degradation of NRP1, treatment with the bispecific antibody construct effectively degraded both PD-L1 and NRP1 in a dose-dependent manner. These results confirmed the ability of the BsA construct comprising a PD-L1 binding domain to degrade PD-L1 in PD-L1-expressing cells.

SEQUENCE LISTING SUMMARY

SEQ ID NO:	Sequence
1	QVQLQESGPGLVKPKSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNPSLKSRLTISI DTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKT VERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMILDSGDSFLLYSLKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSHTPGNSKPTRTPRR
2	QVQLQESGPGLVKPKSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNPSLKSRLTISI DTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKT VERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMILDSGDSFLLYSLKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSW VRQAPGKGLEWVSQISPAAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPYRMM SKVMDVWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQYFSSYLAWY QQKPGKAPKLLIYGASSRASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQLGSPPTFGQGTKEIK
3	QVQLQESGPGLVKPKSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNPSLKSRLTISI DTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKT VERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMILDSGDSFLLYSLKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSW VRQAPGKGLEWVSQISPAAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPYFRM SKVMDVWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQFLSSYLAWY QQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQLASLPATFGQGTKEIK
4	QVQLQESGPGLVKPKSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNPSLKSRLTISI DTSKTQFSLKLSSVTAADTAIYYCVRDRVTGAFDIWGQGTMTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKT VERKCCVECPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTFRVSVLTVVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMILDSGDSFLLYSLKLTVDKSRWQQGNVFSCSVMH EALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSW VRQAPGKGLEWVSQISPAAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPYQYM SKVMDVWGQGTTLTVSSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQYFSSYLAWY QQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQLASLPATFGQGTKEIK
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	EALHNHYTQKSLSLSPGKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSW VRQAPGKGLEWVWSQISPAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPFFRM SQVMDVWGQGTTLTVSSGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQFLSSYLAWY QQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLASPATFGQGTKEIK
6	QVQLQESGPGLVKPKSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNLSKRLTISI DTSKTQFSLKLSVTAADTAIYYCVRDRVTGAFDIWGQGTMTVTVSSASTKGPSVFPLAPCSRSTSESTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSNFGTQTYTCNVDHKPSNTKVDKT VERKCCVECPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK TKPREEQFNSTFRVVSVLTVHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPMLDSGDSFFLYSKLTVDKSRWQQGNVFCFSVMH EALHNHYTQKSLSLSPGKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSW VRQAPGKGLEWVWSQISPAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPYFRM SKVMDVWGQGTTLTVSSGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQFLSSYLAWY QQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLASPATFGQGTKEIK
7	QVQLQESGPGLVKPKSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNLSKRLTISI DTSKTQFSLKLSVTAADTAIYYCVRDRVTGAFDIWGQGTMTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVM HEALHNHYTQKSLSLSPGKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMS WVRQAPGKGLEWVWSQISPAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPYFR MSKVMVWGQGTTLTVSSGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQFLSSYLAWY YQQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLASPATFGQGTKEIK
8	QVQLQESGPGLVKPKSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNLSKRLTISI DTSKTQFSLKLSVTAADTAIYYCVRDRVTGAFDIWGQGTMTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVM HEALHNHYTQKSLSLSPGKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMS WVRQAPGKGLEWVWSQISPAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPYFR MSKVMVWGQGTTLTVSSGDGSSGGGASDIQMTQSPSSLSASVGDRTITCRASQFLSSYLAWYQQK PGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLASPATFGQGTKEIK
9	QVQLQESGPGLVKPKSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNLSKRLTISI DTSKTQFSLKLSVTAADTAIYYCVRDRVTGAFDIWGQGTMTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVM HEALHNHYTQKSLSLSPGKGGGSGGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMS WVRQAPGKGLEWVWSQISPAGGYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPYFR MSKVMVWGQGTTLTVSSGGGSGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRTITCRASQFLS SYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLASPATFGQGT KVEIK
10	QVQLQESGPGLVKPKSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNLSKRLTISI DTSKTQFSLKLSVTAADTAIYYCVRDRVTGAFDIWGQGTMTVTVSSASTKGPSVFPLAPSSKSTSGGTAALG

	CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVM HEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQFLSSYLAWY QQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISLQPEDFATYYCQQYLASPATFGQGTKEIKGG GGSGGGSGGGGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVWSQISPAG GYTNYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCARGELPYFRMSKVMMDVWGQGLTVTVSS
11	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNPSLKSRLTISI DTSKTQFSLKLSVTAADTAIYYCVRDRVTGAFDIWGQGTMTVSSASTKGPSVFPLAPSSKSTSGGTAAALG CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKV EPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHN AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVM HEALHNHYTQKSLSLSPGKGGGGSGGGGSGGGGSEVQLLES GGGLVQPGGSLRLSCAASGFTFSSYAMS WVRQAPGKGLEWVWSQISPAGGYTNYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARGELPYFR MSKVMMDVWGQGLTVTVSSGGGGSGGGGSGGGGSEIVLTQSPGTLSPGERATLSCRASQFLSSYLAWY QQKPGQAPRLIYGASARASGIPDRFSGSGSGTDFTLTISRLEPEDFATYYCQQYLASPATFGQGTKEIK
12	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVPNRFSGSGSGTDFT FTISLQPEDATYFCQHFHDLPLAFGGGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYPREAKV QWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
13	GGGS
14	CAAGTGCAGCTGCAGGAATCCGCCCGGGCTTGTGAAGCCTAGCGAAACACTCTCGCTCACCTGTAC TGTCAGCGGTGGATCAGTGTCTCCGGCGATTACTACTGGACCTGGATTCCGCGAGAGCCCTGGAAG GGACTGGAGTGGATCGGACACATCTACTACTCCGGGAACACTAACAACCCGTCGTTGAAGTCCAG ACTGACGATCAGTATCGATACCTCCAAGACCCAGTTCAGCCTGAAGCTGAGCTCAGTGACAGCCGCCG ACACTGCAATCTACTACTGCGTGCGGGACAGAGTGACCGGAGCCTTCGACATCTGGGGCCAGGGAAC CATGGTCACTGTGTCTGTGCTGCTCAACCAAGGGTCCGTCCGTGTTTCCCTGGCCCCGTGCTCGCGGA GCACCTCCGAGTCCACTGCCGCTTGGGCTGCCTGGTCAAAGACTACTTCCCTGAACCCGTGACTGTCA GCTGGAACCTCCGAGCTCTGACCTCGGGAGTGACACCTTCCCGGCCGTGCTGCAATCGAGCGGCCTC TACTCCCTGTCTCCGTCTGACCGTGCCATCATCAAACCTCGGAACCCAACTTATACGTGCAACGTC GACCACAAGCCCTCCAATACCAAAGTCGACAAGACCGTGAGAGGAAATGCTGCGTGGAGTGTCCGC CTTGCCCCGCGCCCGGTGGCCGGACCTAGCGTGTCTGTTCCCGCCGAAGCCAAAGGACACTCTC ATGATCTCCCGCACCCCTGAAGTCACTTGCCTGCTGGTGGACGTTTCCACGAGGATCCCGAAGTGCA GTTCAATTGGTACGTGGACGGGTGGAAGTACATAACGCCAAGACCAAGCCAGGGAAGAACAGTTT AACTCCACCTTCCGGGTGGTGTCTGCTGCTCACTGTGGTGCATCAGGATTGGCTCAATGGAAAGGAGTA CAAGTGCAAAGTGTGCAACAAGGTCTGCCGCTCCTATTGAAAAGACCATTTCCAAAACCAAGGGAC AGCCCAGAGAGCCTCAGGTCTACACCTGCCTCCGAGCCGCGAGGAAATGACCAAGAACCAAGTGTC TCTGACTTGCCTCGTGAAGGGATTCTACCCCTCCGATATCGCGGTGGAGTGGGAGAGCAACGGGCAG CCAGAGAACAACTATAAGACCACCCGCTATGCTGGACTCCGATGGCTCTTCTTCTTGTACTCGAAG CTGACCGTGGACAAGTCCCGCTGGCAACAGGGAAACGTGTTAGCTGTAGCGTGATGCACGAAGCCC TGCACAACCACTACACCCAGAAGTCCCTGTCGCTTCCCCCGGAAGGGCGGTGGCGGATCCGGCGG CGGGGGCAGCGGGGGCGGCGGTCCCATACCCCGGGGAACCAAAGCCACCCGACTCCACGGCG C
15	CAGGTTCAAGCTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAACACTGTCTCTGACCTGCAC CGTGTCTGGCGCTCTGTGCTCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCTGGCAAAG

	GCCTGGAATGGATCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGG CTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCCTCTGTGACCGCCGCTGAT ACCGCCATCTACTATTGCGTGCGGGACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCAT GGTCACCGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTGCTCCAGATCCAC CTCCGAGTCTACAGTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCTG GAATTCTGGCGCTCTGACATCTGGCGTGACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACTC TCTGTCTCCGTGCTGACCGTGCCTTCTCTAACTTTGGCACCCAGACCTACACCTGTAATGTGGACCAC AAGCCATCCAACACCAAGGTGGACAAGACCGTGGAACGGAAGTGCTGCGTGGAATGCCCTCCTTGTC CTGCTCCTCTGTGGCTGGCCCTTCCGTGTTTCTGTTCCCTCCAAAGCCTAAGGACACCCTGATGATCTC TCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAGGTGCAGTTCAATT GGTACGTGGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCAC CTTCAGAGTGGTGTCCGTGCTGACCGTGGTGCATCAGGATTGGCTGAACGGCAAAGAGTACAAGTGC AAGGTGTCCAACAAGGGCCTGCCTGCTCTATCGAAAAGACCATCTCTAAGACCAAGGGGACAGCCCC GGGAACCTCAGGTTTACACACTGCCTCCAAGCCGGGAAGAGATGACCAAGAACCAGGTGTCCCTGAC CTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCTAATGGCCAGCCTGAGA ACAACCTACAAGACCACCTCCTATGCTGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAG TGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCTGCTCCGTGATGCACGAGGCCCTGCACAA TCACTACACCCAGAAGTCCCTGTCTGTCCCCTGGAAAAGGCGGCGGAGGATCTGGCGGAGGCGGT AGCGGTGGTGGCGGATCTGAAGTTCAGCTGGTGAATCTGGCGGCGGACTGGTTCAACCAGGCGGAT CTCTGAGACTGTCTTGCGCCCTCCGGCTTCACTTCTCCTTTACGCTATGCTCTGGGTCCGACAGGC CCCAGGCAAAGGATTGGAGTGGGTGTCCCAGATCTCTCCGCTGGCGGCTACACCAATTACGCCGACT CTGTGAAGGGCAGATTACCATCTCTGCCGACACCTCCAAGAACACCGCCTACCTGCAGATGAAGTCC CTGAGAGCCGAGGACACCGCCGTGTAATTTGTGCTAGAGGCGAGCTGCCTACTACCGGATGTCCA AAGTGATGGACGTGTGGGGACAGGGAACCTCGTGACAGTTTCTAGCGGTGGCGGAGGTAGCGGAG GCGGTGGAAGCGGCGGAGGCGGAAGTGATATTAGATGACCCAGTCTCCTTCCAGCCTGTCCGCTTCT GTGGGCGATAGAGTGACCATCACCTGTGCGGCCTCTCAGTACTTCTCCTACCTGGCTTGGTATCAG CAGAAGCCTGGCAAGGCCCCCTAAGCTGCTGATCTACGGCGCCTCCTTAGAGCTAGCGGCGTGCCCTC TAGATTCTCCGGATCTGGCTCTGGCACCGACTTTACCTGACAATCTCCAGCCTGCAGCCTGAGGACTT CGCCACCTACTACTGCCAGCAGTACCTGGGCTCTCCTCCAACCTTTGGCCAGGGAACAAAGGTGAGA TCAAGCGCTGA
16	CAGGTTCACTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAACACTGTCTCTGACCTGCAC CGTGTCTGGCGGCTCTGTGTCCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAG GCCTGGAATGGATCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGG CTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCCTCTGTGACCGCCGCTGAT ACCGCCATCTACTATTGCGTGCGGGACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCAT GGTCACCGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTGCTCCAGATCCAC CTCCGAGTCTACAGTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCTG GAATTCTGGCGCTCTGACATCTGGCGTGACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACTC TCTGTCTCCGTGCTGACCGTGCCTTCTCTAACTTTGGCACCCAGACCTACACCTGTAATGTGGACCAC AAGCCATCCAACACCAAGGTGGACAAGACCGTGGAACGGAAGTGCTGCGTGGAATGCCCTCCTTGTC CTGCTCCTCTGTGGCTGGCCCTTCCGTGTTTCTGTTCCCTCCAAAGCCTAAGGACACCCTGATGATCTC TCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAGGTGCAGTTCAATT GGTACGTGGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCAC CTTCAGAGTGGTGTCCGTGCTGACCGTGGTGCATCAGGATTGGCTGAACGGCAAAGAGTACAAGTGC AAGGTGTCCAACAAGGGCCTGCCTGCTCTATCGAAAAGACCATCTCTAAGACCAAGGGGACAGCCCC GGGAACCTCAGGTTTACACACTGCCTCCAAGCCGGGAAGAGATGACCAAGAACCAGGTGTCCCTGAC CTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCTAATGGCCAGCCTGAGA

	ACAACTACAAGACCACACCTCCTATGCTGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAG TGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAA TCACTACACCCAGAAGTCCCTGTCTGTCCCCTGGAAAAGGCGGCGGAGGATCTGGCGGAGGCGGT AGCGGTGGTGGCGGATCTGAAGTTCAGCTGGTTGAATCTGGCGGCGGACTGGTTCAACCAGGCGGAT CTCTGAGACTGTCTTGCCGCCTCCGGCTTACCTTCTCCTCTTACGCTATGCTCTGGGTCCGACAGGC CCCAGGCAAAGGATTGGAGTGGGTGTCCCAGATCTCTCCGCTGGCGGCTACACCAATTACGCCGACT CTGTGAAGGGCAGATTCACCATCTCTGCCGACACCTCCAAGAACACCGCCTACCTGCAGATGAACTCC CTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGGCGAGCTGCCCTACTTCCGGATGTCCAA AGTGATGGACGTGTGGGGACAGGGAACCCTCGTGACAGTTTCTAGCGGTGGCGGAGGTAGCGGAGG CGGTGGAAGCGGCGGAGGCGGAAGTGATATTCAGATGACCCAGTCTCCTTCCAGCCTGTCCGCTTCTG TGGGCGATAGAGTGACCATCACCTGTCGGGCCTCTCAGTTCTCTCTCTACCTGGCTTGGTATCAGC AGAAGCCTGGCAAGGCCCTAAGCTGCTGATCTACGGCGCTTCTGCTAGAGCTTCCGGCGTGCCTCC AGATTTTCTGGCTCTGGATCTGGCACCAGCTTTACCCTGACAATCTCCAGCCTGCAGCCTGAGGACTTC GCCACCTACTACTGCCAGCAGTACCTGGCCTCTCTGCCACATTTGGCCAGGGAACAAAGGTCGAGAT CAAGCGCTGA
17	CAGGTTCAAGAGTCTGGCCTGGCCTGGTCAAGCCTCCGAAACACTGTCTCTGACCTGCAC CGTGTCTGGCGGCTCTGTCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAG GCCTGGAATGGATCGGCCACATCTACTACTCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGG CTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCTGAAGCTGCTCTGTGACCGCCGCTGAT ACCGCCATCTACTATTGCGTGCGGGACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCAT GGTCAACGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCTCTGGCTCCTTGTCTCCAGATCCAC CTCCGAGTCTACAGTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCTG GAATTCTGGCGCTCTGACATCTGGCGTGACACCTTTCAGCTGTGCTGCACTGACGGCCTGTACTC TCTGTCTCCGTGACCGTGCCCTTCTCTAATTTGGCACCCAGACCTACACCTGTAATGTGGACCAC AAGCCATCCAACACCAAGGTGGACAAGACCGTGGAACGGAAGTGTGCGTGGAATGCCCTCCTTGTG CTGCTCCTCCTGTGGCTGGCCCTTCCGTGTTTCTGTTCCCTCCAAAGCCTAAGGACACCCTGATGATCTC TCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAGGTGCAGTTCAATT GGTACGTGGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCAC CTTAGAGTGGTGTCCGTGCTGACCGTGGTGCATCAGGATTGGCTGAACGGCAAAGAGTACAAGTGC AAGGTGTCCAACAAGGGCCTGCCTGCTCCTATCGAAAAGACCATCTCTAAGACCAAGGGGCAGCCCC GGGAACTCAGGTTTACACACTGCCTCCAAGCCGGGAAGAGATGACCAAGAACCAGGTGCCCTGAC CTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCTAATGGCCAGCCTGAGA ACAACTACAAGACCACACCTCCTATGCTGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAG TGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAA TCACTACACCCAGAAGTCCCTGTCTGTCCCCTGGAAAAGGCGGCGGAGGATCTGGCGGAGGCGGT AGCGGTGGTGGCGGATCTGAAGTTCAGCTGGTTGAATCTGGCGGCGGACTGGTTCAACCAGGCGGAT CTCTGAGACTGTCTTGCCGCCTCCGGCTTACCTTCTCCTCTTACGCTATGCTCTGGGTCCGACAGGC CCCAGGCAAAGGATTGGAGTGGGTGTCCCAGATCTCTCCGCTGGCGGCTACACCAATTACGCCGACT CTGTGAAGGGCAGATTCACCATCTCTGCCGACACCTCCAAGAACACCGCCTACCTGCAGATGAACTCC CTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGGCGAGCTGCCCTACTACCAGATGTCCAA AGTGATGGACGTGTGGGGACAGGGAACCCTCGTGACAGTTTCTAGCGGTGGCGGAGGTAGCGGAGG CGGTGGAAGCGGCGGAGGCGGAAGTGATATTCAGATGACCCAGTCTCCTTCCAGCCTGTCCGCTTCTG TGGGCGATAGAGTGACCATCACCTGTCGGGCCTCTCAGTACTTCTCTCTCTATCTGGCATGGTATCAGC AGAAGCCTGGCAAGGCCCTAAGCTGCTGATCTACGGCGCTTCTGCTAGAGCTTCCGGCGTGCCTCC AGATTTTCTGGCTCTGGATCTGGCACCAGCTTTACCCTGACAATCTCCAGCCTGCAGCCTGAGGACTTC GCCACCTACTACTGCCAGCAGTACCTGGCCTCTCTGCCACATTTGGCCAGGGAACAAAGGTCGAGAT CAAGCGCTGA

18	CAGGTTCAAGCTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTCCGAAACACTGTCTCTGACCTGCAC CGTGTCTGGCGGCTCTGTGTCCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAG GCCTGGAATGGATCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGG CTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCTCTGTGACCGCCGCTGAT ACCGCCATCTACTATTGCGTGCGGGACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCAT GGTCACCGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTGCTCCAGATCCAC CTCCGAGTCTACAGCTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCTG GAATTCTGGCGCTCTGACATCTGGCGTGCACACCTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACTC TCTGTCTCCGTCGTGACCGTGCCTTCTCTAACTTTGGCACCCAGACCTACACCTGTAATGTGGACCAC AAGCCATCCAACACCAAGGTGGACAAGACCGTGGAACGGAAGTGCTGCGTGGAATGCCCTCCTTGTC CTGCTCCTCCTGTGGCTGGCCCTCCGTGTTTCTGTTCCCTCCAAAGCCTAAGGACACCTGATGATCTC TCGGACCCCTGAAGTGACCTGCGTGCTGGTGGTGGATGTGTCTCACGAGGATCCCGAGGTGCAGTTCAATT GGTACGTGGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCAC CTTCAGAGTGGTGTCCGTGCTGACCGTGGTGCATCAGGATTGGCTGAACGGCAAAGAGTACAAGTGC AAGGTGTCCAACAGGGCCTGCCTGCTCCTATCGAAAAGACCATCTCTAAGACCAAGGGGCAGCCCC GGGAACCTCAGGTTTACACACTGCCTCCAAGCCGGGAAGAGATGACCAAGAACCAGGTGTCCCTGAC CTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCTAATGGCCAGCCTGAGA ACAACATAAGACCACCTCCTATGCTGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAG TGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAA TCACTACACCCAGAAGTCCCTGTCTGTCTCCCTGGAAAAGGCGGCGGAGGATCTGGCGGAGGCGGT AGCGGTGGTGGCGGATCTGAAGTTCAGCTGGTGAATCTGGCGGCGGACTGGTTCAACCAGGCGGAT CTCTGAGACTGTCTTGTCGCGCTCCGGCTTCACTTCTCCTTTACGCTATGTCTGGGTCCGACAGGC CCCAGGCAAAGGATTGGAGTGGGTGTCCAGATCTCTCCGCTGGCGGTACACCAATTACGCCGACT CTGTGAAGGGCAGATTACCATCTCTGCCGACACCTCCAAGAACACCGCCTACCTGCAGATGAATCC CTGAGAGCCGAGGACACCGCCGTGTAATTTGTGCTAGAGGCGAGCTGCCATTCTTCCGGATGTCCCA AGTGATGGACGTGTGGGGACAGGGAACCTCTGACAGTTTCTAGCGGTGGCGGAGGTAGCGGAGG CGGTGGAAGCGGCGGAGGCGGAAGTGATATTCAGATGACCCAGTCTCCTTCCAGCCTGTCCGCTTCTG TGGGCGATAGAGTGACCATCACCTGTGGGCTCTCAGTTCCTGTCTAGTTATCTGGCATGGTATCAGC AGAAGCCCGGCAAGGCTCCAAGCTGTTGATCTACGGCGCCTCTGCTAGAGCTTCCGGCGTGCCATCT AGATTCTCCGGCTCTGGCTCTGGCACCGACTTTACCCTGACAATCTCCAGCCTGCAGCCTGAGGACTTC GCCACCTACTACTGCCAGCAGTACCTGGCCTCTCCTGCCACATTTGGCCAGGGAACAAAGGTCGAGAT CAAGCGCTGA
19	CAGGTTCAAGCTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTCCGAAACACTGTCTCTGACCTGCAC CGTGTCTGGCGGCTCTGTGTCCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAG GCCTGGAATGGATCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGG CTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCTCTGTGACCGCCGCTGAT ACCGCCATCTACTATTGCGTGCGGGACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCAT GGTCACCGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTGCTCCAGATCCAC CTCCGAGTCTACAGCTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCTG GAATTCTGGCGCTCTGACATCTGGCGTGCACACCTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACTC TCTGTCTCCGTCGTGACCGTGCCTTCTCTAACTTTGGCACCCAGACCTACACCTGTAATGTGGACCAC AAGCCATCCAACACCAAGGTGGACAAGACCGTGGAACGGAAGTGCTGCGTGGAATGCCCTCCTTGTC CTGCTCCTCCTGTGGCTGGCCCTCCGTGTTTCTGTTCCCTCCAAAGCCTAAGGACACCTGATGATCTC TCGGACCCCTGAAGTGACCTGCGTGCTGGTGGTGGATGTGTCTCACGAGGATCCCGAGGTGCAGTTCAATT GGTACGTGGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCTAGAGAGGAACAGTTCAACTCCAC CTTCAGAGTGGTGTCCGTGCTGACCGTGGTGCATCAGGATTGGCTGAACGGCAAAGAGTACAAGTGC

	AAGGTGTCCAACAAGGGCCTGCTGCTCTATCGAAAAGACCATCTCTAAGACCAAGGGGCAGCCCC GGGAACCTCAGGTTTACACACTGCCTCCAAGCCGGAAGAGATGACCAAGAACCAGGTGTCCCTGAC CTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCTAATGGCCAGCCTGAGA ACAACCTACAAGACCACCTCCTATGCTGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAG TGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCACGAGGCCCTGCACAA TCACTACACCCAGAAGTCCCTGTCTGTGCTCCCTGGAAAAGGCGGCGGAGGATCTGGCGGAGGCGGT AGCGGTGGTGGCGGATCTGAAGTTCAGCTGGTTGAATCTGGCGGCGGACTGGTTCAACCAGGCGGAT CTCTGAGACTGTCTTGCCGCCTCCGGCTTACCTTCTCCTTTACGCTATGTCTGGGTCGACAGGC CCCAGGCAAAGGATTGGAGTGGGTGTCCAGATCTCTCCGCTGGCGGCTACACCAATTACGCCGACT CTGTGAAGGGCAGATTACCATCTCTGCCGACACCTCCAAGAACACCGCCTACCTGCAGATGAACTCC CTGAGAGCCGAGGACACCGCCGTGTAATTGTGCTAGAGGCGAGCTGCCCTACTTCCAGATGTCCAA AGTGATGGACGTGTGGGGACAGGGAACCTCGTGACAGTTTCTAGCGGTGGCGGAGGTAGCGGAGG CGGTGGAAGCGGCGGAGGCGGAAGTGATATTAGATGACCCAGTCTCCTTCCAGCCTGTCCGCTCTG TGGGCGATAGAGTGACCATCACCTGTGCGGCCTCTCAGTACTTCTACTCCTATCTGGCTTGGTATCAGC AGAAGCCTGGCAAGGCCCTAAGCTGCTGATCTACGGCGCTTCTGCTAGAGCTTCCGGCGTGCCCTCC AGATTTTCTGGCTCTGGATCTGGCACCAGCTTTACCCTGACAATCTCCAGCCTGCAGCCTGAGGACTTC GCCACCTACTACTGCCAGCAGTACCTGGCCTCTCTGCCACATTTGGCCAGGGAACAAAGGTCGAGAT CAAGCGCTGA
20	CAGGTTCACTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAACACTGTCTCTGACCTGCAC CGTGTCTGGCGGCTCTGTGCTCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAG GCCTGGAATGGATCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGG CTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCTCTGTGACCGCCGCTGAT ACCGCCATCTACTATTGCGTGCGGGACAGAGTGACCGGCGCCTTTGATATTGGGGGCCAGGGCACCAT GGTCACCGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCTCTGGCTCCTTCCAGCAAGTCTAC CTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCT GGAATTCTGGCGCTCTGACATCTGGCGTGACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACT CTCTGTCTCCGTCGTGACCGTGCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACC ACAAGCCATCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCTGCGACAAGACCCACACCTG TCCTCCATGTCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCTCTTCTCCAAAGCCTAAGGA CACCCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCG AAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCTAGAGAGG AACAGTACAACTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGTGACCAAGGATTGGCTGAACGGC AAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCTCCTATCGAAAAGACCATCAGCAAGG CTAAGGGCCAGCCTCGGGAACCCAGGTTTACACATTGCCTCCATCTCGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAA TGGCCAGCCTGAGAACAACCTACAAGACAACCCCTCCTGTGCTGGACTCCGACGGCTCATTCTTCTGTGTA CTCCAAGCTGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCAC GAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCTGTGCTCCCTGGAAAAGGCGGCGGAGGATC TGGCGGAGGTGGAAGCGGAGGCGGTGGATCTGAAGTGACGTGGTTGAAAGTGGCGGCGGATTGG TTCAGCCTGGCGGATCTCTGAGACTGTCTTGCCGCCTCCGGCTTACCTTCTCTCTACGCTATGTC CTGGGTCCGACAGGCTCCCGGAAAAGGACTTGAATGGGTGTCCAGATCTCCCTGCTGGCGGCTAC ACCAATTACGCCGACTCTGTGAAGGGCAGATTACCATCTCTGCCGACACCTCCAAGAACACCGCCTAC CTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGGCGAGCTGCCCT ACTTCCGGATGTCCAAAGTGATGGACGTGTGGGGACAGGGAACCTCGTGACAGTTTCTAGTGGTGG CGGAGGAAGCGGCGGAGGCGGTTCTGGCGGTGGTGGATCTGATATCCAGATGACCCAGTCTCCTAGC AGCCTGTCTGCTCTGTGGGCGATAGAGTGACCATCACCTGTGCGGCCTCTCAGTTCTGTCCAGCTAC CTGGCTTGGTATCAGCAGAAGCCTGGCAAGGCCCTAAGCTGCTGATCTACGGCGCTTCTGCTAGAGC

	TTCCGGCGTGCCCTCCAGATTTTCTGGCTCTGGATCTGGCACCAGACTTTACCCTGACAATCTCCAGCCT GCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCAGTACCTGGCCTCTCCTGCCACATTTGGCCAGG GAACAAAGGTCGAGATCAAGCGCTGA
21	CAGGTTCAAGCTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAACACTGTCTCTGACCTGCAC CGTGTCTGGCGGCTCTGTGTCCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAG GCCTGGAATGGATCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGG CTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCCTCTGTGACCGCCGCTGAT ACCGCCATCTACTATTGCGTGCGGGACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCAT GGTCAACGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTCCAGCAAGTCTAC CTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCTCT GGAATTCTGGCGCTCTGACATCTGGCGTGCACACCTTTCCAGCTGTGCTGCACTAGCGGCCTGTACT CTCTGTCTCCGTCGTGACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACC ACAAGCCATCCAACACCAAGGTGGACAAGAAGGTGGAACCCAGTCTGCGACAAGACCCACACCTG TCCTCCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCTGTTCTCCAAAGCCTAAGGA CACCCTGATGATCTCTCGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCG AAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCTAGAGAGG AACAGTACAACCTCACCTACAGAGTGGTGTCCGTGCTGACCGTGTGCAACAGGATTGGTGAACGGC AAAGAGTACAAGTGCAAGGTGTCAACAAGGCCCTGCTGCTCTATCGAAAAGACCATCAGCAAGG CTAAGGGCCAGCCTCGGGAACCCAGGTTTACACATTGCCTCCATCTCGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAA TGGCCAGCCTGAGAACAACCTACAAGACAACCCCTCTGTGCTGGACTCCGACGGCTCATTCTTCTGTGA CTCCAAGCTGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCTGCTCCGTGATGCAC GAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCTGTCTCCCTGGAAAAGGCGGCGGAGGATC TGGCGGAGGTGGAAGCGGAGGCGGTGGATCTGAAGTGCACTGGTGAAGTGGCGGCGGATTGG TTCAGCCTGGCGGATCTCTGAGACTGTCTTGTGCCGCTCCGGCTTACCTTCTCTCTACGCTATGTC CTGGGTCCGACAGGCTCCCGGAAAAGGACTTGAATGGGTGTCCAGATCTCCCTGCTGGCGGCTAC ACCAATTACGCCGACTCTGTGAAGGGCAGATTACCATCTCTGCCGACACCTCCAAGAACACCGCTAC CTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGGCGAGCTGCCCT ACTTCCGATGTCCAAAGTGATGGACGTGTGGGGACAGGGAACCCCTCTGACAGTGTCTAGCGGAGA TGGATCTAGTGGTGGCGGAGGCGCTTCCGACATCCAGATGACACAGTCTCCCTCCAGCCTGTCTGCCT CTGTGGGCGATAGAGTGACCATCACCTGTGGGCTCTCAGTTCCTGTCCAGCTACCTGGCTTGGTATC AGCAGAAGCCTGGCAAGGCCCTAAGCTGCTGATCTACGGCGCTTCTGCTAGAGCTTCCGGCGTGCCC TCCAGATTTTCTGGCTCTGGATCTGGCACCAGCTTTACCCTGACAATCAGCAGCCTGCAGCCTGAGGAC TTCGCCACCTACTACTGCCAGCAGTACCTGGCCTCTCTGCCACATTTGGCCAGGGAACAAAGGTGCA GATCAAGTGA
22	CAGGTTCAAGCTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAACACTGTCTCTGACCTGCAC CGTGTCTGGCGGCTCTGTGTCCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAG GCCTGGAATGGATCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGG CTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCCTCTGTGACCGCCGCTGAT ACCGCCATCTACTATTGCGTGCGGGACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCAT GGTCAACGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTCCAGCAAGTCTAC CTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCTCT GGAATTCTGGCGCTCTGACATCTGGCGTGCACACCTTTCCAGCTGTGCTGCACTAGCGGCCTGTACT CTCTGTCTCCGTCGTGACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACC ACAAGCCATCCAACACCAAGGTGGACAAGAAGGTGGAACCCAGTCTGCGACAAGACCCACACCTG TCCTCCATGTCCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCTGTTCTCCAAAGCCTAAGGA

	CACCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCC AAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGG AACAGTACAACCTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGC AAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCTCCTATCGAAAAGACCATCAGCAAGG CTAAGGGCCAGCCTCGGGAACCCAGGTTTACACATTGCCTCCATCTCGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAA TGGCCAGCCTGAGAACAACCTACAAGACAACCCCTCCTGTGCTGGACTCCGACGGCTCATTCTTCTGT CTCCAAGCTGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCAC GAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCTGTCCCCTGAAAAAGGCGGCGGAGGATC TGGCGGAGGTGGAAGCGGAGGCGGTGGATCTGAAGTGCAGCTGGTTGAAAAGTGGCGGCGGATTGG TTCAGCCTGGCGGATCTCTGAGACTGTCTTGCCGCCTCCGGCTTACCTTCTCCTCTACGCTATGTC CTGGGTCCGACAGGCTCCCGAAAAAGGACTTGAATGGGTGTCCAGATCTCCCCTGCTGGCGGCTAC ACCAATTACGCCGACTCTGTGAAGGGCAGATTACCCTCTGCGGACACCTCCAAGAACACCGCTAC CTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGGCGAGCTGCCCT ACTTCCGGATGTCAAAGTGATGGACGTGTGGGGACAGGGAACCCCTGTCAGAGTTTCTAGTGGTGG CGGAGGAAGCGGCGGAGGCGGTTCTGGCGGTGGTGGCTGTGGCGGTGGCGGATCTGATATCCAGAT GACCCAGTCTCTAGCAGCCTGTCTGCCTCTGTGGGCGATAGAGTGACCATCACCTGTCGGGCTCTC AGTTCTGTCCAGCTACCTGGCTTGGTATCAGCAGAAGCCTGGCAAGGCCCTAAGCTGCTGATCTAC GGCGCTTCTGCTAGAGCTTCCGGCGTGCCTCCAGATTCTCTGGCTCTGGATCTGGCACCGACTTTACC CTGACAATCTCCAGCCTGCAGCCTGAGGACTTCGCCACCTACTACTGCCAGCAGTACCTGGCCTCTCT GCCACATTTGGCCAGGGAACAAAGGTCGAGATCAAGTGA
23	CAGGTTACAGCTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCGAAACACTGTCTCTGACCTGCAC CGTGTCTGGCGGCTCTGTGTCCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAG GCCTGGAATGGATCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGG CTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCTCTGTGACCGCCGCTGAT ACCGCCATCTACTATTGCGTGCGGGACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCAT GGTCACCGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTAC CTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCT GGAATTCTGGCGCTCTGACATCTGGCGTGACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCCTGTACT CTCTGTCTCCGTCTGTGACCGTGCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACC ACAAGCCATCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAAGTCTGCGACAAGACCCACACCTG TCCTCCATGTCTGTCTCCAGAACTGCTCGGCGGACCTCCGTGTTCTGTTTCTCCAAAGCCTAAGGA CACCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCG AAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGG AACAGTACAACCTCCACCTACAGAGTGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGC AAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCCTGCTCCTATCGAAAAGACCATCAGCAAGG CTAAGGGCCAGCCTCGGGAACCCAGGTTTACACATTGCCTCCATCTCGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAA TGGCCAGCCTGAGAACAACCTACAAGACAACCCCTCCTGTGCTGGACTCCGACGGCTCATTCTTCTGT CTCCAAGCTGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCCTGCTCCGTGATGCAC GAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCTGTCCCCTGAAAAAGGCGGCGGAGGATC TGGCGGAGGTGGAAGCGGAGGCGGTGGATCTGATATCCAGATGACCCAGTCTCTAGCAGCCTGTCT GCCTCTGTGGGCGATAGAGTGACCATCACCTGTGGGCTCTCAGTTCTGTCCAGCTACCTGGCTTG GTATCAGCAGAAGCCTGGCAAGGCCCTAAGCTGCTGATCTACGGCGCTTCTGCTAGAGCTTCCGGCG TGCCCTCCAGATTTCTGGCTCTGGATCTGGCACCGACTTTACCCTGACAATCTCCAGCCTGCAGCCTG AGGACTTCGCCACCTACTACTGCCAGCAGTACCTGGCCTCTCTGCCACATTTGGCCAGGGAACAAAG GTGGAAATCAAAGGTGGCGGCGGTAGTGGTGGCGGAGGAAGCGGCGGAGGCGGCTCTGAAGTTCA

	GCTTGTTGAATCTGGCGGCGGACTGGTTGAGCCTGGCGGATCTCTGAGACTGTCTTGCCGCCAGCG GCTTCACCTTCTCCTCTTACGCTATGTCCTGGGTCCGACAGGCCCCAGGCAAAGGATTGGAGTGGGTG TCCCAGATCTCTCCTGCTGGCGGCTACACCAATTACGCCGACTCTGTGAAGGGCAGATTACCATCTCT GCCGACACCTCCAAGAACACCGCCTACCTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTA CTATTGTGCTAGAGGCGAGCTGCCCTACTTCCGGATGTCCAAAGTGATGGACGTGTGGGGACAGGGA ACCTCGTGACAGTGTCTCTTGA
24	CAGGTTGAGCTGCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTTCCGAAACACTGTCTCTGACCTGCAC CGTGTCTGGCGGCTCTGTGTCCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCCTGGCAAAG GCCTGGAATGGATCGGCCACATCTACTACTCCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGG CTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCTCTGTGACCCGCGTGAT ACCGCCATCTACTATTGCGTGGCGGACAGAGTGACCGGCGCCTTTGATATTGGGGCCAGGGACCAT GGTCACCGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCCTCTGGCTCCTTCCAGCAAGTCTAC CTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCT GGAATTCTGGCGCTCTGACATCTGGCGTGACACCTTTCCAGCTGTGCTGCAGTCTAGCGGCTGTACT CTCTGTCTCCGTCGTGACCGTGCCTTAGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACC ACAAGCCATCCAACCAAGGTGGACAAGAAGGTGGAACCAAGTCTGCGACAAGACCCACACCTG TCCTCCATGTCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCTCTGTTTCTCCAAAGCCTAAGGA CACCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCG AAGTGAAGTTCAATTGGTACGTGGACGGCTGGAAGTGCACAACGCCAAGACCAAGCCTAGAGAGG AACAGTACAACCTCACCTACAGAGTGGTGTCCGTGCTGACCGTGTGACCCAGGATTGGCTGAACGGC AAAGAGTACAAGTGCAAGGTGTCCAACAAGGCCCTGCTGCTCTATCGAAAAGACCATCAGCAAGG CTAAGGGCCAGCCTCGGGAACCCAGGTTTACACATTGCCTCCATCTCGGGACGAGCTGACCAAGAAC CAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAA TGGCCAGCCTGAGAACAACACTACAAGACAACCCCTCTGTGCTGGACTCCGACGGCTATTCTTCTGTA CTCCAAGCTGACAGTGGACAAGTCCAGATGGCAGCAGGGCAACGTGTTCTCTGCTCCGTGATGCAC GAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCTGTCCCTGGAAAAGGCGGCGGAGGATC TGGCGGAGGTGGAAGCGGAGGCGGTGGATCTGAAGTGCAGCTGTTGGAAAGTGGCGGCGGATTGG TTCAGCCTGGCGGATCTCTGAGACTGTCTTGCCGCCTCCGGCTTACCTTCTCCTCTACGCTATGTC CTGGGTCCGACAGGCTCCCGGAAAAGGACTTGAATGGGTGTCCAGATCTCCCTGCTGGCGGCTAC ACCAATTACGCCGACTCTGTGAAGGGCAGATTACCATCTCTCGGACAACCTCCAAGAACACCCGTGA CCTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGGCGAGCTGCCCT ACTTCCGGATGTCCAAAGTGATGGACGTGTGGGGACAGGGAACCCCTCGTGACAGTTTCTAGTGGTGG CGGAGGAAGCGGCGGAGGCGGTTCTGGCGGTGGCGGATCTGAAATTGTGCTGACCCAGTCTCCAGG CACACTAGTTTGAGCCCTGGCGAGAGAGCTACCCTGAGCTGTAGAGCCTCTCAGTTCTCTGTCAGCT ACCTGGCTTGGTATCAGCAGAAGCCAGGACAGGCCCTCGGCTGTTGATCTATGGCGCTTCTGCTAGA GCCAGCGCATCCCTGATAGATTCTCCGGCTCTGGCTCTGGCACCGACTTACCCTGACAATCTCCCGG CTGGAACCTGAGGACTTCGCTGTGTACTACTGCCAGCAGTACCTGGCCTCTCTGCCACATTTGCCAG GGAACAAAGGTCGAGATCAAGTGA
25	GACATCCAGATGACCCAGTCTCCATCATCCCTGTGGCCTCAGTGGGCGACAGAGTGACCATCACTTG TCAAGCCTCCCAAGACATTAGCAACTACCTGAACTGGTACCAGCAGAAGCCCGAAAGGCCCGGAAG CTGCTCATCTATGACGCTTCCAACCTTGAGACTGGAGTGCCTTCGCGCTTCTCCGGCTCCGGGAGCGGT ACCGATTTACCTTACCATCTCTCCCTGCAACCCGAGGACATTGCGACTTACTTCTGCCAACATTTG ATCACCTCCCTCTCGGTTCCGGCGGCGGAACCTAAGGTCGAGATTAAGCGGACCGTGGCTGCCCCGTCC GTGTTTCATCTTCCCGCCGTCCGATGAACAGCTGAAGTCCGGTACCGCATCAGTCGTGTGCTTGTGAAC AACTTCTACCCCGGGAAGCCAAGGTCCAGTGGAAAGTGGACAATGCGCTGCAAGTGGGAACTCGC AGGAATCCGTGACCGAACAGGATTGAAGGACAGCACATACAGCCTGTATCCACCTCACGCTGTG AAGGCCGACTACGAGAAGCACAAAGGTGACGCTGCGAAGTGACCCACCAAGGGCTTAGCAGCCCTG

	TGACCAAGTCCTTCAACCGCGGAGAGTGC
26	GGCGGTGGCGGATCC
27	GGCGGCGGGGGCAGC
28	GGCGGCGGAGGATCT
29	GGCGGAGGCGGTAGC
30	GGTGGTGGCGGATCT
31	GGCGGCGGAGGATCT
32	GGCGGAGGTGGAAGC
33	GGAGGCGGTGGATCT
34	GGTGGCGGAGGAAGC
35	GGCGGAGGCGGTTCT
36	GGCGGTGGCGGATCT
37	GGCGGTGGCGGATCC
38	GGCGGCGGGGGCAGC
39	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYSGNTNYPNPSLKSRITISIDTSKTQFSLKLSVTAADTAIYCVDRDVTGAFDIWGQGTMTVSSASTKGPSVFPLAPSSKSTSGGTAAALGCLVKDYFPEPTVSWNSGALTSKVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKHTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCSCVMHEALHNHYTQKSLSLSPGKGGGSGGGGSGGGGSEVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQISPAGGYTNYADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARGELPYHRMSKVMDEVWGQGLTVTVSSGGGSGGGGSGGGGSEIVLTQSPGTLSPGERATLSCRASQFLSSYLAWYQQKPGQAPRLLIYGASARASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQLASPATFGQGTKVEIK
40	CAGGTTCAAGTCAAGAGTCTGGCCCTGGCCTGGTCAAGCCTCCGAAACACTGTCTCTGACCTGCACCGTGTCTGGCGGCTCTGTCTCTCTGGCGATTACTACTGGACCTGGATCCGGCAGTCTCTGGCAAAGGCCTGGAATGGATCGGCCACATCTACTACTCGGCAACACCAACTACAACCCAGCCTGAAGTCCCGGCTGACCATCTCCATCGACACCAGCAAGACCCAGTTCTCCCTGAAGCTGTCCTCTGTGACCGCCGCTGATACCGCCATCTACTATTGCGTGGGACAGAGTGACCGGCGCCTTTGATATTTGGGGCCAGGGCACCATGGTCACCGTGTCCAGTGCTTCTACCAAGGGACCCAGCGTGTTCCTCTGGCTCCTCCAGCAAGTCTACTCTGGCGGAACAGCTGCTCTGGGCTGTCTGGTCAAGGACTACTTCCCTGAGCCTGTGACCGTGTCTGGAATTCTGGCGCTCTGACATCTGGCGTGACACCTTTCCAGCTGTGCTGCACTAGCGGCCTGTACTCTCTGTCTCCGTCTGACCGTGCCTTCTAGCTCTCTGGGCACCCAGACCTACATCTGCAATGTGAACCAAGCCATCCAACACCAAGGTGGACAAGAAGGTGGAACCCAAGTCTGCGACAAGACCCACACCTGTCTCCATGTCTCTGCTCCAGAACTGCTCGGCGGACCTTCCGTGTTCTGTTCTCCAAAGCCTAAGGACACCTGATGATCTCTCGGACCCCTGAAGTGACCTGCGTGGTGGTGGATGTGTCTCACGAGGATCCCGAAGTGAAGTTCAATTGGTACGTGGACGGCGTGGAAGTGACAACGCCAAGACCAAGCCTAGAGAGGAACAGTACAAGTCAAGGTGTCCAACAAGGCCCTGCTGCTCTATCGAAAAGACCATCAGCAAGGCTAAGGGCCAGCCTCGGGAACCCAGGTTTACACATTGCCTCCATCTCGGGACGAGCTGACCAAGAACAGGTGTCCCTGACCTGTCTCGTGAAGGGCTTCTACCCCTCCGATATCGCCGTGGAATGGGAGTCCAAAGTGGCCAGCCTGAGAACAACTACAAGACAACCCCTCTGTGCTGGACTCCGACGGCTCATTCTTCTGTACTCCAAGCTGACAGTGGACAAGTCCAGATGCGCAGCAGGGCAACGTGTTCTCTGCTCCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGAAGTCCCTGTCTGTCTCCCTGGAAAAGCGGCGGAGGATCTGGCGGAGGTGGAAGCGGAGGCGGTGGATCTGAAGTGACGTGTTGAAAGTGGCGGCGGATTGG

	TTCAGCCTGGCGGATCTCTGAGACTGTCTTGCCGCCTCCGGCTTTACCTTCTCCTCTACGCTATGTC CTGGGTCCGACAGGCTCCCGGAAAAGGACTTGAATGGGTGTCCAGATCTCCCCTGCTGGCGGCTAC ACCAATTACGCCGACTCTGTGAAGGGCAGATTACCATCTCTCGGGACAACCTCCAAGAACACCCTGTA CCTGCAGATGAACTCCCTGAGAGCCGAGGACACCGCCGTGTACTATTGTGCTAGAGGCGAGCTGCCCT ACCACCGGATGTCAAAGTGATGGATGTGTGGGGACAGGGAACCTCTGACAGTCTCTAGTGGTGG CGGAGGAAGCGCGGAGGCGGTTCTGGCGGTGGCGGATCTGAAATTGTGCTGACCCAGTCTCCAGG CACACTCAGTTTGAGCCCTGGCGAGAGAGCTACCTGAGCTGTAGAGCCTCTCAGTTCCTGTCCAGCT ACCTGGCTTGGTATCAGCAGAAGCCAGGACAGGCCCTCGGCTGTTGATCTATGGCGCTTCTGCTAGA GCCAGCGGCATCCCTGATAGATTCTCCGGCTCTGGCTCTGGCACCAGCTTCACCCTGACAATCTCCCGG CTGGAACCTGAGGACTTCGCTGTGTACTACTGCCAGCAGTACCTGGCCTCTCTGCCACATTTGGCCAG GGAACAAAGGTCGAGATCAAG
41	EVQLVESGGGLVQPGGSLRLSCAASGFTSSYAMSWVRQAPGKGLEWVSQISPAGGYTNYADSVKGRFTI SADTSKNTAYLQMNSLRAEDTAVYYCARGELPYFRMSKVMQVWQGTTLTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKHTCTPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHN30AKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQ QGNVFSCSVMEALHNHYTQKSLSPGK
42	EVQLVESGGGLVQPGGSLRLSCAASGFTSSYAMSWVRQAPGKGLEWVSQISPAGGYTNYADSVKGRFTI SADTSKNTAYLQMNSLRAEDTAVYYCARGELPYQMSKVMQVWQGTTLTVSSASTKGPSVFPLAPSSK STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKHTCTPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMEALHNHYTQKSLSPGK
43	EVQLVESGGGLVQPGGSLRLSCAASGFTSSYAMSWVRQAPGKGLEWVSQISPAGGYTNYADSVKGRFTI SADTSKNTAYLQMNSLRAEDTAVYYCARGELPFFRMSQVMDVWQGTTLTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKHTCTPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMEALHNHYTQKSLSPGK
44	EVQLVESGGGLVQPGGSLRLSCAASGFTSSYAMSWVRQAPGKGLEWVSQISPAGGYTNYADSVKGRFTI SADTSKNTAYLQMNSLRAEDTAVYYCARGELPYFRMSKVMQVWQGTTLTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKHTCTPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWY VDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVY TLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMEALHNHYTQKSLSPGK
45	EVQLLESGGGLVQPGGSLRLSCAASGFTSSYAMSWVRQAPGKGLEWVSQISPAGGYTNYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAVYYCARGELPYFRMSKVMQVWQGTTLTVSSASTKGPSVFPLAPSSKS TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP

	SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
46	EVQLLESGGGLVQPGGSLRLSCAASGFTSSYAMSWVRQAPGKGLEWVSQISPAAGGYTNYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGELPYQMSKVM DVWGQGT LTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
47	EVQLLESGGGLVQPGGSLRLSCAASGFTSSYAMSWVRQAPGKGLEWVSQISPAAGGYTNYADSVKGRFTISRDN SKNTLYLQMNSLRAEDTAVYYCARGELPFRRMSQVMDVWGQGT LTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKSRWQQGNVFCFSVMHEALHNHYTQKSLSLSPGK
48	DIQMTQSPSSLSASVGDRVITITCRASQFLSSYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQLASPATFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRKAVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
49	DIQMTQSPSSLSASVGDRVITITCRASQYFSSYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQLASPATFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRKAVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
50	DIQMTQSPSSLSASVGDRVITITCRASQFLSSYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQLASPATFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRKAVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
51	DIQMTQSPSSLSASVGDRVITITCRASQFLSSYLAWYQQKPGKAPKLLIYGASARASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQLASPATFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRKAVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
52	EIVLTQSPGTLSLSPGERATLSCRASQFLSSYLAWYQQKPGQAPRLLIYGASARASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQLASPATFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRKAVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
53	EIVLTQSPGTLSLSPGERATLSCRASQFLSSYLAWYQQKPGQAPRLLIYGASARASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQLASPATFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRKAVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC
54	EIVLTQSPGTLSLSPGERATLSCRASQFLSSYLAWYQQKPGQAPRLLIYGASARASGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQLASPATFGQGTKEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRKAV

	QWKVDNALQSGNSQESVTEQDSKSTYLSSTLTLSKADYEKHKVYACEVTHQGLSPVTKSFNRGEC
55	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGAGCTG CGCCGCCAGCGGCTTACCTTCAGCAGCTACGCCATGAGCTGGGTGAGGCAGGCCCCCGCAAGGGC CTGGAGTGGGTGAGCCAGATCAGCCCCGCCGGCGGCTACACCAACTACGCCGACAGCGTGAAGGGC AGGTTCACCATCAGCGCCGACACCAGCAAGAACACCGCTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGGCGAGCTGCCCTACTTCAGGATGAGCAAGGTGATGGA CGTGTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCTCC CTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACT TCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGC CGTGTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCAGCAGCAGCCTGGGC ACCCAGACCTACATCTGCAACGTGAACCAAGCCAGCAACACCAAGGTGGACAAGAAGGTGGAGC CCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGCCCGCCCCGAGCTGCTGGGCGGCCCCAGC GTGTTCTGTTCCTCCCAAGCCCAAGGACACCTGATGATCAGCAGGACCCCGAGGTGACCTGCGT GGTGGTGGACGTGAGCCACGAGGACCCGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGT GCACAACGCCAAGACCAAGCCAGGGAGGAGCAGTACAACAGCACCTACAGGTGGTGAGCGTGCT GACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCT GCCCCCCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCAGGGAGCCCCAGGTGTACACC CTGCCCCCAGCAGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCT ACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGCCAGCCGAGAACAATAAGACCACCCC CCCCGTGCTGGACAGCGACGGCAGCTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGA GCCTGAGCCTGAGCCCCGGCAAG
56	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGAGCTG CGCCGCCAGCGGCTTACCTTCAGCAGCTACGCCATGAGCTGGGTGAGGCAGGCCCCCGCAAGGGC CTGGAGTGGGTGAGCCAGATCAGCCCCGCCGGCGGCTACACCAACTACGCCGACAGCGTGAAGGGC AGGTTCACCATCAGCGCCGACACCAGCAAGAACACCGCTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGGCGAGCTGCCCTACTACCAGATGAGCAAGGTGATGGA CGTGTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCTCC CTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACT TCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGC CGTGTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCAGCAGCAGCCTGGGC ACCCAGACCTACATCTGCAACGTGAACCAAGCCAGCAACACCAAGGTGGACAAGAAGGTGGAGC CCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGCCCGCCCCGAGCTGCTGGGCGGCCCCAGC GTGTTCTGTTCCTCCCAAGCCCAAGGACACCTGATGATCAGCAGGACCCCGAGGTGACCTGCGT GGTGGTGGACGTGAGCCACGAGGACCCGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGT GCACAACGCCAAGACCAAGCCAGGGAGGAGCAGTACAACAGCACCTACAGGTGGTGAGCGTGCT GACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCT GCCCCCCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCAGGGAGCCCCAGGTGTACACC CTGCCCCCAGCAGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCT ACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGCCAGCCGAGAACAATAAGACCACCCC CCCCGTGCTGGACAGCGACGGCAGCTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGA GCCTGAGCCTGAGCCCCGGCAAG
57	GAGGTGCAGCTGGTGGAGAGCGGCGGCGGCCTGGTGCAGCCCGGCGGCAGCCTGAGGCTGAGCTG CGCCGCCAGCGGCTTACCTTCAGCAGCTACGCCATGAGCTGGGTGAGGCAGGCCCCCGCAAGGGC

	CTGGAGTGGGTGAGCCAGATCAGCCCCGCCGGCGGCTACACCAACTACGCCGACAGCGTGAAGGGC AGGTTACCATCAGCGCCGACACCAGCAAGAACACCGCTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGGCGAGCTGCCCTTCTTCAGGATGAGCCAGGTGATGGA CGTGTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTCCCC CTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCCACCGCCGCTGGGCTGCCTGGTGAAGGACTACT TCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGACACCTTCCCCGC CGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCAGCAGCAGCCTGGGC ACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAGC CCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGCCCGCCCCGAGCTGCTGGGCGGCCCCAGC GTGTTCTGTCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGT GGTGGTGACGTGAGCCACGAGGACCCGAGGTGAAGTTCAACTGGTACGTGGACGCGTGAGGT GCACAACGCCAAGACCAAGCCAGGGAGGAGCAGTACAACAGCACCTACAGGGTGGTGAGCGTGCT GACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCT GCCCCCCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCAGGGAGCCCCAGGTGTACACC CTGCCCCCAGCAGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCT ACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCGAGAACAATAAGACCACCCC CCCCGTGCTGGACAGCGACGGCAGCTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGA GCCTGAGCCTGAGCCCCGGCAAG
58	GAGGTGCAGCTGGTGAGAGCGGCGGCGGCCTGGTGAGCCCGCGGCGCAGCCTGAGGCTGAGCTG CGCCGCCAGCGGCTTACCTTCAGCAGCTACGCCATGAGCTGGGTGAGGCAGGCCCCCGCAAGGGC CTGGAGTGGGTGAGCCAGATCAGCCCCGCCGGCGGCTACACCAACTACGCCGACAGCGTGAAGGGC AGGTTACCATCAGCGCCGACACCAGCAAGAACACCGCTACCTGCAGATGAACAGCCTGAGGGCCG AGGACACCGCCGTGTACTACTGCGCCAGGGGCGAGCTGCCCTACTTCAGGATGAGCAAGGTGATGGA CGTGTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTCCCC CTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCCACCGCCGCTGGGCTGCCTGGTGAAGGACTACT TCCCCGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGACACCTTCCCCGC CGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCAGCAGCAGCCTGGGC ACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAGC CCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGCCCGCCCCGAGCTGCTGGGCGGCCCCAGC GTGTTCTGTCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGT GGTGGTGAGCGTGAGCCACGAGGACCCGAGGTGAAGTTCAACTGGTACGTGGACGCGTGAGGT GCACAACGCCAAGACCAAGCCAGGGAGGAGCAGTACAACAGCACCTACAGGGTGGTGAGCGTGCT GACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCT GCCCCCCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCAGGGAGCCCCAGGTGTACACC CTGCCCCCAGCAGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCT ACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCGAGAACAATAAGACCACCCC CCCCGTGCTGGACAGCGACGGCAGCTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGA GCCTGAGCCTGAGCCCCGGCAAG
59	GAGGTGCAGCTGCTGGAGAGCGGCGGCGGCCTGGTGAGCCCGCGGCGCAGCCTGAGGCTGAGCTGC GCCGCCAGCGGCTTACCTTCAGCAGCTACGCCATGAGCTGGGTGAGGCAGGCCCCCGCAAGGGCC TGGAGTGGGTGAGCCAGATCAGCCCCGCCGGCGGCTACACCAACTACGCCGACAGCGTGAAGGGCA GGTTACCATCAGCAGGGACAACAGCAAGAACACCTGTACCTGCAGATGAACAGCCTGAGGGCCGA GGACACCGCCGTGTACTACTGCGCCAGGGGCGAGCTGCCCTACTTCAGGATGAGCAAGGTGATGGAC GTGTGGGGCCAGGGCACCCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTCCCCC

	TGGCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTT CCCCAGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGACACCTTCCCCGCC GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGC ACCCAGACCTACATCTGCAACGTGAACACAAGCCAGCAACACCAAGGTGGACAAGAAGGTGGAGC CCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGCCCGCCCCGAGCTGCTGGGCGGCCCCAGC GTGTTCTGTTCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGT GGTGGTGGACGTGAGCCACGAGGACCCGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGT GCACAACGCCAAGACCAAGCCAGGGAGGAGCAGTACAACAGCACCTACAGGGTGGTGAAGCGTGT GACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCT GCCCGCCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCAGGGAGCCCCAGGTGTACACC CTGCCCCCAGCAGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGTTCT ACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCGAGAACTACAAGACCACCCC CCCCCTGTGGACAGCGACGGCAGTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGA GCCTGAGCCTGAGCCCCGGCAAG
60	GAGGTGCAGCTGCTGGAGAGCGGCGGCGGCTGGTGCAGCCGGCGGCAGCCTGAGGCTGAGCTGC GCCGCCAGCGGCTTACCTTCAGCAGCTACGCCATGAGCTGGGTGAGGCAGGCCCCGGCAAGGGCC TGGAGTGGGTGAGCCAGATCAGCCCCGCGGCGGCTACACCAACTACGCCGACAGCGTGAAGGGCA GGTTCACCATCAGCAGGGACAACAGCAAGAACCCTGTACCTGCAGATGAACAGCCTGAGGGCCGA GGACACCGCCGTGTACTACTGCGCCAGGGGCGAGCTGCCCTACTACCAGATGAGCAAGGTGATGGAC GTGTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTCCCCC TGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTT CCCCAGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGACACCTTCCCCGCC GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGC ACCCAGACCTACATCTGCAACGTGAACACAAGCCAGCAACACCAAGGTGGACAAGAAGGTGGAGC CCAAGAGCTGCGACAAGACCCACACCTGCCCCCCTGCCCGCCCCGAGCTGCTGGGCGGCCCCAGC GTGTTCTGTTCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGT GGTGGTGGACGTGAGCCACGAGGACCCGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGT GCACAACGCCAAGACCAAGCCAGGGAGGAGCAGTACAACAGCACCTACAGGGTGGTGAAGCGTGT GACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCT GCCCGCCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCAGGGAGCCCCAGGTGTACACC CTGCCCCCAGCAGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGTTCT ACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCGAGAACTACAAGACCACCCC CCCCCTGTGGACAGCGACGGCAGTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTAGCTGCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGA GCCTGAGCCTGAGCCCCGGCAAG
61	GAGGTGCAGCTGCTGGAGAGCGGCGGCGGCTGGTGCAGCCGGCGGCAGCCTGAGGCTGAGCTGC GCCGCCAGCGGCTTACCTTCAGCAGCTACGCCATGAGCTGGGTGAGGCAGGCCCCGGCAAGGGCC TGGAGTGGGTGAGCCAGATCAGCCCCGCGGCGGCTACACCAACTACGCCGACAGCGTGAAGGGCA GGTTCACCATCAGCAGGGACAACAGCAAGAACCCTGTACCTGCAGATGAACAGCCTGAGGGCCGA GGACACCGCCGTGTACTACTGCGCCAGGGGCGAGCTGCCCTTCTCAGGATGAGCCAGGTGATGGAC GTGTGGGGCCAGGGCACCTGGTGACCGTGAGCAGCGCCAGCACCAAGGGCCCCAGCGTGTCCCCC TGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACCGCCGCCCTGGGCTGCCTGGTGAAGGACTACTT CCCCAGAGCCCGTGACCGTGAGCTGGAACAGCGGCGCCCTGACCAGCGGCGTGACACCTTCCCCGCC GTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGC ACCCAGACCTACATCTGCAACGTGAACACAAGCCAGCAACACCAAGGTGGACAAGAAGGTGGAGC

	CCAAGAGCTGCGACAAGACCCACACCTGCCCCCTGCCCGCCCCGAGCTGCTGGGCGGCCCCAGC GTGTTCTGTTCCTCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCGAGGTGACCTGCGT GGTGGTGGACGTGAGCCACGAGGACCCCGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGAGGT GCACAACGCCAAGACCAAGCCAGGGAGGAGCAGTACAACAGCACCTACAGGGTGGTGAGCGTGCT GACCGTGCTGCACCAGGACTGGCTGAACGGCAAGGAGTACAAGTGCAAGGTGAGCAACAAGGCCCT GCCCCCCCCATCGAGAAGACCATCAGCAAGGCCAAGGGCCAGCCAGGGAGCCCCAGGTGTACAC CTGCCCCCAGCAGGGAGGAGATGACCAAGAACCAGGTGAGCCTGACCTGCCTGGTGAAGGGCTTCT ACCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCGAGAACAACTACAAGACCACCC CCCCGTGCTGGACAGCGACGGCAGCTTCTTCTGTACAGCAAGCTGACCGTGGACAAGAGCAGGTGG CAGCAGGGCAACGTGTTCACTGTCAGCGTGATGCACGAGGCCCTGCACAACCACTACACCCAGAAGA GCCTGAGCCTGAGCCCCGGCAAG
62	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCT GCAGGGCCAGCCAGTTCTGAGCAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGAAGGCCCCCAA GCTGCTGATCTACGGCGCCAGCGCCAGGGCCAGCGGCGTGCCAGCAGGTTAGCGGCAGCGGCAG CGGCACCGACTTCACCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGC AGTACCTGGCCAGCCCCGCCACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGC CCCCAGCGTGTTTCTTCTCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCC TGCTGAACAACTTCTACCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCG GCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
63	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCT GCAGGGCCAGCCAGTACTTCAGCAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGAAGGCCCCCAA GCTGCTGATCTACGGCGCCAGCGCCAGGGCCAGCGGCGTGCCAGCAGGTTAGCGGCAGCGGCAG CGGCACCGACTTCACCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGC AGTACCTGGCCAGCCCCGCCACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGC CCCCAGCGTGTTTCTTCTCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCC TGCTGAACAACTTCTACCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCG GCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
64	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCT GCAGGGCCAGCCAGTTCTGAGCAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGAAGGCCCCCAA GCTGCTGATCTACGGCGCCAGCGCCAGGGCCAGCGGCGTGCCAGCAGGTTAGCGGCAGCGGCAG CGGCACCGACTTCACCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGC AGTACCTGGCCAGCCCCGCCACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGC CCCCAGCGTGTTTCTTCTCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCC TGCTGAACAACTTCTACCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCG GCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
65	GACATCCAGATGACCCAGAGCCCCAGCAGCCTGAGCGCCAGCGTGGGCGACAGGGTGACCATCACCT GCAGGGCCAGCCAGTTCTGAGCAGCTTCTGGCCTGGTACCAGCAGAAGCCCGGAAGGCCCCCAA GCTGCTGATCTACGGCGCCAGCGCCAGGGCCAGCGGCGTGCCAGCAGGTTAGCGGCAGCGGCAG

	CGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTACTACTGCCAGC AGTACCTGGCCAGCCCCGCCACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGC CCCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCC TGCTGAACAACTTCTACCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCG GCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCACCC TGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
66	GAGATCGTGCTGACCCAGAGCCCCGGCACCTGAGCCTGAGCCCCGGCGAGAGGGCCACCCTGAGCT GCAGGGCCAGCCAGTTCTGAGCAGCTACCTGGCCTGGTACCAGCAGAAGCCCCGGCCAGGCCCCCAG GCTGCTGATCTACGGCGCCAGCGCCAGGGCCAGCGGCATCCCCGACAGGTTGAGCGGCAGCGGCAGC GGCACCGACTTCACCCTGACCATCAGCAGGCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCAGCA GTACCTGGCCAGCCCCGCCACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGCC CCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGG CAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCACCT GACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
67	GAGATCGTGCTGACCCAGAGCCCCGGCACCTGAGCCTGAGCCCCGGCGAGAGGGCCACCCTGAGCT GCAGGGCCAGCCAGTTCTGAGCAGCTACCTGGCCTGGTACCAGCAGAAGCCCCGGCCAGGCCCCCAG GCTGCTGATCTACGGCGCCAGCGCCAGGGCCAGCGGCATCCCCGACAGGTTGAGCGGCAGCGGCAGC GGCACCGACTTCACCCTGACCATCAGCAGGCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCAGCA GTACCTGGCCAGCCCCGCCACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGCC CCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGG CAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCACCT GACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
68	GAGATCGTGCTGACCCAGAGCCCCGGCACCTGAGCCTGAGCCCCGGCGAGAGGGCCACCCTGAGCT GCAGGGCCAGCCAGTTCTGAGCAGCTACCTGGCCTGGTACCAGCAGAAGCCCCGGCCAGGCCCCCAG GCTGCTGATCTACGGCGCCAGCGCCAGGGCCAGCGGCATCCCCGACAGGTTGAGCGGCAGCGGCAGC GGCACCGACTTCACCCTGACCATCAGCAGGCTGGAGCCCGAGGACTTCGCCGTGTACTACTGCCAGCA GTACCTGGCCAGCCCCGCCACCTTCGGCCAGGGCACCAAGGTGGAGATCAAGAGGACCGTGGCCGCC CCCAGCGTGTTTCATCTTCCCCCCCAGCGACGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGTGCCT GCTGAACAACTTCTACCCAGGGAGGCCAAGGTGCAGTGGAAGGTGGACAACGCCCTGCAGAGCGG CAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACAGCACCTACAGCCTGAGCAGCACCT GACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGCGAGGTGACCCACCAGGGCCT GAGCAGCCCCGTGACCAAGAGCTTCAACAGGGGCGAGTGC
69	QVQLQESGPGLVKPSSETLSLTCTVSGGSVSSGDYYWTWIRQSPGKGLEWIGHIYYSN TNYNPSLSRLTISIDTSKTQFSLKLSSVTAADTAIYYCVRDRVTFGAFDIWGQGTMTVSS (Anti-EGFR VH AA Seq)
70	DIQMTQSPSSLSASVGDRVTITCQASQDISNYLNWYQQKPGKAPKLLIYDASNLETGVP SRFSGSGSGTDFTFTISSLPEDIATYFCQHFHDLPLAFGGGTVKVEIK (Anti-EGFR VL AA Seq)

71	SGDYYWT (Anti-EGFR VH CDR1 AA Seq)
72	HIYYSGNTNYPNPSLK (Anti-EGFR VH CDR2 AA Seq)
73	RVTGAFDI (Anti-EGFR VH CDR3 AA Seq)
74	QASQDISNYL (Anti-EGFR VL CDR1 AA Seq)
75	ASNLET (Anti-EGFR VL CDR2 AA Seq)
76	QHFDHLPLA (Anti-EGFR VL CDR3 AA Seq)
77	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSQISPAGGYTN YADSVKGRFTISRDNKNTLYLQMNSLRAEDTAVYYCARGELPYFRMSKVMMDVWGQGT LVTSS (Anti-NRP1 VH AA Seq)
78	EIVLTQSPGTLSPGERATLSCRASQFLSSYLAWYQQKPGQAPRLLIYGASARASG IPDRFSGSdGSGTDFTLTISRLEPEDFAVYYCQQLASPATFGQGTKVEIK (Anti-NRP1 VL AA Seq)
79	FTFSSYAM (Anti-NRP1 VH CDR1 AA Seq)
80	QISPAGGYTNYADSVK (Anti-NRP1 VH CDR2 AA Seq)
81	GELPYFRMSKVMMDV (Anti-NRP1 VH CDR3 AA Seq)
82	GELPYHRMSKVMMDV (Anti-NRP1 VH CDR3 AA Seq)
83	GELPYYQMSKVMMDV (Anti-NRP1 VH CDR3 AA Seq)
84	GELPFFRMSQVMMDV (Anti-NRP1 VH CDR3 AA Seq)
85	RASQFLSSYLA (Anti-NRP1 VL CDR1 AA Seq)
86	RASQYFSSYLA (Anti-NRP1 VL CDR1 AA Seq)
87	RASQFLSSFLA (Anti-NRP1 VL CDR1 AA Seq)
88	GASARAS (Anti-NRP1 VL CDR2 AA Seq)
89	QQYLASPAT (Anti-NRP1 VL CDR3 AA Seq)

CLAIMS

What is claimed is:

1. A bispecific binding molecule comprising:
 - (a) a target protein binding domain that specifically binds to a target protein, wherein the target protein is a non-Receptor Tyrosine Kinase (non-RTK) protein; and
 - (b) a neuropilin-1 (NRP1) binding domain that binds to NRP1 comprising an antibody or NRP-1-binding fragment thereof,wherein binding of the bispecific binding molecule to the target protein and to NRP1 results in lysosomal degradation of the target protein in a target cell.
2. The bispecific binding molecule of claim 1, wherein the non-RTK protein is selected from integrins, G-protein coupled receptors (GPCRs), immune checkpoint receptors, and ion channel receptors.
3. The bispecific binding molecule of claim 1, wherein the non-RTK protein is an integrin.
4. The bispecific binding molecule of claim 3, wherein the non-RTK protein is integrin $\alpha V\beta$.
5. The bispecific binding molecule of claim 3, wherein the non-RTK protein is integrin $\alpha V\beta 3$.
6. The bispecific binding molecule of claim 1, wherein the non-RTK protein is a GPCR.
7. The bispecific binding molecule of claim 1, wherein the non-RTK protein is an immune checkpoint receptor.
8. The bispecific binding molecule of claim 7, wherein the immune checkpoint receptor is PD-L1.

9. The bispecific binding molecule of claim 1, wherein the non-RTK protein is an ion channel receptor.
10. The bispecific binding molecule of any one of claims 1-9, wherein the target cell is a cancer cell.
11. The bispecific binding molecule of claim 10, wherein the cancer cell is selected from the group consisting of lung cancer, breast cancer, colon and rectum cancer, head and neck cancer, esophagogastric cancer, liver cancer, glioblastoma, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, kidney cancer, and pancreatic cancer.
12. The bispecific binding molecule of claim 10, wherein the cancer cell is a non-small cell lung cancer (NSCLC) cell.
13. The bispecific binding molecule of any one of claims 1-9, wherein the target protein binding domain and the NRP1 binding domain are each independently selected from the group consisting of IgG, half antibodies, single-domain antibodies, nanobodies, Fabs, monospecific Fab2, Fc, scFv, minibodies, IgNAR, V-NAR, hcIgG, VHH domain, camelid antibodies, and peptibodies.
14. The bispecific binding molecule of claim 1, wherein the NRP1 binding domain comprises:
- (i) an antibody heavy chain variable (VH) domain comprising CDR1, CDR2 and CDR3 regions (HCDR1, HCDR2 and HCDR3, respectively), wherein HCDR1 consists of the sequence shown in SEQ ID NO: 79, HCDR2 consists of the sequence shown in SEQ ID NO: 80, and HCDR3 consists of the sequence shown in any one of SEQ ID NOs: 81-84; and
 - (ii) an antibody light chain variable (VL) domain comprising CDR1, CDR2 and CDR3 regions (LCDR1, LCDR2 and LCDR3, respectively), wherein LCDR1 consists of the sequence shown in any one of SEQ ID NOs: 85-87, LCDR2 consists of

the sequence shown in SEQ ID NO: 88, and LCDR3 consists of the sequence shown in SEQ ID NO: 89.

15. The bispecific binding molecule of claim 14, wherein:
 - (i) HCDR1 consists of the sequence shown in SEQ ID NO: 79, HCDR2 consists of the sequence shown in SEQ ID NO: 80, and HCDR3 consists of the sequence shown in any one of SEQ ID NO: 84; and
 - (ii) LCDR1 consists of the sequence shown in SEQ ID NO: 85, LCDR2 consists of the sequence shown in SEQ ID NO: 88, and LCDR3 consists of the sequence shown in SEQ ID NO: 89.
16. The bispecific binding molecule of any one of claims 1-15, which is part of an antibody-drug conjugate (ADC).
17. A nucleic acid encoding the bispecific binding molecule of any one of claims 1-15.
18. An expression vector comprising the nucleic acid of claim 17.
19. A cell capable of protein expression comprising the expression vector of claim 18.
20. A use of the bispecific binding molecule of any one of claims 1-15 in the manufacture of a medicament for treating cancer in a subject.
21. A method of inducing lysosomal degradation of a target protein in a cell, the method comprising contacting the cell with the bispecific binding molecule of any one of claims 1-15 such that lysosomal degradation of the target protein is induced in the cell.
22. The method of claim 21, wherein the cell comprises one or more mutations in the target protein and/or overexpresses the target protein.

23. The method of claim 21, wherein the target protein is an integrin.
24. The method of claim 21, wherein the target protein is a GPCR.
25. The method of claim 21, wherein the target protein is an immune checkpoint receptor.
26. The method of claim 21, wherein the target protein is an ion channel receptor.
27. The method of claim 21, wherein the cell is resistant or refractory to responsiveness to an inhibitor of the target protein.
28. A method of inhibiting tumor growth in a subject having a tumor, the method comprising administering to the subject the bispecific binding molecule of any one of claims 1-15 such that growth of the tumor in the subject is inhibited.
29. The method of claim 28, wherein the tumor comprises one or more mutations in the target protein and/or overexpresses the target protein.
30. The method of claim 28, wherein the target protein is an integrin.
31. The method of claim 28, wherein the target protein is a GPCR.
32. The method of claim 28, wherein the target protein is an immune checkpoint receptor.
33. The method of claim 28, wherein the target protein is an ion channel receptor.
34. The method of claim 28, wherein the tumor is resistant or refractory to responsiveness to an inhibitor of the target protein.
35. The method of claim 28, wherein the bispecific binding molecule is administered intravenously, intraperitoneally, intrathecally, intraventricularly, or intraparenchymally.