BONE-TARGETED ANTIBODIES AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to United States Provisional Application Serial No. 63/558,602, filed February 27, 2024, the entirety of which is incorporated herein by reference.

BACKGROUND

[0002] Antibody-based therapies have proved to be of great value in treatment of neoplastic disorders including cancers. Despite the clinical success of some of these biopharmaceuticals, reaching targets in the bone microenvironment has proved to be difficult due to the relatively low vascularization of bone tissue and the presence of physical barriers. Accordingly, there exists a need for new antibody-based therapies which may target, e.g., bone metastases of cancers, e.g., prostate cancers.

SUMMARY

[0003] In some embodiments, the present disclosure provides an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to a prostate cancer-associated antigen and wherein the antibody or antigen-binding fragment thereof comprises a bone-targeting moiety. In some embodiments, a prostate cancer-associated antigen comprises or is PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2. In some embodiments, a prostate cancer-associated antigen comprises or is PSMA. In some embodiments, the present disclosure provides an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to a sarcoma-associated antigen and wherein the antibody or antigen-binding fragment thereof comprises a bone-targeting moiety. In some embodiments, the present disclosure provides an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to a sarcoma-associated antigen and wherein the antibody or antigen-binding fragment thereof comprises a bone-targeting moiety. In some embodiments, the present disclosure provides an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to an

osteosarcoma-associated antigen and wherein the antibody or antigen-binding fragment thereof comprises a bone-targeting moiety. In some embodiments, an osteosarcoma-associated antigen comprises or is IFITM5, uPARAP, CD99, or LRRC15. In some embodiments, an antibody or antigen-binding fragment thereof comprises or is a monoclonal antibody.

[0004] In some embodiments, a bone-targeting moiety comprises a bone-targeting peptide. In some embodiments, a bone-targeting moiety is a negatively charged peptide. In some embodiments, a bone-targeting moiety comprises one or more carboxylic peptides. In some embodiments, a bone-targeting peptide comprises or is Asp^3, Asp^4, Asp^5, Asp^6, Asp^7, Asp^8, Asp^9, Asp^{10}, Asp^{11}, Asp^{12}, Asp^{13}, Asp^{14}, or Asp^{15}. In some embodiments, a bone-targeting peptide comprises or is Asp^6. In some embodiments, a bone-targeting peptide comprises or is Asp^6. In some embodiments, a bone-targeting peptide comprises or is Glu^3, Glu^4, Glu^5, Glu^6, Glu^7, Glu^8, Glu^9, Glu^{10}, Glu^{11}, Glu^{12}, Glu^{13}, Glu^{14}, or Glu^{15}. In some embodiments, a bone-targeting peptide comprises or is $(Asp\text{-}Ser\text{-}Ser)_1$, $(Asp\text{-}Ser\text{-}Ser)_2$, $(Asp\text{-}Ser\text{-}Ser)_3$, $(Asp\text{-}Ser\text{-}Ser)_4$, $(Asp\text{-}Ser\text{-}Ser)_5$, $(Asp\text{-}Ser\text{-}Ser)_6$, $(Asp\text{-}Ser\text{-}Ser)_7$, $(Asp\text{-}Ser\text{-}Ser)_8$, $(Asp\text{-}Ser\text{-}Ser)_9$, or $(Asp\text{-}Ser\text{-}Ser)_{10}$. In some embodiments, a bone-targeting peptide comprises or is KNFQSRSH, KRRTPVRE, KTYASMQW, VTKHLNQISQSY, IVQSKHTLSNQY, DHMDDMDDEDDDDHVDSQDSIDSNDSDDVDDTDDSH, SVSVGMKPSPRP, NNHYLPR, QPYHPTIPQSVH, CQYPTLKSC, HAPVQPQ, TMGFTAPRFPHY, PGEKADRAEKADRA, PGEKSHSASDRTA, PGYINLSYEKSHSQAINTDRTA, TMRNPITSLISV, TVFLDHENANKILNQPKSYNSGKLAEPRREVAELEPRREVAEL, AEPRREVAELEPRREVAEL, AAFVSKQEGSEVVKQPRSYLYQWLGAPVPYPDPLAEPRREVAELEPRREVAELNPDCDELADHI GFQEAYRRFYGPV, KEIPPIPLLAPS, NNVSQKWQQRLI, NSMIAHNKTRMH, GIHVPWMPPVAF, QRSWTLDSALSM, SGHQLLLNKMPN, SSTLKTFFGFPD, DSSNPIFWRPSS, NYSHLRVKLPTP, ATWSHHLSSAGL, SYSQMDPPRSLP, LLADTTHRPWT, TMRNPITSLISVGGGS, LLADTTHHRPWTGGGS, KEIPPIPLLAPSGGGS, NNVSQKWQQRLIGGGS, NSMIAHNKTRMHGGGS, GIHVPWMPPVAFGGGS, QRSWTLDSALSMGGGS, SGHQLLLNKMPNGGGS, SSTLKTFFGFPDGGGS, DSSNPIFWRPSSGGGS, NYSHLRVKLPTPGGGS, ATWSHHLSSAGLGGGS, or SYSQMDPPRSLPGGGS.

[0005] In some embodiments, a bone-targeting peptide is attached to a N-terminus or C-terminus of a light chain or a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting peptide is attached to a N-terminus or C-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting peptide is attached to a N-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting peptide is attached to a C-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting peptide is attached to a N-terminus or C-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting peptide is

attached to a N-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting peptide is attached to a C-terminus of a heavy chain of an antibody or antigen-binding fragment thereof.

[0006] In some embodiments, a bone-targeting peptide is inserted at an internal permissive site of an antibody or antigen-binding fragment thereof. In some embodiments, an internal permissive site is an internal permissive site of a light chain or an internal permissive site of a heavy chain. In some embodiments, an internal permissive site is an internal permissive site of a light chain. In some embodiments, an internal permissive site is an internal permissive site of a heavy chain. In some embodiments, an internal permissive site of a light chain is or corresponds to A153, optionally wherein the bone-targeting peptide is inserted following A153. In some embodiments, an internal permissive site of a heavy chain is or corresponds to G118, P123, A165, P243, D283, N344, or G361, optionally wherein the bone-targeting peptide is inserted following G118, P123, A165, P243, D283, N344, or G361. In some embodiments, an internal permissive site of a heavy chain is or corresponds to G118. In some embodiments, an internal permissive site of a heavy chain is or corresponds to P123. In some embodiments, an internal permissive site of a heavy chain is or corresponds to A165. In some embodiments, an internal permissive site of a heavy chain is or corresponds to P243. In some embodiments, an internal permissive site of a heavy chain is or corresponds to D283. In some embodiments, an internal permissive site of a heavy chain is or corresponds to N344. In some embodiments, an internal permissive site of a heavy chain is or corresponds to G361. In some embodiments, an internal permissive site is an internal permissive site in a loop region of a light chain or an internal permissive site in a loop region of a heavy chain. In some embodiments, an internal permissive site is an internal permissive site that is an externally facing site of a light chain or an internal permissive site that is an externally facing site of a heavy chain. In some embodiments, an internal permissive site is an internal permissive site that is an externally facing site in a loop region of a light chain or an internal permissive site that is an externally facing site in a loop region of a heavy chain.

[0007] In some embodiments, at least one internal permissive site is an internal permissive site in a loop region of a light chain and/or an internal permissive site in a loop region of a heavy chain. In some embodiments, at least one internal permissive site is an internal permissive site that is an externally facing site of a light chain and/or an internal permissive site that is an externally facing site of a heavy chain. In some embodiments, at least one internal permissive site is an internal permissive site that is an externally facing site in a loop region of a light chain and/or an internal permissive site that is an externally facing site in a loop region of a heavy chain.

[0008] In some embodiments, 1 to (n + 15) amino-acid residues are deleted from an antibody or antigen-binding fragment thereof following an insertion of a bone-targeting peptide, wherein n is the number of amino-acid residues in the bone-targeting peptide.

[0009] In some embodiments, an antibody or antigen-binding fragment thereof comprises a second bone-targeting moiety. In some embodiments, a second bone-targeting moiety is the same as a first bone-targeting moiety. In some embodiment, a second bone-targeting moiety is different than a first bone-targeting moiety. In some embodiments, a second bone-targeting moiety is a negatively charged peptide. In some embodiments, a second bone-targeting moiety comprises one or more carboxylic peptides. In some embodiments, a second bone-targeting moiety comprises or is a bone-targeting peptide. In some embodiments, a second bone-targeting peptide comprises or is Asp^3, Asp^4, Asp^5, Asp^6, Asp^7, Asp^8, Asp^9, Asp^{10}, Asp^{11}, Asp^{12}, Asp^{13}, Asp^{14}, or Asp^{15}. In some embodiments, a second bone-targeting peptide comprises or is Asp^6. In some embodiments, a second bone-targeting peptide comprises or is Glu^3, Glu^4, Glu^5, Glu^6, Glu^7, Glu^8, Glu^9, Glu^{10}, Glu^{11}, Glu^{12}, Glu^{13}, Glu^{14}, or Glu^{15}. In some embodiments, a second bone-targeting peptide is attached to a N-terminus or C-terminus of a light chain or a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a second bone-targeting peptide is inserted at an internal permissive site of an antibody or antigen-binding fragment thereof. In some embodiments, 1 to (n + 15) amino-acid residues are deleted from an antibody or antigen-binding fragment thereof following an insertion of a second bone-targeting peptide, wherein n is the number of amino-acid residues in the second bone-targeting peptide.

[0010] In some embodiments, an antibody or antigen-binding fragment thereof that comprises at least two bone-targeting moieties may comprise at least one bone-targeting moiety that preferentially targets and/or binds osteoclastic bone and at least one bone-targeting moiety that preferentially targets and/or binds osteoblastic bone. For example, without wishing to be bound by any one theory, an antibody or antigen-binding fragment thereof may comprise a first bone-targeting moiety that is or comprises Asp^n and a second bone-targeting moiety that is or comprises $(Asp\text{-}Ser\text{-}Ser)_n$. In some embodiments, an antibody or antigen-binding fragment thereof that comprises at least two bone-targeting moieties may comprise only bone-targeting moieties that preferentially target and/or bind osteoclastic bone. In some embodiments, an antibody or antigen-binding fragment thereof that comprises at least two bone-targeting moieties may comprise only bone-targeting moieties that preferentially target and/or bind osteoblastic bone.

[0011] In some embodiments, an antibody or antigen-binding fragment thereof comprises one or more additional bone-targeting moieties. In some embodiments, one or more additional bone-targeting moieties comprise 3 bone-targeting moieties (e.g., 3 inserted bone-targeting moieties). In some embodiments, one or more additional bone-targeting moieties comprise 4 bone-targeting moieties (e.g., 4 inserted bone-targeting moieties). In some embodiments, one or more additional bone-targeting moieties comprise 5

bone-targeting moieties (e.g., 5 inserted bone-targeting moieties). In some embodiments, one or more additional bone-targeting moieties are inserted at one or more permissive internal sites provided herein, e.g., A153 of a light chain or G118, P123, A165, P243, D283, N344, or G361 of a heavy chain.

[0012] In some embodiments, an antibody or antigen-binding fragment thereof comprises a light chain comprising a sequence selected from Table 1. In some embodiments, an antibody or antigen-binding fragment thereof comprises a heavy chain comprising a sequence selected from Table 2. In some embodiments, an antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 2. In some embodiments, an antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 3. In some embodiments, an antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 4. In some embodiments, an antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence of SEQ ID NO: 19. In some embodiments, an antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence of SEQ ID NO: 24. In some embodiments, an antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 2 and a heavy chain comprising an amino-acid sequence of SEQ ID NO: 19. In some embodiments, an antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 3 and a heavy chain comprising an amino-acid sequence of SEQ ID NO: 24. In some embodiments, an antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 4 and a heavy chain comprising an amino-acid sequence of SEQ ID NO: 24.

[0013] In some embodiments, an antibody or antigen-binding fragment thereof is associated with a target agent. In some embodiments, an antibody or antigen-binding fragment thereof is conjugated to a target agent. In some embodiments, an antibody or antigen-binding fragment thereof is directly or indirectly linked to a target agent. In some embodiments, an antibody or antigen-binding fragment thereof is directly or indirectly covalently linked to a target agent.

[0014] In some embodiments, a target agent comprises an anti-cancer agent, an alkylating agent, an antitumor antibiotic, an antimetabolite, an antimitotic agent, a cytotoxic agent, a hormone, a nitrosourea, a plant alkaloid, a taxane, a radioligand, or any combination thereof. In some embodiments, a radioligand comprises an alpha emitter or a beta emitter. In some embodiments, a radioligand comprises actinium, lutetium, indium, radium, Pb-212, Cu-67, astatine, or thorium. In some embodiments, a target agent comprises calicheamicin, deruxtecan, govitecan SN-38, monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF), maytansinoid, SG3199, duocarmycin, exatecan, tubulysin, PNU-159682, TOP2 inhibitor, TLR agonist, STING agonist, amanitin, cribulin, MMAU, hemiasterlin, or any combination or derivative thereof. In some embodiments, a target agent comprises an androgen receptor degrader, integrin

inhibitor, EZH2, adenosine receptor inhibitors (CD73), WNT pathway inhibitor, AKT inhibitor, steroidogenesis inhibitor (e.g., ODM-208), PARP inhibitor, immune activator (e.g., TLR3 agonist), BET inhibitor, pyrrolobenzodiazepine (PBD), MYC pathway inhibitor, RAS pathway inhibitor, PI3K inhibitor, NRG1 inhibitor, SMARCA2 degrader, SMARCA2 inhibitor, SMARCA4 degrader, SMARCA4 inhibitor, farnesyl pyrophosphate synthase inhibitor, mTOR inhibitor, CDK4 inhibitor, CDK6 inhibitor, VEGFR2 inhibitor, MET inhibitor, tyrosine kinase inhibitor, histone deacetylase inhibitor, Janus kinase inhibitor, BCL-2 inhibitor, KRAS inhibitor, ALK5 inhibitor, pseudomonas exotoxin A (PEA), diphtheria toxin, or any combination thereof.

[0015] In some embodiments, an antibody or antigen-binding fragment thereof comprises one or more bone targeting moieties comprising a combination of Asp and Glu residues.

[0016] In some embodiments, the present disclosure provides a method of delivering a target agent to a cancer cell in a system, comprising administering or delivering to the system an effective amount of an antibody or antigen-binding fragment thereof provided herein. In some embodiments, the present disclosure provides a method of delivering a target agent to a cancer cell in a system, comprising administering or delivering to the system an effective amount of an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to a prostate cancer-associated antigen and wherein the antibody or antigen-binding fragment thereof comprises a bone-targeting moiety.

[0017] In some embodiments, the present disclosure provides a method of killing a cancer cell in a system, comprising administering or delivering to the system an effective amount of an antibody or antigen-binding fragment thereof provided herein. In some embodiments, the present disclosure provides a method of killing a cancer cell in a system, comprising administering or delivering to the system an effective amount of an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to a prostate cancer-associated antigen and wherein the antibody or antigen-binding fragment thereof comprises a bone-targeting moiety. In some embodiments, an antibody or antigen-binding fragment thereof is delivered using one or more of a cell therapy, extracellular vesicle, mRNA, LNP, or VLP. In some embodiments, a system comprises or is a population of cells. In some embodiments, a system comprises or is a subject. In some embodiments, a system comprises or is an animal. In some embodiments, a system comprises or is a mammal. In some embodiments, a system comprises or is a human. In some embodiments, a system expresses a prostate cancer-associated antigen. In some embodiments, a system expresses one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6,

MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2. In some embodiments, a system expresses PSMA. In some embodiments, a system expresses a sarcoma-associated antigen. In some embodiments, a system expresses an osteosarcoma-associated antigen. In some embodiments, a system expresses one or both of IFITM5, uPARAP, CD99, or LRRC15.

[0018] In some embodiments, the present disclosure provides a method of treating a condition, disorder, or disease, comprising administering or delivering to a subject suffering therefrom a therapeutically effective amount of an antibody or antigen-binding fragment thereof provided herein. In some embodiments, the present disclosure provides a method of treating a condition, disorder, or disease, comprising administering or delivering to a subject suffering therefrom a therapeutically effective amount of an antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof binds to a prostate cancer-associated antigen and wherein the antibody or antigen-binding fragment thereof comprises a bone-targeting moiety.

[0019] In some embodiments, the present disclosure provides methods of treating prostate cancer comprising administering or delivering to a subject suffering therefrom a therapeutically effective amount of an immune stimulating or immune checkpoint inhibiting antibody or antigen-binding fragment thereof. In some embodiments, an antibody or antigen-binding fragment thereof comprises a bone-targeting moiety.

[0020] In some embodiments, a prostate cancer-associated antigen is a membrane bound protein expressed in prostate cancer cells. In some embodiments, a prostate cancer-associated antigen is an immune checkpoint inhibitor. In some embodiments, a prostate cancer-associated antigen is a membrane bound protein expressed in prostate cancer cells. In some embodiments, a prostate cancer-associated antigen is a membrane bound protein expressed in prostate tumor stroma. In some embodiments, a prostate cancer-associated antigen is a membrane bound protein encoded by tumorigenic transforming viruses. In some embodiments, a prostate cancer-associated antigen is a membrane bound protein that promotes tumor cell growth. In some embodiments, a prostate cancer-associated antigen is a membrane bound protein whose inhibition. In some embodiments, a prostate cancer-associated antigen is a receptor tyrosine kinase. In some embodiments, a prostate cancer-associated antigen is a receptor protein serine/threonine kinases. In some embodiments, a prostate cancer-associated antigen is an enzyme. In some embodiments, a prostate cancer-associated antigen is a membrane bound protein expressed in prostate cancer cells. In some embodiments, a prostate cancer-associated antigen is a Matrix metalloproteinase. In some embodiments, a prostate cancer-associated antigen is a membrane bound protease. In some embodiments, a prostate cancer-associated antigen is a membrane bound ion channel. In some embodiments, a prostate cancer-associated

antigen is a membrane bound solute carrier. In some embodiments, a prostate cancer-associated antigen is a membrane bound ABC transporter. In some embodiments, a prostate cancer-associated antigen is a cytokine. In some embodiments, a prostate cancer-associated antigen is an integrin. In some embodiments, a prostate cancer-associated antigen is a protein that binds to the extra cellular matrix. In some embodiments, a prostate cancer-associated antigen is a growth factor receptor. In some embodiments, a prostate cancer-associated antigen is a growth factor. In some embodiments, a prostate cancer-associated antigen is a cytokine receptor. In some embodiments, a prostate cancer-associated antigen is a membrane bound glycoprotein. In some embodiments, a prostate cancer-associated antigen is a membrane bound protein that undergoes endocytosis. In some embodiments, a prostate cancer-associated antigen that has undergone cancer-dependent changes in glycosylation. In some embodiments, a prostate cancer-associated antigen is a G-protein coupled receptor. In some embodiments, a prostate cancer-associated antigen is an angiogenic factor. In some embodiments, a prostate cancer-associated antigen is an HLA-expressed antigen. In some embodiments, a prostate cancer-associated antigen is an HLA. In some embodiments, a prostate cancer-associated antigen is an immune co-stimulatory protein. In some embodiments, a prostate cancer-associated antigen is a T cell stimulating protein. In some embodiments, a prostate cancer-associated antigen is an NK cell stimulating protein. In some embodiments, a prostate cancer-associated antigen is a neuropeptide receptor. In some embodiments, a prostate cancer-associated antigen is an endocrine hormone receptor. In some embodiments, a prostate cancer-associated antigen is a peptide hormone receptor. In some embodiments, a prostate cancer-associated antigen is a peptide hormone receptor. In some embodiments, a prostate cancer-associated antigen is a membrane bound tumor necrosis factor. In some embodiments, a prostate cancer-associated antigen is a proteoglycan. In some embodiments, a prostate cancer-associated antigen is a cell adhesion molecule.

[0021] In some embodiments, a condition, disorder, or disease comprises or is a cancer. In some embodiments, a condition, disorder, or disease comprises or is prostate cancer. In some embodiments, a condition, disorder, or disease comprises or is a bone metastasis. In some embodiments, a condition, disorder, or disease comprises or is a prostate cancer bone metastasis. In some embodiments, a condition, disorder, or disease comprises or is a tumor. In some embodiments, a condition, disorder, or disease comprises or is a prostate tumor. In some embodiments, a condition, disorder, or disease comprises or is a bone tumor.

[0022] In some embodiments, a subject is an animal. In some embodiments, a subject is a mammal. In some embodiments, a subject is a human. In some embodiments, a subject is a patient.

[0023] It is contemplated that any method or composition described herein can be implemented with respect to any other method or composition described herein. Other objects, features and advantages of the present disclosure will become apparent from the following detailed description. It should be understood,

however, that the detailed description and the specific examples, while indicating specific embodiments of the disclosure, are given by way of illustration only, since various changes and modifications within the spirit and scope of the disclosure will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] Figure 1. Plot of Root Mean Square Deviation (RMSD) for OT-402 (left) and OT-402B (right).

[0025] Figure 2. Plot of Root Mean Square Fluctuation for heavy chains of OT-402 (wild) and OT-402B (MUT) and light chains of OT-402 (wild) and OT-402B (MUT).

[0026] Figure 3. Exemplary gel images of SDS-PAGE of OT-402 (left) and OT-402B (right) under non-reduced (NR) and reduced (R) conditions. L = affinity chromatography load; FT = affinity chromatography full-through; E = affinity chromatography elute; M = molecular weight standard.

[0027] Figure 4. Exemplary spectra from LC-ESI-MS of non-reduced OT-402 (left) and non-reduced OT-402B (right).

[0028] Figure 5A. Exemplary spectra from LC-ESI-MS of reduced OT-402 heavy chain (left) and OT-402B heavy chain (right).

[0029] Figure 5B. Exemplary spectra from LC-ESI-MS of reduced OT-402 light chain (left) and OT-402B light chain (right).

[0030] Figure 6A. Exemplary results from a surface plasmon resonance (SPR) assay of OT-402. Curves are shown for various concentrations (300 nM, 100 nM, 33.33 nM, 11.11 nM, 3.7 nM, 1.23 nM, 0.41 nM) of antibody. The X-axis depicts time in seconds; the Y-axis depicts response in relative units.

[0031] Figure 6B. Exemplary results from a surface plasmon resonance (SPR) assay of OT-402B. Curves are shown for various concentrations (300 nM, 100 nM, 33.33 nM, 11.11 nM, 3.7 nM, 1.23 nM, 0.41 nM) of antibody. The X-axis depicts time in seconds; the Y-axis depicts response in relative units.

[0032] Figure 7. Graphs of exemplary results from a hydroxyapatite (HA)-binding assay of anti-PSMA antibodies (OT-401, OT-401B, OT-402, OT-402B, OT-403, OT-403B). In top left graph, top plotted line represents data for OT-401B and bottom plotted line represents data for OT-401. In top right graph, top plotted line represents data for OT-402B and bottom plotted line represents data for OT-402. In bottom center graph, top plotted line represents data for OT-403B and bottom plotted line represents data for OT-403.

[0033] Figure 8A. Exemplary results from a baculovirus-based off-target binding assay of anti-PSMA antibodies (OT-401, OT-401B, OT-402, OT-402B, OT-403, OT-403B). At a concentration of 250 ug/ml, plotted lines represent, from top to bottom, data for OT-402B, Positive control, OT-401B, OT-402, OT-403B, OT-401, OT-403, and Negative control. At a concentration of 50 ug/ml, plotted lines represent, from

top to bottom, data for OT-401B, OT-402B, Positive control, OT-402, OT-403B, OT-401, OT-403, and Negative control.

[0034] Figure 8B. Exemplary results from a DNA-based off-target binding assay of anti-PSMA antibodies (OT-401, OT-401B, OT-402, OT-402B, OT-403, OT-403B). At a concentration of 250 ug/ml, plotted lines represent, from top to bottom, data for Positive control, OT-402, OT-401B, OT-402B, OT-401, OT-403, OT-403B, and Negative control.

[0035] Figure 9A. Exemplary results from a complete blood count (CBC) using serum from mice at day 14 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean white blood cell (WBC) counts. Right graph depicts mean red blood cell (RBC) counts. Error bars represent standard error of the mean (SEM).

[0036] Figure 9B. Exemplary results from a complete blood count (CBC) using serum from mice at day 14 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean platelet (PLT) counts. Right graph depicts reticulocyte (RET) counts. Error bars represent standard error of the mean (SEM).

[0037] Figure 9C. Exemplary results from a complete blood count (CBC) using serum from mice at day 14 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean neutrophil (NEUT) counts. Right graph depicts mean neutrophil percentage of white blood cells. Error bars represent standard error of the mean (SEM).

[0038] Figure 9D. Exemplary results from a complete blood count (CBC) using serum from mice at day 14 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean lymphocyte (LYMPH) counts. Right graph depicts mean lymphocyte percentage of white blood cells. Error bars represent standard error of the mean (SEM).

[0039] Figure 9E. Exemplary results from a complete blood count (CBC) using serum from mice at day 14 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean monocyte (MONO) counts. Right graph depicts mean monocyte percentage of white blood cells. Error bars represent standard error of the mean (SEM).

[0040] Figure 9F. Exemplary results from a complete blood count (CBC) using serum from mice at day 14 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts

mean eosinophil (EOS) counts. Right graph depicts mean eosinophil percentage of white blood cells. Error bars represent standard error of the mean (SEM).

[0041] Figure 10A. Exemplary results from a complete blood count (CBC) using serum from mice at day 21 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean white blood cell (WBC) counts. Right graph depicts mean red blood cell (RBC) counts. Error bars represent standard error of the mean (SEM).

[0042] Figure 10B. Exemplary results from a complete blood count (CBC) using serum from mice at day 21 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean platelet (PLT) counts. Right graph depicts reticulocyte (RET) counts. Error bars represent standard error of the mean (SEM).

[0043] Figure 10C. Exemplary results from a complete blood count (CBC) using serum from mice at day 21 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean neutrophil (NEUT) counts. Right graph depicts mean neutrophil percentage of white blood cells. Error bars represent standard error of the mean (SEM).

[0044] Figure 10D. Exemplary results from a complete blood count (CBC) using serum from mice at day 21 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean lymphocyte (LYMPH) counts. Right graph depicts mean lymphocyte percentage of white blood cells. Error bars represent standard error of the mean (SEM).

[0045] Figure 10E. Exemplary results from a complete blood count (CBC) using serum from mice at day 21 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean monocyte (MONO) counts. Right graph depicts mean monocyte percentage of white blood cells. Error bars represent standard error of the mean (SEM).

[0046] Figure 10F. Exemplary results from a complete blood count (CBC) using serum from mice at day 21 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean eosinophil (EOS) counts. Right graph depicts mean eosinophil percentage of white blood cells. Error bars represent standard error of the mean (SEM).

[0047] Figure 11A. Exemplary results from a liver enzyme assay using serum from mice at day 21 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody

X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean levels of alanine aminotransferase (ALT). Right graph depicts mean levels of aspartate aminotransferase (AST). Error bars represent standard error of the mean (SEM).

[0048] Figure 11B. Exemplary results from a liver enzyme assay using serum from mice at day 21 post-administration of a single dose of anti-PSMA antibodies (Antibody X, Bone-Targeted (BT) Antibody X, Antibody W, Bone-Targeted (BT) Antibody W) or vehicle (PBS) control. Left graph depicts mean levels of alkaline phosphatase (ALP). Right graph depicts mean levels of calcium. Error bars represent standard error of the mean (SEM).

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0049] Technologies of the present disclosure may be understood more readily by reference to the following detailed description of certain embodiments. Among other things, the present disclosure provides antibodies or antigen-binding fragments thereof, conjugates, compositions, and methods for treating various conditions, diseases, and disorders (e.g., cancers, tumors, metastases). In some embodiments, the present disclosure provides bone-targeted antibodies or antigen-binding fragments thereof. In some embodiments, the present disclosure provides conjugates comprising a bone-targeted antibody or antigen-binding fragment thereof and one or more target agents. In some embodiments, the present disclosure provides methods for killing a cancer cell in a system. In some embodiments, the present disclosure provides methods for delivering a target agent to a cancer cell in a system. In some embodiments, the present disclosure provides methods for treating various conditions, diseases, and disorders, e.g., cancer, e.g., prostate cancer, in a subject.

Definitions

[0050] As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001.

[0051] As used herein in the present disclosure, unless otherwise clear from context, (i) the term "a" or "an" may be understood to mean "at least one"; (ii) the term "or" may be understood to mean "and/or"; (iii) the terms "comprising", "comprise", "including" (whether used with "not limited to" or not), and "include" (whether used with "not limited to" or not) may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components

or steps; (iv) the term "another" may be understood to mean at least an additional/second one or more; (v) the terms "about" and "approximately" may be understood to permit standard variation as would be understood by those of ordinary skill in the art; and (vi) where ranges are provided, endpoints are included.

[0052] About: As used herein, the term "about", when used herein in reference to a value, refers to a value that is similar, in context to the referenced value. In general, those skilled in the art, familiar with the context, will appreciate the relevant degree of variance encompassed by "about" in that context. For example, in some embodiments, the term "about" may encompass a range of values that within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less of the referred value.

[0053] Administering: As used herein, the term "administering" or "administration" typically refers to the administration of a composition to a subject to achieve delivery of an agent that is, or is included in, a composition to a target site or a site to be treated. Those of ordinary skill in the art will be aware of a variety of routes that may, in appropriate circumstances, be utilized for administration to a subject, for example a human. For example, in some embodiments, administration may be parenteral. In some embodiments, administration may be intravenous. In some embodiments, administration may be oral. In some embodiments, administration may be via injection. In some embodiments, administration may be systemic. In some embodiments, administration may involve only a single dose. In some embodiments, administration may involve application of a fixed number of doses. In some embodiments, administration may involve dosing that is intermittent (e.g., a plurality of doses separated in time) and/or periodic (e.g., individual doses separated by a common period of time) dosing. In some embodiments, administration may involve continuous dosing (e.g., infusion, perfusion) for at least a selected period of time.

[0054] Agent: In general, the term "agent", as used herein, is used to refer to an entity (e.g., for example, a lipid, metal, nucleic acid, polypeptide, polysaccharide, small molecule, etc., or complex, combination, mixture or system (e.g., cell, tissue, organism) thereof), or phenomenon (e.g., heat, electric current or field, magnetic force or field, etc.). In appropriate circumstances, as will be clear from context to those skilled in the art, the term may be utilized to refer to an entity that is or comprises a cell or organism, or a fraction, extract, or component thereof. Alternatively or additionally, as context will make clear, the term may be used to refer to a natural product in that it is found in and/or is obtained from nature. In some instances, again as will be clear from context, the term may be used to refer to one or more entities that is man-made in that it is designed, engineered, and/or produced through action of the hand of man and/or is not found in nature. In some embodiments, an agent may be utilized in isolated or pure form; in some embodiments, an agent may be utilized in crude form. In some embodiments, potential agents may be provided as collections or libraries, for example that may be screened to identify or characterize active agents within them. In some cases, the term "agent" may refer to a compound or entity that is or comprises

a polymer; in some cases, the term may refer to a compound or entity that comprises one or more polymeric moieties. In some embodiments, the term "agent" may refer to a compound or entity that is not a polymer and/or is substantially free of any polymer and/or of one or more particular polymeric moieties. In some embodiments, the term may refer to a compound or entity that lacks or is substantially free of any polymeric moiety.

[0055] Animal: As used herein, the term "animal" refers to any member of the animal kingdom. In some embodiments, "animal" refers to humans, at any stage of development. In some embodiments, "animal" refers to non-human animals, at any stage of development. In certain embodiments, the non-human animal is a mammal (e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate and/or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish and/or worms. In some embodiments, an animal may be a transgenic animal, a genetically-engineered animal and/or a clone.

[0056] Antibody: As used herein, the term "antibody" refers to an immunoglobulin molecule, or fragment thereof, that binds specifically to an epitope (e.g., of an antigen). Naturally-occurring human antibodies typically include two identical heavy chains and two identical light chains, each of which includes a variable domain and a constant domain. The constant domain defines the antibody isotype (IgG, IgA, IgM, IgE, etc.). Those skilled in the art are aware that different animal species utilize different antibody structures in nature. For example, camelid antibodies are single chain antibodies. Those skilled in the art will further be aware that antibody variable domains are typically characterized by framework region (FR) sequences and complement-determining-region (CDR) sequences. Each variable domain typically includes three CDRs – CDR1, CDR2, and CDR3, which together contribute to specificity and/or affinity of epitope binding. In some embodiments, antibodies may be produced in or by organisms. In some embodiments, antibodies may be produced in or by cells in vitro (e.g., by hybridomas and/or by engineered cells). In some embodiments, antibody fragment(s) (e.g., as may be produced by cleavage or recombinantly) may be generated and/or utilized in accordance with the present disclosure. Those skilled in the art are aware that a variety of technologies have been developed to incorporate binding features (e.g., one or more CDRs and/or FR sequences, and in particular sets of 3 CDRs, optionally together with FR sequences) into new contexts. In some embodiments, CDR sequences may be maintained and other elements changed – e.g., as is done in humanization. Alternatively or additionally, in some embodiments, variable regions may be associated with alternative constant regions (e.g., with constant regions from a different organism and/or that include one or more particular sequence features or elements desired, for example, to impart a particular attribute to the antibody agent. Those skilled in the art are further aware of a variety of technologies commonly utilized to associate binding features of two or more different antibodies with one another – e.g., in a single multispecific (most commonly bi-specific) agent. Various known formats of antibody agents

(i.e., agents that incorporate antibody binding sequences such as one or more CDRs, or a full set of CDRs) include, for instance: antibody fragments such as Fab fragments, Fab' fragments, F(ab')2 fragments, Fd' fragments, Fd fragments, and isolated CDRs or sets thereof; single chain Fvs; polypeptide-Fc fusions; single domain antibodies (e.g., shark single domain antibodies such as IgNAR or fragments thereof); camelid antibodies; masked antibodies (e.g., Probodies); Small Modular ImmunoPharmaceuticals ("SMIPsTM"); single chain or Tandem diabodies (TandAb); VHHs; Anticalins; Nanobodies minibodies; BiTEs; ankyrin repeat proteins or DARPINs; Avimers; DARTs; TCR-like antibodies;, Adnectins; Affilins; Trans-bodies; Affibodies; TrimerX; MicroProteins; Fynomers, Centyrins; KALBITORs, Zybodies, etc.

[0057] Antigen: As used herein, the term "antigen", as used herein, refers to (i) an agent that elicits an immune response; and/or (ii) an agent that binds to a T cell receptor (e.g., when presented by an MHC molecule) or to an antibody. In some embodiments, an antigen elicits a humoral response (e.g., including production of antigen-specific antibodies); in some embodiments, an elicits a cellular response (e.g., involving T-cells whose receptors specifically interact with the antigen). In some embodiments, and antigen binds to an antibody and may or may not induce a particular physiological response in an organism. In general, an antigen may be or include any chemical entity such as, for example, a small molecule, a nucleic acid, a polypeptide, a carbohydrate, a lipid, a polymer (in some embodiments other than a biologic polymer [e.g., other than a nucleic acid or amino acid polymer) etc. In some embodiments, an antigen is or comprises a polypeptide. In some embodiments, an antigen is or comprises a glycan. Those of ordinary skill in the art will appreciate that, in general, an antigen may be provided in isolated or pure form, or alternatively may be provided in crude form (e.g., together with other materials, for example in an extract such as a cellular extract or other relatively crude preparation of an antigen-containing source). In some embodiments, antigens utilized in accordance with the present invention are provided in a crude form. In some embodiments, an antigen is a recombinant antigen.

[0058] Associated: Two events or entities are "associated" with one another, as that term is used herein, if the presence, level, degree, type and/or form of one is correlated with that of the other. For example, a particular entity (e.g., polypeptide, genetic signature, metabolite, microbe, etc.) is considered to be associated with a particular disease, disorder, or condition, if its presence, level and/or form correlates with incidence of, susceptibility to, severity of, stage of, etc. the disease, disorder, or condition (e.g., across a relevant population). In some embodiments, two or more entities are physically "associated" with one another if they interact, directly or indirectly, so that they are and/or remain in physical proximity with one another. In some embodiments, two or more entities that are physically associated with one another are covalently linked to one another; in some embodiments, two or more entities that are physically associated with one another are not covalently linked to one another but are non-covalently associated, for example by means of hydrogen bonds, van der Waals interaction, hydrophobic interactions, magnetism, and

combinations thereof.

[0059] Binding: It will be understood that the term "binding", as used herein, typically refers to a non-covalent association between or among two or more entities. "Direct" binding involves physical contact between entities or moieties; indirect binding involves physical interaction by way of physical contact with one or more intermediate entities. Binding between two or more entities can typically be assessed in one or more of a variety of contexts – for example, in some embodiments where interacting entities or moieties are studied in isolation, and/or in some embodiments where interacting entities or moieties are studied in the context of more complex systems (e.g., while covalently or otherwise associated with a carrier entity and/or in a biological system or cell). Binding between two entities may be considered "specific" if, under the conditions assessed, the relevant entities are more likely to associate with one another than with other available binding partners. Those skilled in the art will be aware of circumstances where a particular degree of preference for one potential binding partner over another is required for binding to be deemed sufficiently "specific" for a particular purpose or situation.

[0060] Binding agent: In general, the term "binding agent" is used herein to refer to any entity that binds to a target of interest as described herein. In many embodiments, a binding agent of interest is one that binds specifically with its target in that it discriminates its target from other potential binding partners in a particular interaction contact. In general, a binding agent may be or comprise an entity of any chemical class (e.g., polymer, non-polymer, small molecule, polypeptide, carbohydrate, lipid, nucleic acid, etc.). In some embodiments, a binding agent is a single chemical entity. In some embodiments, a binding agent is a complex of two or more discrete chemical entities associated with one another under relevant conditions by non-covalent interactions. For example, those skilled in the art will appreciate that in some embodiments, a binding agent may comprise a "generic" binding moiety (e.g., one of biotin/avidin/streptavidin and/or a class-specific antibody) and a "specific" binding moiety (e.g., an antibody or aptamers with a particular molecular target) that is linked to the partner of the generic biding moiety. In some embodiments, such an approach can permit modular assembly of multiple binding agents through linkage of different specific binding moieties with the same generic binding moiety partner. In some embodiments, binding agents are or comprise polypeptides (including, e.g., antibodies or antibody fragments). In some embodiments, binding agents are or comprise small molecules. In some embodiments, binding agents are or comprise nucleic acids. In some embodiments, binding agents are aptamers. In some embodiments, binding agents are polymers; in some embodiments, binding agents are not polymers. In some embodiments, binding agents are non-polymeric in that they lack polymeric moieties. In some embodiments, binding agents are or comprise carbohydrates. In some embodiments, binding agents are or comprise lectins. In some embodiments, binding agents are or comprise peptidomimetics. In some embodiments, binding agents are or comprise scaffold proteins. In some embodiments, binding agents are

or comprise mimotopes. In some embodiments, binding agents are or comprise stapled peptides. In certain embodiments, binding agents are or comprise nucleic acids, such as DNA or RNA.

[0061] Bispecific antibody: As used herein, refers to a bispecific binding agent in which at least one, and typically both, of the binding moieties is or comprises an antibody component. A variety of different bispecific antibody structures are known in the art. In some embodiments, each binding moiety in a bispecific antibody that is or comprises an antibody component includes VH and/or VL regions; in some such embodiments, the VH and/or VL regions are those found in a particular monoclonal antibody. In some embodiments, where the bispecific antibody contains two antibody component-binding moieties, each includes VH and/or VL regions from different monoclonal antibodies. In some embodiments, where the bispecific antibody contains two antibody component binding moieties, wherein one of the two antibody component binding moieties includes an immunoglobulin molecule having VH and/or VL regions that contain CDRs from a first monoclonal antibody, and one of the two antibody component binding moieties includes an antibody fragment (e.g., Fab, F(ab'), F(ab')2, Fd, Fv, dAB, scFv, etc.) having VH and/or VL regions that contain CDRs from a second monoclonal antibody.

[0062] Bispecific binding agent: As used herein, refers to a polypeptide agent with two discrete binding moieties, each of which binds with a distinct target. In some embodiments, a bispecific binding agent is or comprises a single polypeptide; in some embodiments, a bispecific binding agent is or comprises a plurality of peptides which, in some such embodiments may be covalently associated with one another, for example by cross-linking. In some embodiments, the two binding moieties of a bispecific binding agent recognize different sites (e.g., epitopes) the same target (e.g., antigen); in some embodiments, they recognize different targets. In some embodiments, a bispecific binding agent is capable of binding simultaneously to two targets that are of different structure.

[0063] Cancer: The term "cancer" is used herein to generally refer to a disease or condition in which cells of a tissue of interest exhibit relatively abnormal, uncontrolled, and/or autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell proliferation. In some embodiments, cancer may comprise cells that are precancerous (e.g., benign), malignant, pre-metastatic, metastatic, and/or non-metastatic.

[0064] Detectable entity: The term "detectable entity" as used herein refers to an element, molecule, functional group, compound, fragment, or moiety that is detectable. In some embodiments, a detectable entity is provided or utilized alone. In some embodiments, a detectable entity is provided and/or utilized in association with (e.g., joined to) another agent. Examples of detectable entities include, but are not limited to: various ligands, radionuclides (e.g., ^{3}H, ^{14}C, ^{18}F, ^{19}F, ^{32}P, ^{35}S, ^{135}I, ^{125}I, ^{123}I, ^{64}Cu, ^{187}Re, ^{111}In, ^{90}Y, ^{99m}Tc, ^{177}Lu, ^{89}Zr etc.), fluorescent dyes (for specific exemplary fluorescent dyes, see below), chemiluminescent agents (such as, for example, acridinium esters, stabilized dioxetanes, and the like),

bioluminescent agents, spectrally resolvable inorganic fluorescent semiconductors nanocrystals (i.e., quantum dots), metal nanoparticles (e.g., gold, silver, copper, platinum, etc.) nanoclusters, paramagnetic metal ions, enzymes (for specific examples of enzymes, see below), colorimetric labels (such as, for example, dyes, colloidal gold, and the like), biotin, digoxigenin, haptens, and proteins for which antisera or monoclonal antibodies are available.

[0065] Humanized: As is known in the art, the term "*humanized*" is commonly used to refer to antibodies (or antibody components) whose amino acid sequence includes V_H and V_L region sequences from a reference antibody raised in a non-human species (e.g., a mouse), but also includes modifications in those sequences relative to the reference antibody intended to render them more "*human-like*", i.e., more similar to human germline variable sequences. In some embodiments, a "*humanized*" antibody (or antibody component) is one that immunospecifically binds to an antigen of interest and that has a framework (FR) region having substantially the amino acid sequence as that of a human antibody, and a complementary determining region (CDR) having substantially the amino acid sequence as that of a non-human antibody. A humanized antibody comprises substantially all of at least one, and typically two, variable domains (Fab, Fab', $F(ab')_2$, FabC, Fv) in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin (i.e., donor immunoglobulin) and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. In some embodiments, a humanized antibody also comprises at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin constant region. In some embodiments, a humanized antibody contains both the light chain as well as at least the variable domain of a heavy chain. The antibody also may include a C_H1, hinge, C_H2, C_H3, and, optionally, a C_H4 region of a heavy chain constant region. In some embodiments, a humanized antibody only contains a humanized V_L region. In some embodiments, a humanized antibody only contains a humanized V_H region. In some certain embodiments, a humanized antibody contains humanized V_H and V_L regions.

[0066] Identity: As used herein, the term "identity" refers to the overall relatedness between polymeric molecules, e.g., between nucleic acid molecules (e.g., oligonucleotides, DNA, RNA, etc.) and/or between polypeptide molecules. In some embodiments, polymeric molecules are considered to be "substantially identical" to one another if their sequences are at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identical. Calculation of the percent identity of two nucleic acid or polypeptide sequences, for example, can be performed by aligning the two sequences for optimal comparison purposes (e.g., gaps can be introduced in one or both of a first and a second sequences for optimal alignment and non-identical sequences can be disregarded for comparison purposes). In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or substantially 100% of the

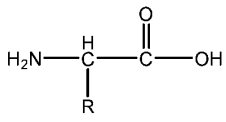
length of a reference sequence. The nucleotides at corresponding positions are then compared. When a position in the first sequence is occupied by the same residue (e.g., nucleotide or amino acid) as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which needs 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 a mathematical algorithm. For example, the percent identity between two nucleotide sequences can be determined using the algorithm of Meyers and Miller (CABIOS, 1989, 4: 11-17), which has been incorporated into the ALIGN program (version 2.0). In some exemplary embodiments, nucleic acid sequence comparisons made with the ALIGN program use a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. The percent identity between two nucleotide sequences can, alternatively, be determined using the GAP program in the GCG software package using an NWSgapdna.CMP matrix.

[0067] In vitro: As used herein, the term "in vitro" refers to events that occur in an artificial environment, e.g., in a test tube or reaction vessel, in cell culture, etc., rather than within an organism (e.g., animal, plant and/or microbe).

[0068] In vivo: As used herein, the term "in vivo" refers to events that occur within an organism (e.g., animal, plant and/or microbe).

[0069] Linker: As used herein, is used to refer to that portion of a multi-element agent that connects different elements to one another. For example, those of ordinary skill in the art appreciate that a polypeptide whose structure includes two or more functional or organizational domains often includes a stretch of amino acids between such domains that links them to one another. In some embodiments, a polypeptide comprising a linker element has an overall structure of the general form S1-L-S2, wherein S1 and S2 may be the same or different and represent two domains associated with one another by the linker. In some embodiments, a polypeptide linker is at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more amino acids in length. In some embodiments, a linker is characterized in that it tends not to adopt a rigid three-dimensional structure, but rather provides flexibility to the polypeptide. A variety of different linker elements that can appropriately be used when engineering polypeptides (e.g., fusion polypeptides) known in the art (see, e.g., Holliger, P., et al. (1993) Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak, R. J., et al. (1994) Structure 2: 1 121-1123).

[0070] Non-natural amino acid: The phrase "non-natural amino acid" refers to an entity having the

chemical structure of an amino acid (e.g., ) and therefore being capable of participating in at least two peptide bonds, but having an R group that differs from those found in nature. In some embodiments, non-natural amino acids may also have a second R group rather than a hydrogen, and/or may have one or more other substitutions on the amino or carboxylic acid moieties.

[0071] Patient: As used herein, the term "patient" refers to any organism to which a provided composition is or may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical patients include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and/or humans). In some embodiments, a patient is a human. In some embodiments, a patient is suffering from or susceptible to one or more conditions, diseases, or disorders. In some embodiments, a patient displays one or more symptoms of a condition, disease, or disorder. In some embodiments, a patient has been diagnosed with one or more conditions, diseases, or disorders. In some embodiments, the patient is receiving or has received certain therapy to diagnose and/or to treat a condition, disease, or disorder.

[0072] Pharmaceutical composition: As used herein, the term "pharmaceutical composition" refers to an active agent, formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, an active agent is present in a unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[0073] Pharmaceutically acceptable: As used herein, the phrase "pharmaceutically acceptable" refers to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0074] Pharmaceutically acceptable carrier: As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid

filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: 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 as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and 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; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

[0075] Polypeptide: The term "polypeptide", as used herein, generally has its art-recognized meaning of a polymer of at least three amino acids. Those of ordinary skill in the art will appreciate that the term "polypeptide" is intended to be sufficiently general as to encompass not only polypeptides having a complete sequence recited herein, but also to encompass polypeptides that represent functional fragments (i.e., fragments retaining at least one activity) of such complete polypeptides. Moreover, those of ordinary skill in the art understand that protein sequences generally tolerate some substitution without destroying activity. Thus, any polypeptide that retains activity and shares at least about 30-40% overall sequence identity, often greater than about 50%, 60%, 70%, or 80%, and further usually including at least one region of much higher identity, often greater than 90% or even 95%, 96%, 97%, 98%, or 99% in one or more highly conserved regions, usually encompassing at least 3-4 and often up to 20 or more amino acids, with another polypeptide of the same class, is encompassed within the relevant term "polypeptide" as used herein. Polypeptides may contain L-amino acids, D-amino acids, or both and may contain any of a variety of amino acid modifications or analogs known in the art. Useful modifications include, e.g., terminal acetylation, amidation, methylation, etc. In some embodiments, proteins may comprise natural amino acids, non-natural amino acids, synthetic amino acids, and combinations thereof. The term "peptide" is generally used to refer to a polypeptide having a length of less than about 100 amino acids, less than about 50 amino acids, less than 20 amino acids, or less than 10 amino acids. In some embodiments, proteins are antibodies, antibody fragments, biologically active portions thereof, and/or characteristic portions thereof.

[0076] Specific: The term "specific", when used herein with reference to an agent having an activity, is understood by those skilled in the art to mean that the agent discriminates between potential target entities or states. For example, in some embodiments, an agent is said to bind "specifically" to its target if it binds

preferentially with that target in the presence of one or more competing alternative targets. In many embodiments, specific interaction is dependent upon the presence of a particular structural feature of the target entity (e.g., an epitope, a cleft, a binding site). It is to be understood that specificity need not be absolute. In some embodiments, specificity may be evaluated relative to that of the binding agent for one or more other potential target entities (e.g., competitors). In some embodiments, specificity is evaluated relative to that of a reference specific binding agent. In some embodiments specificity is evaluated relative to that of a reference non-specific binding agent. In some embodiments, the agent or entity does not detectably bind to the competing alternative target under conditions of binding to its target entity. In some embodiments, binding agent binds with higher on-rate, lower off-rate, increased affinity, decreased dissociation, and/or increased stability to its target entity as compared with the competing alternative target(s).

[0077] Subject: As used herein, the term "subject" or "test subject" refers to any organism to which a compound (e.g., an oligonucleotide) or composition is administered in accordance with the present disclosure e.g., for experimental, diagnostic, prophylactic and/or therapeutic purposes. Typical subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans; insects; worms; etc.) and plants. In some embodiments, a subject is a human. In some embodiments, a subject may be suffering from and/or susceptible to a disease, disorder, and/or condition. In some embodiments, a subject may be suffering from and/or susceptible to a cancer. In some embodiments, a subject displays one or more symptoms of a disease, disorder, and/or condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered.

[0078] Suffering from: An individual who is "suffering from" a disease, disorder, and/or condition has been diagnosed with and/or displays one or more symptoms of a disease, disorder, and/or condition.

[0079] Susceptible to: An individual who is "susceptible to" a disease, disorder, and/or condition is one who has a higher risk of developing the disease, disorder, and/or condition than does a member of the general public. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition may not have been diagnosed with the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition may exhibit symptoms of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition may not exhibit symptoms of the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In some embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[0080] Therapeutic agent: As used herein, the term "therapeutic agent" in general refers to any agent

that elicits a desired effect (e.g., a desired biological, clinical, or pharmacological effect) when administered to a subject. In some embodiments, an agent is considered to be a therapeutic agent if it demonstrates a statistically significant effect across an appropriate population. In some embodiments, an appropriate population is a population of subjects suffering from and/or susceptible to a disease, disorder or condition. In some embodiments, an appropriate population is a population of model organisms. In some embodiments, an appropriate population may be defined by one or more criterion such as age group, gender, genetic background, preexisting clinical conditions, prior exposure to therapy. In some embodiments, a therapeutic agent is a substance that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms or features of a disease, disorder, and/or condition in a subject when administered to the subject in an effective amount. In some embodiments, a "therapeutic agent" is an agent that has been or is required to be approved by a government agency before it can be marketed for administration to humans. In some embodiments, a "therapeutic agent" is an agent for which a medical prescription is required for administration to humans. In some embodiments, a therapeutic agent is a provided compound, composition, or complex.

[0081] Therapeutically effective amount: As used herein, the term "therapeutically effective amount" means an amount of a substance (e.g., a therapeutic agent, composition, and/or formulation) that elicits a desired biological response when administered as part of a therapeutic regimen. In some embodiments, a therapeutically effective amount of a substance is an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a substance may vary depending on such factors as the desired biological endpoint, the substance to be delivered, the target cell or tissue, etc. For example, the effective amount of compound in a formulation to treat a disease, disorder, and/or condition is the amount that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms or features of the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is administered in a single dose; in some embodiments, multiple unit doses are required to deliver a therapeutically effective amount.

[0082] Treat: As used herein, the term "treat," "treatment," or "treating" refers to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who exhibits only early signs of the disease, disorder, and/or condition, for example for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition. In some embodiments, treatment may be

administered to a subject who exhibits a disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who is suffering from a disease, disorder, and/or condition.

[0083] Tumor: As used herein, the term "tumor" refers to an abnormal growth of cells or tissue. In some embodiments, a tumor may comprise cells that are precancerous (e.g., benign), malignant, pre-metastatic, metastatic, and/or non-metastatic. In some embodiments, a tumor is associated with, or is a manifestation of, a cancer. In some embodiments, a tumor may be a disperse tumor or a liquid tumor. In some embodiments, a tumor may be a solid tumor.

Antibodies and Antigen-Binding Fragments Thereof

[0084] Among other things, the present disclosure provides various antibodies and antigen-binding fragments thereof. In some embodiments, the present disclosure provides various bone-targeted antibodies and antigen-binding fragments thereof. In some embodiments, the present disclosure provides various antibodies and antigen-binding fragments thereof, e.g., bone-targeted antibodies and antigen-binding fragments thereof, that are useful in various methods, e.g., methods of treating a condition, disorder, or disease.

[0085] In some embodiments, an antibody or antigen-binding fragment thereof comprises a monoclonal antibody or antigen-binding fragment thereof. In some embodiments, an antibody or antigen-binding fragment thereof is a monoclonal antibody or antigen-binding fragment thereof. As known in the art, a monoclonal antibody or antigen-binding fragment thereof is directed, e.g., recognizes, binds, to a single epitope of a particular antigen.

[0086] In some embodiments, an antibody or antigen-binding fragment thereof comprises a chimeric antibody or antigen-binding fragment thereof. In some embodiments, an antibody or antigen-binding fragment thereof is a chimeric antibody or antigen-binding fragment thereof.

[0087] In some embodiments, an antibody or antigen-binding fragment thereof comprises a humanized antibody or antigen-binding fragment thereof. In some embodiments, an antibody or antigen-binding fragment thereof is a humanized antibody or antigen-binding fragment thereof.

[0088] An antigen-binding fragment of an antibody may comprise a portion of an antibody, e.g., an antigen-binding or variable region of the antibody. Non-limiting examples of antibody fragments include Fab, Fab′, F(ab′)2, dimers and trimers of Fab conjugates, Fv, scFv, minibodies, dia-, tria-, and tetrabodies, and linear antibodies. Fab and Fab′ are antigen-binding fragments can comprise VH and CH1 domains of a heavy chain linked to VL and CL domains of a light chain via a disulfide bond. A F(ab′)2 can comprise two Fab or Fab′ joined by disulfide bonds. A Fv can comprise the VH and VL domains held together by non-covalent interactions. A scFv (single-chain variable fragment) is a fusion protein that can comprise the VH and VL domains connected by a peptide linker. Manipulation of orientation of VH and VL domains

and linker length can be used to create different forms of molecules that can be monomeric, dimeric (diabody), trimeric (triabody), or tetrameric (tetrabody).

[0089] In some embodiments, an antigen is preferentially associated with a cancer cell. In some embodiments, an antigen is preferentially associated with a prostate cancer cell. In some embodiments, an antigen is preferentially associated with a tumor cell. In some embodiments, an antigen is preferentially associated with a bone tumor cell. In some embodiments, an antigen is preferentially associated with a cell of a metastasis. In some embodiments, an antigen is preferentially associated with a cell of a bone metastasis. In some embodiments, an antigen is preferentially associated with a cell of a prostate cancer bone metastasis.

[0090] In some embodiments, an antigen is expressed by a cell, e.g., a cancer cell, e.g., a prostate cancer cell. In some embodiments, an antigen is present in a cell, e.g., a cancer cell, e.g., a prostate cancer cell. In some embodiments, an antigen is present on a cell, e.g., a cancer cell, e.g., a prostate cancer cell. In some embodiments, an antigen is present in an extracellular environment associated with a cell, e.g., a cancer cell, e.g., a prostate cancer cell.

[0091] In some embodiments, an antigen comprises or is a cancer antigen. In some embodiments, an antigen comprises or is a prostate cancer antigen. In some embodiments, an antigen comprises or is a bone cancer antigen. In some embodiments, an antigen comprises or is a tumor antigen. In some embodiments, an antigen comprises or is a prostate tumor antigen. In some embodiments, an antigen comprises or is a bone tumor antigen. In some embodiments, an antigen comprises or is a metastasis antigen. In some embodiments, an antigen comprises or is a prostate metastasis antigen. In some embodiments, an antigen comprises or is a bone metastasis antigen. In some embodiments, an antigen comprises or is a sarcoma antigen. In some embodiments, an antigen comprises or is an osteosarcoma antigen.

[0092] In some embodiments, an antigen (e.g., a cancer antigen, a tumor antigen) comprises or is PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2. In some embodiments, an antigen is PSMA. In some embodiments, an antigen is AKT. In some embodiments, an antigen is AXL. In some embodiments, an antigen is androgen receptor. In some embodiments, an antigen is B7-H3. In some embodiments, an antigen is CCL20. In some embodiments, an antigen is CCR5.

In some embodiments, an antigen is CCR6. In some embodiments, an antigen is CD24. In some embodiments, an antigen is CD44. In some embodiments, an antigen is CD46. In some embodiments, an antigen is CD63. In some embodiments, an antigen is CD73. In some embodiments, an antigen is CD99. In some embodiments, an antigen is CD133. In some embodiments, an antigen is CD155. In some embodiments, an antigen is CD166. In some embodiments, an antigen is CDCP1. In some embodiments, an antigen is CDH1. In some embodiments, an antigen is CEACAM5. In some embodiments, an antigen is CHRNB2. In some embodiments, an antigen is CLDN3. In some embodiments, an antigen is CLDN4. In some embodiments, an antigen is CTLA-4. In some embodiments, an antigen is DLL-3. In some embodiments, an antigen is EGFR. In some embodiments, an antigen is Epcam. In some embodiments, an antigen is EphA2. In some embodiments, an antigen is EZH1. In some embodiments, an antigen is EZH2. In some embodiments, an antigen is FAP. In some embodiments, an antigen is FGFR1. In some embodiments, an antigen is FZD7. In some embodiments, an antigen is GPC3. In some embodiments, an antigen is GRPR. In some embodiments, an antigen is GSPT1. In some embodiments, an antigen is HER3. In some embodiments, an antigen is IGF-1R. In some embodiments, an antigen is IL-30. In some embodiments, an antigen is integrin alpha V. In some embodiments, an antigen is integrin alpha 5. In some embodiments, an antigen is integrin alpha 6. In some embodiments, an antigen is integrin alpha 9. In some embodiments, an antigen is integrin alpha II. In some embodiments, an antigen is integrin beta 2. In some embodiments, an antigen is integrin beta 7. In some embodiments, an antigen is ITGA3. In some embodiments, an antigen is KLK2. In some embodiments, an antigen is LAMP1. In some embodiments, an antigen is LGR5. In some embodiments, an antigen is LGALS3BP. In some embodiments, an antigen is LRP6. In some embodiments, an antigen is MCAM. In some embodiments, an antigen is MUC1. In some embodiments, an antigen is Myc. In some embodiments, an antigen is Nectin-4. In some embodiments, an antigen is Notch1. In some embodiments, an antigen is PARP. In some embodiments, an antigen is PD-1. In some embodiments, an antigen is PDL1. In some embodiments, an antigen is PROM1. In some embodiments, an antigen is PSCA. In some embodiments, an antigen is PTEN. In some embodiments, an antigen is PTPRZ1. In some embodiments, an antigen is RET. In some embodiments, an antigen is ROR1. In some embodiments, an antigen is SCARB1. In some embodiments, an antigen is SEZ6. In some embodiments, an antigen is SEZ6L. In some embodiments, an antigen is Siglec-7. In some embodiments, an antigen is Siglec-9. In some embodiments, an antigen is Siglec-15. In some embodiments, an antigen is SLC1A5. In some embodiments, an antigen is SLC39A6. In some embodiments, an antigen is SLC45A3. In some embodiments, an antigen is SLC7A5. In some embodiments, an antigen is SSTR2. In some embodiments, an antigen is STEAP1. In some embodiments, an antigen is STEAP2. In some embodiments, an antigen is TACSTD2. In some embodiments, an antigen is TGFb. In some embodiments, an antigen is TIM-3. In some embodiments, an antigen is TMEFF2. In

some embodiments, an antigen is TMPRSS2. In some embodiments, an antigen is TNFRSF10B. In some embodiments, an antigen is TNFRSF21. In some embodiments, an antigen is TNFSF10. In some embodiments, an antigen is TROP2.

[0093] In some embodiments, an antigen (e.g., a cancer antigen, a tumor antigen) comprises or is IFITM5, uPARAP, CD99, or LRRC15. In some embodiments, an osteosarcoma-associated antigen comprises or is IFITM5, uPARAP, CD99, or LRRC15.

[0094] In some embodiments, a cancer antigen comprises or is PSMA. In some embodiments, a prostate cancer antigen comprises or is PSMA. In some embodiments, a tumor antigen comprises or is PSMA. In some embodiments, a prostate tumor antigen comprises or is PSMA. In some embodiments, a metastasis antigen comprises or is PSMA.

[0095] In some embodiments antibody or antigen-binding fragment thereof, an antibody or antigen-binding fragment thereof comprises or is an anti- anti-PSMA antibody or antigen-binding fragment thereof, AKT antibody or antigen-binding fragment thereof, AXL antibody or antigen-binding fragment thereof, androgen receptor antibody or antigen-binding fragment thereof, B7-H3 antibody or antigen-binding fragment thereof, CCL20 antibody or antigen-binding fragment thereof, CCR5 antibody or antigen-binding fragment thereof, CCR6 antibody or antigen-binding fragment thereof, CD24 antibody or antigen-binding fragment thereof, CD44 antibody or antigen-binding fragment thereof, CD46 antibody or antigen-binding fragment thereof, CD63 antibody or antigen-binding fragment thereof, CD73 antibody or antigen-binding fragment thereof, CD99 antibody or antigen-binding fragment thereof, CD133 antibody or antigen-binding fragment thereof, CD155 antibody or antigen-binding fragment thereof, CD166 antibody or antigen-binding fragment thereof, CDCP1 antibody or antigen-binding fragment thereof, CDH1 antibody or antigen-binding fragment thereof, CEACAM5 antibody or antigen-binding fragment thereof, CHRNB2 antibody or antigen-binding fragment thereof, CLDN3 antibody or antigen-binding fragment thereof, CLDN4 antibody or antigen-binding fragment thereof, CTLA-4 antibody or antigen-binding fragment thereof, DLL-3 antibody or antigen-binding fragment thereof, EGFR antibody or antigen-binding fragment thereof, Epcam antibody or antigen-binding fragment thereof, EphA2 antibody or antigen-binding fragment thereof, EZH1 antibody or antigen-binding fragment thereof, EZH2 antibody or antigen-binding fragment thereof, FAP antibody or antigen-binding fragment thereof, FGFR1 antibody or antigen-binding fragment thereof, FZD7 antibody or antigen-binding fragment thereof, GPC3 antibody or antigen-binding fragment thereof, GRPR antibody or antigen-binding fragment thereof, GSPT1 antibody or antigen-binding fragment thereof, HER3 antibody or antigen-binding fragment thereof, IGF-1R antibody or antigen-binding fragment thereof, IL-30 antibody or antigen-binding fragment thereof, integrin alpha V antibody or antigen-binding fragment thereof, integrin alpha 5 antibody or antigen-binding fragment thereof, integrin alpha 6 antibody or antigen-binding fragment thereof, integrin alpha 9 antibody or antigen-binding fragment thereof, integrin

alpha II antibody or antigen-binding fragment thereof, integrin beta 2 antibody or antigen-binding fragment thereof, integrin beta 7 antibody or antigen-binding fragment thereof, ITGA3 antibody or antigen-binding fragment thereof, KLK2 antibody or antigen-binding fragment thereof, LAMP1 antibody or antigen-binding fragment thereof, LGR5 antibody or antigen-binding fragment thereof, LGALS3BP antibody or antigen-binding fragment thereof, LRP6 antibody or antigen-binding fragment thereof, MCAM antibody or antigen-binding fragment thereof, MUC1 antibody or antigen-binding fragment thereof, Myc antibody or antigen-binding fragment thereof, Nectin-4 antibody or antigen-binding fragment thereof, Notch1 antibody or antigen-binding fragment thereof, PARP antibody or antigen-binding fragment thereof, PD-1 antibody or antigen-binding fragment thereof, PDL1 antibody or antigen-binding fragment thereof, PROM1 antibody or antigen-binding fragment thereof, PSCA antibody or antigen-binding fragment thereof, PTEN antibody or antigen-binding fragment thereof, PTPRZ1 antibody or antigen-binding fragment thereof, RET antibody or antigen-binding fragment thereof, ROR1 antibody or antigen-binding fragment thereof, SCARB1 antibody or antigen-binding fragment thereof, SEZ6 antibody or antigen-binding fragment thereof, SEZ6L antibody or antigen-binding fragment thereof, Siglec-7 antibody or antigen-binding fragment thereof, Siglec-9 antibody or antigen-binding fragment thereof, Siglec-15 antibody or antigen-binding fragment thereof, SLC1A5 antibody or antigen-binding fragment thereof, SLC39A6 antibody or antigen-binding fragment thereof, SLC45A3 antibody or antigen-binding fragment thereof, SLC7A5 antibody or antigen-binding fragment thereof, SSTR2 antibody or antigen-binding fragment thereof, STEAP1 antibody or antigen-binding fragment thereof, STEAP2 antibody or antigen-binding fragment thereof, TACSTD2 antibody or antigen-binding fragment thereof, TGFb antibody or antigen-binding fragment thereof, TIM-3 antibody or antigen-binding fragment thereof, TMEFF2 antibody or antigen-binding fragment thereof, TMPRSS2 antibody or antigen-binding fragment thereof, TNFRSF10B antibody or antigen-binding fragment thereof, TNFRSF21 antibody or antigen-binding fragment thereof, TNFSF10 antibody or antigen-binding fragment thereof, or TROP2 antibody or antigen-binding fragment thereof.

[0096] In some embodiments, an antibody or antigen-binding fragment thereof comprises an anti-PSMA antibody or antigen-binding fragment thereof. In some embodiments, an antibody or antigen-binding fragment thereof is an anti-PSMA antibody or antigen-binding fragment thereof. Various anti-PSMA antibodies are known in the art. In some embodiments, an anti-PSMA antibody or antigen-binding fragment thereof is J591 or fragment thereof. In some embodiments, an anti-PSMA antibody is humanized J591 or fragment thereof. Additional anti-PSMA antibodies include, but are not limited to those described in WO 2019/191728, WO 2021/000018, and/or WO 2023/088966.

[0097] In some embodiments, an antibody or antigen-binding fragment thereof is a multifunctional or multispecific molecule, e.g., a multispecific antibody or antigen-binding fragment thereof. A multifunctional or a multispecific molecule can be, e.g., a molecule that has two or more functionalities,

e.g., two or more binding specificities. In some embodiments, an antibody or antigen-binding fragment thereof is a bifunctional or bispecific molecule, e.g., a bispecific antibody or antigen-binding fragment thereof. In some embodiments, a multispecific antibody, e.g., a bispecific antibody, comprises or is a T-cell engager, e.g., a bi-specific T-cell engager. In some embodiments, a multispecific antibody, e.g., a bispecific antibody, binds to a prostate cancer-associated antigen and an effector antigen comprising CD3, CD28, CD137, CTLA-4, PD-1, ICOS, Integrin Beta 6, Integrin Beta 1, Integrin Beta 3, an IL-18 activator, an IL23 activator, or Jagged-1.

Bone-Targeting Moieties

[0098] Among other things, the present disclosure provides various bone-targeting moieties. In some embodiments, the present disclosure provides various bone-targeting moieties, which may be attached to or inserted into various antibodies or antigen-binding fragments thereof.

[0099] Bones are composed in part of hydroxyapatite (HA) crystals, which are insoluble salts of calcium and phosphate. Hydroxyapatite crystals reportedly have surfaces with varying levels of crystallinity. Surfaces with higher levels of crystallinity are characterized by the presence of bone resorption surfaces and are known as the osteolytic bone metastatic niche. In some embodiments, a bone-targeting moiety can bind to bone at an osteolytic bone metastatic niche. In some embodiments, a bone-targeting peptide can bind to bone at an osteolytic bone metastatic niche. In some embodiments, an oligomer can bind to bone at an osteolytic bone metastatic niche. In some embodiments, a bone-targeting moiety preferentially binds to bone at an osteolytic bone metastatic niche. In some embodiments, a bone-targeting peptide preferentially binds to bone at an osteolytic bone metastatic niche. In some embodiments, an oligomer preferentially binds to bone at an osteolytic bone metastatic niche. Osteolytic bone metastases are reportedly common in, e.g., breast cancers (Kozlow and Guise, J Mammary Gland Biol Neoplasia. 2005 Apr;10(2):169-80). In contrast, bone formation surfaces, e.g., osteoblastic bone, reportedly exhibits newly formed hydroxyapatite that is less mature, less crystalline, and less ordered as compared to bone resorption surfaces, e.g., osteolytic bone (Blair et al., Tissue Eng Part B Rev. 2017 Jun;23(3):268-280). Prostate cancers are reportedly most commonly associated with osteoblastic bone metastases (Goode et al., Oncol Lett. 2023 Mar 8;25(4):163). In some embodiments, a bone-targeting moiety can bind to bone at an osteoblastic bone metastatic niche. In some embodiments, a bone-targeting peptide can bind to bone at an osteoblastic bone metastatic niche. In some embodiments, an oligomer can bind to bone at an osteoblastic bone metastatic niche. In some embodiments, a bone-targeting moiety preferentially binds to bone at an osteoblastic bone metastatic niche. In some embodiments, a bone-targeting peptide preferentially binds to bone at an osteoblastic bone metastatic niche. In some embodiments, an oligomer preferentially binds to bone at an osteoblastic bone metastatic niche. Furthermore, osteolytic bone metastases and osteoblastic

bone metastases reportedly exhibit opposing environments related to activation of different cell types (e.g., osteoclasts or osteoblasts), different intracellular pathways (e.g., RUNX2 or NFATc1), and different secreted regulatory ligands (e.g., WNT, NOTCH, FGF, and TGFB or RankL). Such differing environments can provide a challenge for implementation and successful therapeutic usage of any compound or composition in both an osteolytic environment and an osteoblastic environment.

[0100] Accordingly, bone-targeting moieties may encounter different bone structure, e.g., different hydroxyapatite structure, based on the type of bone metastases present, e.g., in a subject. Previous reports have focused on usage of bone-targeting moieties with osteolytic bone, e.g., in conditions, disorders, or diseases characterized by bone resorption and/or osteolytic bone metastases, e.g., breast cancer bone metastases. In some embodiments, the present disclosure provides technologies (e.g., antigen-recognizing peptides, antibodies, conjugates, complexes, compositions, methods) for targeting bone metastases. In some embodiments, a bone-targeted antigen-recognizing peptide, e.g., a bone-targeted antibody, can be targeted to a bone metastasis. In some embodiments, a bone metastasis is an osteolytic bone metastasis. In some embodiments, a bone metastasis is an osteoblastic bone metastasis. In some embodiments, a bone metastasis is a prostate cancer bone metastasis.

[0101] Formation of osteolytic bone lesions can be driven by paracrine crosstalk among cancer cells, osteoblasts, and osteoclasts. Cancer cells secrete molecules, such as parathyroid hormone-related protein (PTHrP) and interleukin 8, that stimulate osteoclast formation directly or indirectly by acting to modulate expression of osteoblast genes, such as receptor activator of nuclear factor-KB ligand (RANKL) and osteoprotegerin (OPG). Consequent increase in bone resorption reportedly leads to release of growth factors (e.g., IGF1) that reciprocally stimulate tumor growth. Cancer cells can also secrete cancer-specific surface markers, such as STEAP1, STEAP2, PSMA, uPARAP, CD99, LRRC15, B7-H3, PSCA, TROP2, KLK2, TGFb, DLL-3, SSTR2, Epcam, GPC3, FAP, GRPR, ROR1, HER3, and IFITM5.

[0102] In some embodiments, a bone-targeting moiety is attached to an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is attached to a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is attached to a heavy chain of an antibody or antigen-binding fragment thereof.

[0103] In some embodiments, a bone-targeting moiety is covalently linked to an antibody or an antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is covalently linked to a light chain of an antibody or an antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is covalently linked to a heavy chain of an antibody or an antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is directly covalently linked to an antibody or an antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is directly covalently linked to a light chain of an antibody or an antigen-binding fragment thereof. In some embodiments, a bone-targeting

moiety is directly covalently linked to a heavy chain of an antibody or an antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is indirectly covalently linked to an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is indirectly covalently linked to a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is indirectly covalently linked to a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is linked by a linker to an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is linked by a linker to a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is linked by a linker to a heavy chain of an antibody or antigen-binding fragment thereof.

[0104] In some embodiments, a bone-targeting moiety is attached to one or both of a N-terminus or a C-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is attached to a N-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is attached to a C-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is covalently linked to a N-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is covalently linked to a C-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is directly covalently linked to a N-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is directly covalently linked to a C-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is indirectly covalently linked to a N-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is indirectly covalently linked to a C-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is linked by a linker to a N-terminus of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is linked by a linker to a C-terminus of a light chain of an antibody or antigen-binding fragment thereof.

[0105] In some embodiments, a bone-targeting moiety is attached to one or both of a N-terminus or a C-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is attached to a N-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is attached to a C-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is covalently linked to a N-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is covalently linked to a C-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is directly

covalently linked to a N-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is directly covalently linked to a C-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is indirectly covalently linked to a N-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is indirectly covalently linked to a C-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is linked by a linker to a N-terminus of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is linked by a linker to a C-terminus of a heavy chain of an antibody or antigen-binding fragment thereof.

[0106] In some embodiments, a bone-targeting moiety is attached to a C-terminus of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the C-terminus is or corresponds to residue G449.

[0107] In some embodiments, a bone-targeting moiety is attached to an antibody or antigen-binding fragment thereof as described in WO 2018/136698 or WO 2023/004348. In some embodiments, a bone-targeting moiety is attached to a light chain of an antibody or antigen-binding fragment thereof as described in WO 2018/136698 or WO 2023/004348. In some embodiments, a bone-targeting moiety is attached to a heavy chain of an antibody or antigen-binding fragment thereof as described in WO 2018/136698 or WO 2023/004348. In some embodiments, a bone-targeting moiety is linked by a linker to an antibody or antigen-binding fragment thereof as described in WO 2018/136698 or WO 2023/004348. In some embodiments, a bone-targeting moiety is linked by a linker to a light chain of an antibody or antigen-binding fragment thereof as described in WO 2018/136698 or WO 2023/004348. In some embodiments, a bone-targeting moiety is linked by a linker to a heavy chain of an antibody or antigen-binding fragment thereof as described in WO 2018/136698 or WO 2023/004348.

[0108] In some embodiments, a bone-targeting moiety is attached via a linker to an antibody or antigen-binding fragment thereof. In some embodiments, a linker comprises or is a non-amino-acid linker. In some embodiments, a linker comprises or is an amino-acid linker, e.g., a peptide linker or a polypeptide linker. In some embodiments, a linker comprises or is a peptide comprising glycine residues and/or serine residues. In some embodiments, a linker comprises or is a peptide comprising one or more repeats of glycine residues and/or serine residues. In some embodiments, a linker comprises or is a peptide linker comprising an amino-acid sequence of $(G_nS_m)_x$, wherein n is 1-10, m is 1-10, and x is 1-10. In some embodiments, a linker comprises or is a peptide comprising one or more repeats of an amino-acid sequence of GGGGS. In some embodiments, a linker comprises or is a peptide comprising an amino-acid sequence of $(G_4S_1)_1$, i.e., GGGGS. In some embodiments, a linker comprises or is a peptide comprising an amino-acid sequence of $(G_4S_1)_2$, i.e., GGGGSGGGGS. In some embodiments, a linker comprises or is a linker described in WO 2018/136698.

[0109] In some embodiments, a bone-targeting moiety is inserted in an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted in a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted in a heavy chain of an antibody or antigen-binding fragment thereof.

[0110] In some embodiments, a bone-targeting moiety is attached to an internal permissive site of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is attached to an internal permissive site of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is attached to an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a light chain of an antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof.

[0111] In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to a site described in WO 2012/097333, WO 2015/187428, or WO 2023/004348. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a light chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to a site described in WO 2012/097333, WO 2015/187428, or WO 2023/004348. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to a site described in WO 2012/097333, WO 2015/187428, or WO 2023/004348. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to a site described in Huang et al., MAbs. 2018 Nov-Dec;10(8):1182-1189. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a light chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to a site described in Huang et al., MAbs. 2018 Nov-Dec;10(8):1182-1189. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to a site described in Huang et al., MAbs. 2018 Nov-Dec;10(8):1182-1189.

[0112] In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a light chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to A153. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a light chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site

is or corresponds to A153, optionally wherein the bone-targeting moiety is inserted following A153.

[0113] In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to G118, P123, A165, P243, D283, N344, or G361. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to G118, P123, A165, P243, D283, N344, or G361, optionally wherein the bone-targeting moiety is inserted following G118, P123, A165, P243, D283, N344, or G361. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to G118. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to G118, optionally wherein the bone-targeting moiety is inserted following G118. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to P123. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to P123, optionally wherein the bone-targeting moiety is inserted following P123. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to A165. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to A165, optionally wherein the bone-targeting moiety is inserted following A165. In some embodiments, a site that is or corresponds to A165 is referred to as CH1. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to P243. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to P243, optionally wherein the bone-targeting moiety is inserted following P243. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to D283. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to D283, optionally wherein the bone-targeting moiety is inserted following D283. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein

the internal permissive site is or corresponds to N344. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to N344, optionally wherein the bone-targeting moiety is inserted following N344. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to G361. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is or corresponds to G361, optionally wherein the bone-targeting moiety is inserted following G361.

[0114] As understood by those skilled in the art, the internal permissive sites disclosed herein, e.g., of a light chain (e.g., A153) or a heavy chain (e.g., G118, P123, A165, P243, D283, N344, or G361) are referenced according to standardized numbering, e.g., Kabat numbering. Accordingly, such residues may be numbered differently (e.g., using a different standardized numbering system as known in the art, using a numbering of a particular sequence) based on the particular antibody or antigen-binding fragment thereof wherein a bone-targeted moiety, e.g., a bone-targeted peptide, is inserted. In some embodiments, A153 corresponds to A153 in a sequence in Table 1. In some embodiments, G118 corresponds to G120 in a sequence in Table 2. In some embodiments, P123 corresponds to P126 in a sequence in Table 2. In some embodiments, A165 corresponds to A160 in a sequence in Table 2. In some embodiments, P243 corresponds to P228 in a sequence in Table 2. In some embodiments, D283 corresponds to D267 in a sequence in Table 2. In some embodiments, N344 corresponds to N323 in a sequence in Table 2. In some embodiments, G361 corresponds to G339 in a sequence in Table 2.

[0115] The present disclosure provides the understanding that a bone-targeting moiety may be inserted into an antibody or antigen-binding fragment thereof in a loop region without altering, e.g., disrupting, structure and/or functionality (e.g., antigen binding) of the antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is located in a loop region of the antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a light chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is located in a loop region of the light chain of the antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is located in a loop region of the heavy chain of the antibody or antigen-binding fragment thereof.

[0116] The present disclosure also provides the understanding that a bone-targeting moiety may be inserted into an antibody or antigen-binding fragment thereof in an externally facing site without altering,

e.g., disrupting, structure and/or functionality (e.g., antigen binding) of the antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is located at an externally facing site of the antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a light chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is located at an externally facing site of the light chain of the antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is located at an externally facing site of the heavy chain of the antibody or antigen-binding fragment thereof.

[0117] In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is located in a loop region of the antibody or antigen-binding fragment thereof and wherein the internal permissive site is located at an externally facing site of the antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a light chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is located in a loop region of the light chain of the antibody or antigen-binding fragment thereof and wherein the internal permissive site is located at an externally facing site of the light chain of the antibody or antigen-binding fragment thereof. In some embodiments, a bone-targeting moiety is inserted at an internal permissive site of a heavy chain of an antibody or antigen-binding fragment thereof, wherein the internal permissive site is located in a loop region of the heavy chain of the antibody or antigen-binding fragment thereof and wherein the internal permissive site is located at an externally facing site of the heavy chain of the antibody or antigen-binding fragment thereof.

[0118] In some embodiments, a bone-targeting moiety comprises a species (e.g., chemical groups, molecules, nucleic acids, amino acids, peptides) that is charged at physiological pH. In some embodiments, a bone-targeting moiety comprises or is an oligomer of a species that is charged at physiological pH. In some embodiments, a bone-targeting moiety comprises a species that is negatively charged, positively charged, or Zwitterionic at physiological pH. In some embodiments, a bone-targeting moiety comprises or is an oligomer of a species that is negatively charged, positively charged, or Zwitterionic at physiological pH. In some embodiments, a bone-targeting moiety comprises a species that is negatively charged at physiological pH. In some embodiments, a bone-targeting moiety comprises or is an oligomer of a species that is negatively charged at physiological pH.

[0119] In some embodiments, a bone-targeting moiety comprises a bone-targeting peptide. In some embodiments, a bone-targeting moiety is a bone-targeting peptide. In some embodiments, a bone-targeting

moiety, e.g., a bone-targeting peptide, comprises one or more charged amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises one or more negatively charged amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises one or more amino-acid residues with acidic side chains. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of one or more charged amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of one or more negatively charged amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of one or more amino-acid residues with acidic side chains. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a negatively charged peptide. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a carboxylic peptide.

[0120] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of carboxylic amino-acid residues. In some embodiments, a carboxylic amino-acid residue comprises or is aspartate, glutamate, or carboxyglutamate. In some embodiments, a carboxylic amino-acid residue comprises or is aspartate. In some embodiments, a carboxylic amino-acid residue comprises or is glutamate. In some embodiments, a carboxylic amino-acid residue comprises or is carboxyglutamate.

[0121] As used herein and as appreciated by those skilled in the art, aspartate may refer to either aspartate or aspartic acid. As used herein and as appreciated by those skilled in the art, glutamate may refer to either glutamate or glutamic acid. As used herein and as appreciated by those skilled in the art, carboxyglutamate may be refer to either carboxyglutamate or carboxyglutamic acid.

[0122] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises 1 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 2 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 3 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 4 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 5 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 6 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 7 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 8 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 9 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 10 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 11 or more carboxylic

amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 12 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 13 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 14 or more carboxylic amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 15 or more carboxylic amino-acid residues.

[0123] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is poly-aspartate. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of aspartate residues.

[0124] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 3 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 4 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 5 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 6 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 7 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 8 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 9 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 10 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 11 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 12 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 13 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 14 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 15 aspartate residues.

[0125] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 3 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 4 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 5 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 6 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 7 aspartate residues. In some embodiments, a bone-targeting

moiety, e.g., a bone-targeting peptide, comprises no more than 8 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 9 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 10 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 11 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 12 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 13 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 14 aspartate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 15 aspartate residues.

[0126] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, is represented as Asp^n, wherein n represents the number of aspartate residues forming the bone-targeting peptide, e.g., Asp^6 represents a bone-targeting moiety, e.g., a bone-targeting peptide, comprising six aspartate residues, i.e., Asp-Asp-Asp-Asp-Asp-Asp. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is Asp^3, Asp^4, Asp^5, Asp^6, Asp^7, Asp^8, Asp^9, Asp^{10}, Asp^{11}, Asp^{12}, Asp^{13}, Asp^{14}, or Asp^{15}. In some embodiments, each aspartate residue in a bone-targeting moiety, e.g., a bone-targeting peptide, is independently and optionally L-Asp or D-Asp. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^3, L-Asp^4, L-Asp^5, L-Asp^6, L-Asp^7, L-Asp^8, L-Asp^9, L-Asp^{10}, L-Asp^{11}, L-Asp^{12}, L-Asp^{13}, L-Asp^{14}, or L-Asp^{15}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^3. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^4. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^5. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^6. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^7. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^8. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^9. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^{10}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^{11}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^{12}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^{13}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^{14}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Asp^{15}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^3, D-Asp^4, D-Asp^5, D-Asp^6, D-Asp^7, D-Asp^8, D-Asp^9, D-Asp^{10}, D-Asp^{11}, D-Asp^{12}, D-Asp^{13}, D-Asp^{14}, or D-Asp^{15}. In some embodiments, a bone-targeting moiety,

e.g., a bone-targeting peptide, comprises or is D-Asp^{3}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{4}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{5}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{6}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{7}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{8}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{9}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{10}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{11}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{12}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{13}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{14}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Asp^{15}. Without wishing to be bound by any one theory, a bone-targeting moiety, e.g., a bone-targeting peptide that comprises or is Asp^{n} may preferentially target and/or bind to regions of bone with recently resorbed hydroxyapatite, e.g., osteoclastic bone.

[0127] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises poly-glutamate. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of glutamate residues.

[0128] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 3 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 4 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 5 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 6 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 7 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 8 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 9 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 10 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 11 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 12 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 13 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises at least 14 glutamate residues. In some embodiments, a bone-targeting moiety,

e.g., a bone-targeting peptide, comprises at least 15 glutamate residues.

[0129] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 3 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 4 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 5 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 6 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 7 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 8 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 9 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 10 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 11 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 12 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 13 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 14 glutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises no more than 15 glutamate residues.

[0130] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, is represented as Glu^n, wherein n represents the number of glutamate residues forming the bone-targeting peptide, e.g., Glu^6 represents a bone-targeting moiety, e.g., a bone-targeting peptide, comprising six glutamate residues, i.e., Glu-Glu-Glu-Glu-Glu-Glu. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is Glu^3, Glu^4, Glu^5, Glu^6, Glu^7, Glu^8, Glu^9, Glu^{10}, Glu^{11}, Glu^{12}, Glu^{13}, Glu^{14}, or Glu^{15}. In some embodiments, each glutamate residue in a bone-targeting moiety, e.g., a bone-targeting peptide, is independently and optionally L-Glu or D-Glu. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^3, L-Glu^4, L-Glu^5, L-Glu^6, L-Glu^7, L-Glu^8, L-Glu^9, L-Glu^{10}, L-Glu^{11}, L-Glu^{12}, L-Glu^{13}, L-Glu^{14}, or L-Glu^{15}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^3. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^4. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^5. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^6. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^7. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^8. In some embodiments, a bone-targeting moiety, e.g., a bone-

targeting peptide, comprises or is L-Glu^{9}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^{10}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^{11}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^{12}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^{13}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^{14}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is L-Glu^{15}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{3}, D-Glu^{4}, D-Glu^{5}, D-Glu^{6}, D-Glu^{7}, D-Glu^{8}, D-Glu^{9}, D-Glu^{10}, D-Glu^{11}, D-Glu^{12}, D-Glu^{13}, D-Glu^{14}, or D-Glu^{15}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{3}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{4}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{5}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{6}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{7}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{8}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{9}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{10}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{11}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{12}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{13}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{14}. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is D-Glu^{15}.

[0131] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, that comprises an oligomer of carboxylic amino-acid residues may comprise one or more non-carboxylic amino-acid residues inserted at one or more sites in the bone-targeting moiety. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, that comprises an oligomer of aspartate amino-acid residues, e.g., Asp^{n}, may comprise one or more non-aspartate amino-acid residues inserted at one or more sites in the bone-targeting moiety. In some embodiments, one or more non-aspartate residues comprise glutamate. In some embodiments, one or more non-aspartate residues comprise carboxyglutamate. In some embodiments, one or more non-glutamate residues comprise glycine. For example, a glycine residue may be inserted in a bone-targeting moiety comprising Asp^{5} to form a bone-targeting moiety comprising an amino-acid sequence of DDGDDD. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, that comprises an oligomer of glutamate amino-acid residues, e.g., Glu^{n}, may comprise one or more non-glutamate amino-acid residues inserted at one or more sites in the bone-targeting moiety. In some

embodiments, one or more non-glutamate residues comprise aspartate. In some embodiments, one or more non-glutamate residues comprise carboxyglutamate. In some embodiments, one or more non-glutamate residues comprise glycine. For example, a glycine residue may be inserted in a bone-targeting moiety comprising Glu^5 to form a bone-targeting moiety comprising an amino-acid sequence of EEEGEE.

[0132] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is poly-carboxyglutamate. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of carboxyglutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises one or more carboxyglutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 1, 2, 3, 4, or 5 or more carboxyglutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises two or more carboxyglutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises three or more carboxyglutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises four or more carboxyglutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises five or more carboxyglutamate residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 1, 2, 3, 4, or 5 or more carboxyglutamate residues in a peptide with a length of about z + y, wherein z is the number of carboxyglutamate residues in the peptide and y is the number of non-carboxyglutamate amino-acid residues in the peptide and y is 1-20 (e.g., 5-20, 1-15, 5-15, 5-10, or 1-10, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20). In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises 1, 2, 3, 4, or 5 or more carboxyglutamate residues in a peptide with a length of about z + y, wherein z is the number of carboxyglutamate residues in the peptide and y is the number of non-carboxylic amino-acid residues in the peptide and y is 1-20 (e.g., 5-20, 1-15, 5-15, 5-10, or 1-10, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20). In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises $(Nba_p\text{-}Gla_q\text{-}Nba_r)_x$, wherein Nba represents a non-carboxylic amino-acid residue, Gla represents a carboxyglutamate amino-acid residue, each p independently represents a number of Nba residues and is independently 0-10 (e.g., 1-10, 5-10, or 1-5, or 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10), each q independently represents a number of Gla residues and is independently 1-5 (e.g., 1-4, 1-3, or 1-2, or 1, 2, 3, 4, or 5), each r independently represents a number of Nba residues and is independently 0-10 (e.g., 1-10, 5-10, or 1-5, or 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10), and x is 1-5 (e.g., 1-4, 1-3, or 1-2, or 1, 2, 3, 4, or 5). For example, $(Nba_2\text{-}Gla_1\text{-}Nba_3)$ represents a peptide of Nba-Nba-Gla-Nba-Nba-Nba, wherein each Nba is a non-carboxylic amino-acid residue and each Gla is a carboxyglutamate. For example, $(Nba_p\text{-}Gla_q\text{-}Nba_r)_2$ represents $(Nba_p\text{-}Gla_q\text{-}Nba_r)(Nba_{p'}\text{-}Gla_{q'}\text{-}Nba_{r'})$, wherein Nba represents a non-carboxylic amino-acid residue, Gla represents a carboxyglutamate amino-acid residue, p represents a number of Nba residues and is 0-10 (e.g., 1-10, 5-10, or 1-5, or 0, 1, 2,

3, 4, 5, 6, 7, 8, 9, or 10), q represents a number of Gla residues and is 1-5 (e.g., 1-4, 1-3, or 1-2, or 1, 2, 3, 4, or 5), r represents a number of Nba residues and is 0-10 (e.g., 1-10, 5-10, or 1-5, or 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10), each p' represents a number of Nba residues and is 0-10 (e.g., 1-10, 5-10, or 1-5, or 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10), q' represents a number of Gla residues and is 1-5 (e.g., 1-4, 1-3, or 1-2, or 1, 2, 3, 4, or 5), r' represents a number of Nba residues and is 0-10 (e.g., 1-10, 5-10, or 1-5, or 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10).

[0133] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of two amino-acid residues. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of two amino-acid residues, wherein a first amino-acid residue comprises a negatively-charged sidechain and a second amino-acid residue comprises a neutral, polar side chain. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of two amino-acid residues, wherein a first amino-acid residue comprises a carboxylate side chain and a second amino-acid residue comprises a hydroxyl side chain. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is an oligomer of aspartate and serine residues.

[0134] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, is represented as $(Asp\text{-}Ser\text{-}Ser)_n$, wherein n is 1-100, e.g., 1-50, 1-25, or 1-10, e.g., $(Asp\text{-}Ser\text{-}Ser)_2$ represents a bone-targeting moiety, e.g., a bone-targeting peptide, comprising Asp-Ser-Ser-Asp-Ser-Ser. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_1$, $(Asp\text{-}Ser\text{-}Ser)_2$, $(Asp\text{-}Ser\text{-}Ser)_3$, $(Asp\text{-}Ser\text{-}Ser)_4$, $(Asp\text{-}Ser\text{-}Ser)_5$, $(Asp\text{-}Ser\text{-}Ser)_6$, $(Asp\text{-}Ser\text{-}Ser)_7$, $(Asp\text{-}Ser\text{-}Ser)_8$, $(Asp\text{-}Ser\text{-}Ser)_9$, or $(Asp\text{-}Ser\text{-}Ser)_{10}$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_1$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_2$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_3$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_4$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_5$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_6$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_7$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_8$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_9$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is $(Asp\text{-}Ser\text{-}Ser)_{10}$. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a bone-targeting moiety described in Zhang et al., Nat Med. 2012 Jan 29;18(2):307-14, the entirety of which is incorporated herein by reference. Without wishing to be bound by any one theory, a bone-targeting

moiety, e.g., a bone-targeting peptide that comprises or is $(Asp\text{-}Ser\text{-}Ser)_n$ may preferentially target and/or bind to bone-formation surfaces, e.g., regions of bone with recently synthesized hydroxyapatite, e.g., osteoblastic bone.

[0135] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a peptide described in Bang et al., Sci Rep. 2020;10(1):10576, the entirety of which is incorporated herein by reference. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 87.5%, 90%, 95%, or 100% identical to KNFQSRSH. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is KNFQSRSH. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 87.5%, 90%, 95%, or 100% identical to KRRTPVRE. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is KRRTPVRE. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 87.5%, 90%, 95%, or 100% identical to KTYASMQW. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is KTYASMQW. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to DHMDDMDDEDDDDHVDSQDSIDSNDSDDVDDTDDSH. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is DHMDDMDDEDDDDHVDSQDSIDSNDSDDVDDTDDSH.

[0136] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a peptide described in Ramaswamy et al., Biomaterials. 2015;73:120-130, the entirety of which is incorporated herein by reference. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to VTKHLNQISQSY. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is VTKHLNQISQSY.

[0137] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a peptide described in Ling et al. Langmuir. 2020;36(10):2729-2739, the entirety of which is incorporated herein by reference. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to IVQSKHTLSNQY. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is IVQSKHTLSNQY.

[0138] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a peptide described in Duanis-Assaf et al., Langmuir. 2022;38(3):968-978, the entirety of which is incorporated herein by reference. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting

peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to SVSVGMKPSPRP. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is SVSVGMKPSPRP.

[0139] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a peptide described in Mao et al., Materials (Basel). 2016;9(8):700, the entirety of which is incorporated herein by reference. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 95%, or 100% identical to NNHYLPR. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is NNHYLPR.

[0140] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a peptide described in Chung et al., Langmuir. 2011;27(12):7620-7628, the entirety of which is incorporated herein by reference. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to QPYHPTIPQSVH. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is QPYHPTIPQSVH. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 76%, 77%, 78%, 79%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 95%, or 100% identical to CQYPTLKSC. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is CQYPTLKSC. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 95%, or 100% identical to HAPVQPQ. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is HAPVQPQ. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to TMGFTAPRFPHY. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is TMGFTAPRFPHY.

[0141] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a peptide described in Gungormus et al., ACS Biomater Sci Eng. 2020;6(7):3791-3798, the entirety of which is incorporated herein by reference. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 76%, 77%, 78%, 79%, 80%, 85%, 90%, 91%, 92%, 93%, 94% 95%, or 100% identical to PGEKADRAEKADRA. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is PGEKADRAEKADRA. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 76%, 77%, 78%, 79%, 80%, 85%, 90%, 91%, 92%, 93%, 94% 95%, or 100% identical to PGEKSHSASDRTA. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is PGEKSHSASDRTA. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 95%, or 100% identical to

PGYINLSYEKSHSQAINTDRTA. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is PGYINLSYEKSHSQAINTDRTA.

[0142] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a peptide described in Lee et al., Chembiochem. 2011;12(11):1669-1673, the entirety of which is incorporated herein by reference. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to AAFVSKQEGSEVVKQPRSYLYQWLGAPVPYPDPLAEPRREVAELEPRREVAELNPDCDELADHI GFQEAYRRFYGPV. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is AAFVSKQEGSEVVKQPRSYLYQWLGAPVPYPDPLAEPRREVAELEPRREVAELNPDCDELADHI GFQEAYRRFYGPV. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to TVFLDHENANKILNQPKSYNSGKLAEPRREVAELEPRREVAEL. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is TVFLDHENANKILNQPKSYNSGKLAEPRREVAELEPRREVAEL. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100% identical to AEPRREVAELEPRREVAEL. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is AEPRREVAELEPRREVAEL.

[0143] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a peptide described in US 7,323,542, the entirety of which is incorporated herein by reference. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to TMRNPITSLISV. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is TMRNPITSLISV. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to LLADTTHRPWT. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is LLADTTHRPWT. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to KEIPPIPLLAPS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is KEIPPIPLLAPS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to NNVSQKWQQRLI. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is NNVSQKWQQRLI. In some embodiments, a bone-targeting moiety,

e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to NSMIAHNKTRMH. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is NSMIAHNKTRMH. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to GIHVPWMPPVAF. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is GIHVPWMPPVAF. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to QRSWTLDSALSM. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is QRSWTLDSALSM. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to SGHQLLLNKMPN. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is SGHQLLLNKMPN. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to SSTLKTFFGFPD. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is SSTLKTFFGFPD. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to DSSNPIFWRPSS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is DSSNPIFWRPSS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to NYSHLRVKLPTP. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is NYSHLRVKLPTP. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to ATWSHHLSSAGL. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is ATWSHHLSSAGL. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to SYSQMDPPRSLP. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is SYSQMDPPRSLP.

[0144] In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide, comprises or is a peptide described in US 7,323,542, the entirety of which is incorporated herein by reference. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to TMRNPITSLISVGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-

targeting peptide comprises or is TMRNPITSLISVGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to LLADTTHHRPWTGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is LLADTTHHRPWTGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to KEIPPIPLLAPSGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is KEIPPIPLLAPSGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to NNVSQKWQQRLIGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is NNVSQKWQQRLIGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to NSMIAHNKTRMHGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is NSMIAHNKTRMHGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to GIHVPWMPPVAFGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is GIHVPWMPPVAFGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to QRSWTLDSALSMGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is QRSWTLDSALSMGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to SGHQLLLNKMPNGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is SGHQLLLNKMPNGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to SSTLKTFFGFPDGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is SSTLKTFFGFPDGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to DSSNPIFWRPSSGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide

comprises or is DSSNPIFWRPSSGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to NYSHLRVKLPTPGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is NYSHLRVKLPTPGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to ATWSHHLSSAGLGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is ATWSHHLSSAGLGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises a sequence that is at least about 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, or 100% identical to SYSQMDPPRSLPGGGS. In some embodiments, a bone-targeting moiety, e.g., a bone-targeting peptide comprises or is SYSQMDPPRSLPGGGS.

[0145] In some embodiments, 1 to (n + 15) amino-acid residues are deleted from an antibody or antigen-binding fragment thereof following an insertion of a bone-targeting peptide, wherein n is the number of amino-acid residues in the bone-targeting peptide.

[0146] Certain bone-targeting moieties, e.g., bone-targeting peptides, may be preferred for inclusion in antibodies that bind certain antigens. For example, bone-targeting moieties, e.g., bone-targeting peptides, that preferentially target and/or bind bone regions with recently resorbed hydroxyapatite (e.g., osteoclastic bone) may be preferred for inclusion in antibodies that bind antigens that are primarily expressed (e.g., in a tumor, cancer, or metastasis) near recently resorbed hydroxyapatite in bone. Similarly, bone-targeting moieties, e.g., bone-targeting peptides, that preferentially target and/or bind bone regions with recently synthesized hydroxyapatite (e.g., osteoblastic bone) may be preferred for inclusion in antibodies that bind antigens that are primarily expressed (e.g., in a tumor, cancer, or metastasis) near recently synthesized hydroxyapatite in bone. For example, bone metastases related to prostate cancer that express PSMA have been reported to overlap with bisphosphonates, which target and/or bind to newly formed hydroxyapatite, in PET scans. See, e.g., Harmon et al., Oncotarget. 2018;9(102):37676-37688 and Kabunda et al., Clin Nucl Med. 2021;46(7):562-568, which are hereby incorporated by reference in their entirety. And thus, without wishing to be bound by any one theory, inclusion of a bone-targeting moiety, e.g., a bone-targeting peptide, that preferentially binds to these osteoblastic regions in an anti-PSMA antibody may provide certain benefits.

[0147] In some embodiments, a bone-targeting moiety comprises or is a bisphosphonate (BP). Bisphosphonates generally comprise a structure containing two phosphonate groups (e.g., PO_3) bound, by the phosphate (P), to a central carbon (C). Further, bisphosphonates may comprise two R-groups (R_1 and R_2) also bound to the central carbon, wherein the R-groups can be substituted to provide various chemical

properties to the bisphosphonate. Due to the negative charges carried in by the phosphonate groups, bisphosphonates reportedly preferentially associate with bone, e.g., hydroxyapatite of bone.

[0148] Various bisphosphonates are known in the art. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is alenodronate, aminomethylene bisphonic acid, clodronate, etidronate, ibandronate, medronic acid, neridronate, olpadronate, oxidronate, pamidronate, risderonate, tiludronate, or zoledronate. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is alendronate. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is aminomethylene bisphonic acid. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is clodronate. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is etidronate. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is ibandronate. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is neridronate. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is olpadronate. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is oxidronate. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is medronic acid. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is pamidronate. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is risedronate. In some embodiments, a bone-targeting moiety, e.g., a bisphosphonate, comprises or is zoledronate.

[0149] Various bisphosphonates are known in the art. In some embodiments, a bisphosphonate is a bisphosphonate described in WO 2022/159492, the entirety of which is incorporated herein by reference. In some embodiments, a bisphosphonate is associated with an antibody or antigen-binding fragment thereof or a conjugate provided herein as described in WO 2022/159492. In some embodiments, a bisphosphonate is associated with an antibody or antigen-binding fragment thereof or a conjugate provided herein using a method described in WO 2022/159492. In some embodiments, a bisphosphonate is attached to an antibody or antigen-binding fragment thereof or a conjugate provided herein as described in WO 2022/159492. In some embodiments, a bisphosphonate is attached to an antibody or antigen-binding fragment thereof or a conjugate provided herein using a method described in WO 2022/159492. In some embodiments, a bisphosphonate is attached to an antibody or antigen-binding fragment thereof at a location described in WO 2022/159492. In some embodiments, a bisphosphonate is linked to an antibody or antigen-binding fragment thereof or a conjugate provided herein as described in WO 2022/159492. In some embodiments, a bisphosphonate is linked to an antibody or antigen-binding fragment thereof or a conjugate provided herein using a method described in WO 2022/159492. In some embodiments, a bisphosphonate is linked to an antibody or antigen-binding fragment thereof at a location described in WO 2022/159492.

Exemplary Bone-Targeted Antibodies

[0150] In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises or is an antibody or antigen-binding fragment thereof provided herein. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises or is an antibody or antigen-binding fragment thereof provided herein and further comprising one or more bone-targeting moieties as provided herein. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises or is an antibody or antigen-binding fragment thereof provided herein modified to comprise one or more bone-targeting moieties as provided herein. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises or is an antibody or antigen-binding fragment thereof comprising a bone-targeting moiety. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises or is an antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties.

[0151] In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises or is an anti-PSMA antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises or is a bone-targeted J591 antibody, e.g., a J591 antibody modified to comprise one or more bone-targeting moieties as provided herein. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises or is a bone-targeted humanized J591 antibody, e.g., a humanized J591 antibody modified to comprise one or more bone-targeting moieties as provided herein. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises or is an antibody described in WO 2019/191728 modified to comprise one or more bone-targeting moieties as provided herein.

[0152] In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises 1, 2, 3, 4, 5, or 6 of the CDRs in Table 28. In some embodiments, an anti-PSMA antibody comprises 1, 2, 3, 4, 5, or 6 of the CDRs in Table 28. In some embodiments, a bone-targeted anti-PSMA antibody comprises 1, 2, 3, 4, 5, or 6 of the CDRs in Table 28. In some embodiments, a humanized J591 antibody, e.g., a humanized J591 antibody modified to comprise one or more bone-targeting moieties provided herein, comprises 1, 2, 3, 4, 5, or 6 of the CDRs in Table 28. In some embodiments, a light chain comprises SEQ ID NOs: 100, 101, or 102. In some embodiments, a light chain comprises SEQ ID NOs: 100, 101, and 102. In some embodiments, a heavy chain comprises SEQ ID NOs: 103, 104, and/or 105. In some embodiments, a heavy chain comprises SEQ ID NOs: 103, 104, and 105. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises SEQ ID NOs: 100, 101, 102, 103, 104, and/or 105. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises SEQ ID NOs: 100, 101, 102, 103, 104, and 105.

TABLE 28

CDR	SEQ ID NO:	Amino-acid sequence
CDR L1	100	KASQDVGTAVD
CDR L2	101	WASTRHT
CDR L3	102	QQYNSYPLT
CDR H1	103	GYTFTEYTIH
CDR H2	104	NINPNNGGTTYNQKFED
CDR H3	105	GWNFDY

[0153] In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising a sequence provided herein. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising a sequence provided in Table 1. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising any one of SEQ ID NOs: 1-16. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 1. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 2. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 3. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 4. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 5. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 6. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 7. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 8. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 9. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 10. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 11. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 12. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 13. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain

comprising an amino-acid sequence comprising SEQ ID NO: 14. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 15. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 16.

TABLE 1

SEQ ID NO:	Amino-acid sequence
1	DIQMTQSPSSLSTSVGDRVTLTCKASQDVGTAVDWYQQKPGQSPKLLIYWA STRHTGIPSRFSGSGSGTDFTLTISSLQPEDFADYYCQQYNSYPLTFGAGTKV DIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
2	DIQMTQSPSSLSTSVGDRVTLTCKASQDVGTAVDWYQQKPGPSPKLLIYWA STRHTGIPSRFSGSGSGTDFTLTISSLQPEDFADYYCQQYNSYPLTFGPGTKV DIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
3	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQQKPGKAPKLLIYWA STRHTGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
4	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQQKPGKAPKLLIYWA STRHTGVPSRFSGSGSGTEFTLTISSLQSEDFATYYCQQYNSYPLTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGEC
5	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQQKPGKAPKLLIYWA STRHTGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNADD DDDDQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVT KSFNRGEC
6	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQQKPGKAPKLLIYWA STRHTGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNADD DDDDLQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG LSSPVTKSFNRGEC
7	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQQKPGKAPKLLIYWA STRHTGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNADD DDDDGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSS PVTKSFNRGEC
8	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQQKPGKAPKLLIYWA STRHTGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS

	GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGECDDDDDD
9	DIQMTQSPSSLSTSVGDRVTLTCKASQDVGTAVDWYQQKPGPSPKLLIYWA STRHTGIPSRFSGSGSGTDFTLTISSLQPEDFADYYCQQYNSYPLTFGPGTKV DIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNADD DDDDQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC
10	DIQMTQSPSSLSTSVGDRVTLTCKASQDVGTAVDWYQQKPGPSPKLLIYWA STRHTGIPSRFSGSGSGTDFTLTISSLQPEDFADYYCQQYNSYPLTFGPGTKV DIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGECDDDDDD
11	DIQMTQSPSSLSTSVGDRVTLTCKASQDVGTAVDWYQQKPGPSPKLLIYWA STRHTGIPSRFSGSGSGTDFTLTISSLQPEDFADYYCQQYNSYPLTFGPGTKV DIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNADD DDDDQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGECDDDDDD
12	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQQKPGKAPKLLIYWA STRHTGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNADD DDDDQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC
13	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQQKPGKAPKLLIYWA STRHTGVPSRFSGSGSGTEFTLTISSLQPEDFATYYCQQYNSYPLTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNADD DDDDQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGECDDDDDD
14	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQQKPGKAPKLLIYWA STRHTGVPSRFSGSGSGTEFTLTISSLQSEDFATYYCQQYNSYPLTFGGGTKV EIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNADD DDDDQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGEC
15	DIQMTQSPSSLSTSVGDRVTLTCKASQDVGTAVDWYQQKPGPSPKLLIYWA STRHTGIPSRFSGSGSGTDFTLTISSLQSEDFADYYCQQYNSYPLTFGPGTKV DIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQS GNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS FNRGECDDDDDD
16	DIQMTQSPSSLSTSVGDRVTLTCKASQDVGTAVDWYQQKPGPSPKLLIYWA STRHTGIPSRFSGSGSGTDFTLTISSLQPEDFADYYCQQYNSYPLTFGPGTKV DIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNADD DDDDQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL SSPVTKSFNRGECDDDDDD

[0154] In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising a sequence provided herein. In some embodiments, a bone-targeted antibody or

antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising a sequence provided in Table 2. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising any one of SEQ ID NOs: 17-51. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 17. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 18. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 19. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 20. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 21. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 22. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 23. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 24. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 25. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 26. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 27. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 28. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 29. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 30. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 31. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 32. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 33. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 34. In some embodiments, a bone-targeted antibody or antigen-binding fragment

thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 35. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 36. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 37. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 38. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 39. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 40. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 41. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 42. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 43. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 44. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 45. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 46. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 47. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 48. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 49. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 50. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 51.

[0155] In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising any one of SEQ ID NOs: 52-99. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 52. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 53. In some embodiments, a bone-targeted antibody or antigen-binding fragment

thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 54. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 55. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 56. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 57. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 58. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 59. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 60. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 61. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 62. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 63. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 64. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 65. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 66. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 67. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 68. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 69. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 70. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 71. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 72. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 73. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence

comprising SEQ ID NO: 74. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 75. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 76. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 77. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 78. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 79. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 80. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 81. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 82. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 83. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 84. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 85. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 86. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 87. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 88. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 89. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 90. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 91. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 92. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 93. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 94. In some embodiments, a bone-targeted

antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 95. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 96. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 97. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 98. In some embodiments, a bone-targeted antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 99.

TABLE 2

SEQ ID NO:	Amino-acid sequence
17	EVQLVQSGPEVKKPGATVKISCKTSGYTFTEYTIHWVKQAPGKGLEWIGNIN PNNGGTTYNQKFEDKATLTVDKSTDTAYMELSSLRSEDTAVYYCAAGWNF DYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDDDDDDDDD
18	EVQLVQSGPEVKKPGATVKISCKTSGYTFTEYTIHWVKQAPGKGLEWIGNIN PNNGGTTYNQKFEDKATLTVDKSTDTAYMELSSLRSEDTAVYYCAAGWNF DYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSN TKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTC VVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKN QVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
19	EVQLVQSGPEVKKPGATVKISCKTSGYTFTEYTIHWVKQAPGKGLEWIGNIN PNNGGTTYNQKFEDKATLTVDKSTDTAYMELSSLRSEDTAVYYCAAGWNF DYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGADDDDDDGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDD
20	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGADDDDDDTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK

	NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
21	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGADDDDDDLTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
22	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGADDDDDDDGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
23	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDD
24	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGADDDDDDDGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDDD
25	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGDDDDDDDAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

26	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGDDDDDDPSVFPLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
27	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGDDDDDDFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
28	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPDDDDDDSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
29	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPDDDDDDLAPSSKSTSGGTAALGCLVK DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
30	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPDDDDDDSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
31	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV

	TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPDDDDDDGPSVFLFPPKPKDTLMISRTPE VTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
32	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPDDDDDDAPELLGGPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYR VVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLP PSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSF FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
33	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPDDDDDDLLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
34	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDDDDDDDDWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTV LHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
35	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDDDDDDDDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
36	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDDDDDDDKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV

	LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
37	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNDDDDDDIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
38	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNDDDDDDDKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
39	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNDDDDDDDPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
40	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGDDDDDDDVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
41	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGDDDDDDDQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG

42	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGDDDDDDEPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
43	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
44	EVQLVQSGPEVKKPGATVKISCKTSGYTFTEYTIHWVKQAPGKGLEWIGNIN PNNGGTTYNQKFEDKATLTVDKSTDTAYMELSSLRSEDTAVYYCAAGWNF DYWGQGTLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTV SWNSGADDDDDDGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNH KPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTP EVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLT VLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELT KNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLT VDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
45	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDDDDDDDDD
46	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGDDDDDDFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDDD
47	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPDDDDDDSSKSTSGGTAALGCLVKDYF

	PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDEL TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDD
48	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPDDDDDDLLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDD
49	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDDDDDDDDKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDD
50	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNDDDDDDPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDD
51	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGDDDDDDDEPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDD
52	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL

	HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKNFQSRSH
53	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKRRTPVRE
54	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKTYASMQW
55	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGVTKHLNQISQSY
56	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGIVQSKHTLSNQY
57	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDSSDSSDSSDSSDSSDSS

58	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGSVSVGMKPSPRP
59	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGNNHYLPR
60	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGQPYHPTIPQSVH
61	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGCQYPTLKSC
62	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDHMDDMDDEDDDDHV DSQDSIDSNDSDDVDDTDDSH
63	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW

	NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGHAPVQPQ
64	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGTMGFTAPRFPHY
65	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGPGEKADRAEKADRA
66	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGPGEKSHSASDRTA
67	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGPGYINLSYEKSHSQAIN TDRTA
68	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP

	SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGAAFVSKQEGSEVVKQP RSYLYQWLGAPVPYPDPLAEPRREVAELEPRREVAELNPDCDELADHIGFQE AYRRFYGPV
69	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGTVFLDHENANKILNQPK SYNSGKLAEPRREVAELEPRREVAEL
70	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGEEEEEE
71	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGAEPRREVAELEPRREVA EL
72	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGTMRNPITSLISV
73	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV

	TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGLLADTTHRPWT
74	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGKEIPPIPLLAPS
75	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGNNVSQKWQQRLI
76	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGNSMIAHNKTRMH
77	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGIHVPWMPPVAF
78	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL

	HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGQRSWTLDSALSM
79	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGSGHQLLLNKMPN
80	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGSSTLKTFFGFPD
81	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDSSNPIFWRPSS
82	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGNYSHLRVKLPTP
83	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGADDDDDDLTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYIC NVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLM ISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRV VSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPS RDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFL YSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDDDDDDDDDD

	DDD
84	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGATWSHHLSSAGL
85	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGSYSQMDPPRSLP
86	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLE WMGNINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAV YYCAAGWNFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGTMRNPITSLISVGGGS
87	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLE WMGNINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAV YYCAAGWNFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGLLADTTHHRPWTGGGS
88	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLE WMGNINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAV YYCAAGWNFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP

	IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGKEIPPIPLLAPSGGGS
89	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLE WMGNINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAV YYCAAGWNFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGNNVSQKWQQRLIGGGS
90	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLE WMGNINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAV YYCAAGWNFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAAL GCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPS SSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGP SVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVH NAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVE WESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGNSMIAHNKTRMHGGGS
91	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGGIHVPWMPPVAFGGGS
92	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGQRSWTLDSALSMGGGS
93	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV

	TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGSGHQLLLNKMPNGGGS
94	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGSSTLKTFFGFPDGGGS
95	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDSSNPIFWRPSSGGGS
96	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGNYSHLRVKLPTPGGGS
97	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGATWSHHLSSAGLGGGS
98	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVL HQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTK NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV

	DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGSYSQMDPPRSLPGGGS
99	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHWVRQAPGQRLEWMG NINPNNGGTTYNQKFEDRVTITRDTSASTAYMELSSLRSEDTAVYYCAAGW NFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPV TVSWNSGADDDDDDGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISR TPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDE LTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGDSSDSSDSSDSSDSS DSS

[0156] In some embodiments, a bone-targeted antibody comprises a light chain comprising an amino-acid sequence comprising a sequence provided in Table 1 and a heavy chain comprising an amino-acid sequence comprising a sequence provided in Table 2. In some embodiments, a bone-targeted antibody comprises a light chain comprising an amino-acid sequence comprising any one of SEQ ID NOs: 1-16 and a heavy chain comprising an amino-acid sequence comprising any one of SEQ ID NOs: 17-51. In some embodiments, a bone-targeted antibody comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 2 and a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 19. In some embodiments, a bone-targeted antibody comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 3 or 4 and a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 24. In some embodiments, a bone-targeted antibody comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 3 and a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 24. In some embodiments, a bone-targeted antibody comprises a light chain comprising an amino-acid sequence comprising SEQ ID NO: 4 and a heavy chain comprising an amino-acid sequence comprising SEQ ID NO: 24.

[0157] In some embodiments, a bone-targeted antibody comprises a light chain comprising an amino-acid sequence comprising any one of SEQ ID NOs: 1-16 and a heavy chain comprising an amino-acid sequence comprising any one of SEQ ID NOs: 52-99.

[0158] In some embodiments, a bone-targeted antibody comprises a light chain comprising an amino-acid sequence with about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity to a sequence in Table 1. In some embodiments, a bone-targeted antibody comprises a heavy chain comprising an amino-acid sequence with about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity to a sequence in Table 2. In some embodiments, a bone-targeted antibody comprises a light chain comprising an amino-acid sequence with about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity to a sequence in Table 1 and a heavy chain comprising an amino-acid sequence with about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity to a sequence in Table 2.

Target Agents

[0159] Various target agents can be associated with (e.g., attached to, linked to, conjugated to) an antibody or antigen-binding fragment thereof (e.g., a bone-targeted antibody or antigen-binding fragment thereof) provided herein. Non-limiting examples of target agents that can be conjugated to the complex include exogenous materials that do not exist naturally in virions, such as nucleic acid molecules such as DNA (e.g., nuclear DNA and mitochondrial DNA), RNA such as mRNA, tRNA, miRNA, shRNA, and siRNA, aptamers and other nucleic acid-containing molecules, peptides, proteins, ribozymes, carbohydrates, polymers, therapeutics, and small molecules. In some embodiments, the heterologous sequence can be a peptide, nucleic acid, antibody, or fragment thereof.

[0160] In some embodiments, a target agent is an anti-cancer agent. Various suitable anti-cancer agents are known in the art, and can belong to any of various classes of compounds including, but not limited to, small molecules, peptides, saccharides, steroids, antibodies, fusion proteins, antisense polynucleotides, ribozymes, small interfering RNAs, peptidomimetics, and the like. Similarly, suitable anti-cancer agents can be found among any of a variety of classes of anti-cancer agents including, but not limited to, alkylating agents, anti-metabolite drugs, anti-mitotic antibiotics, alkaloidal anti-cancer agents, hormones and anti-hormones, interferons, non-steroidal anti-inflammatory drugs, and various other anti-cancer agents. In some embodiments, a target agent is an anti-cancer agent selected from the group consisting of alkylating drugs (e.g., mechlorethamine, chlorambucil, cyclophosphamide, melphalan, ifosfamide), antimetabolites (e.g., methotrexate), purine antagonists and pyrimidine antagonists (e.g., 6-mercaptopurine, 5-fluorouracil, cytarabile, gemcitabine), spindle poisons (e.g., vinblastine, vincristine, vinorelbine, paclitaxel), podophyllotoxins (e.g., etoposide, irinotecan, topotecan), antibiotics (e.g., doxorubicin, bleomycin, mitomycin), nitrosoureas (e.g., carmustine, lomustine), inorganic ions (e.g., cisplatin, carboplatin), enzymes (e.g., asparaginase), and hormones (e.g., tamoxifen, leuprolide, flutamide, and megestrol).

[0161] In some embodiments, a target agent is a detectable moiety, e.g., a detectable entity. Suitable detectable moieties include, but are not limited to: various ligands, radionuclides; fluorescent dyes; chemiluminescent agents (such as, for example, acridinium esters, stabilized dioxetanes, and the like); bioluminescent agents; spectrally resolvable inorganic fluorescent semiconductors nanocrystals (i.e., quantum dots); microparticles; metal nanoparticles (e.g., gold, silver, copper, platinum, etc.); nanoclusters; paramagnetic metal ions; enzymes; colorimetric labels (such as, for example, dyes, colloidal gold, and the like); biotin; dioxigenin; haptens; and proteins for which antisera or monoclonal antibodies are available. In some embodiments, a target agent is a radioactive and/or paramagnetic isotope or ion.

[0162] In some embodiments, a toxin is monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF), ozogamicin, tiuxetan, vedotin, pasudotox-tdfx, mafodotin, calicheamicin, maytansine, deruxtecan, eribulin, MMAU, hemiasterlin, or derivatives or combinations thereof. MMAU is described in, e.g., Goldberg et al., Mol Cancer Ther. 2024;23(11):1530-1543, which is hereby incorporated by reference in its entirety.

[0163] In some embodiments, a radioligand is astatine-211, carbon-14, chromium-51, chlorine-36, cobalt-57, cobalt-58, copper-67, europium-152, gallium-67, hydrogen-3, iodine-123, iodine-125, iodine-131, indium-111, iron-59, lutetium-177, phosphorus-32, rhenium-186, rhenium-188, selenium-75, sulfur-35, technetium-99m, or yttrium-90. In some embodiments, a radioligand is an alpha emitter or a beta emitter. In some embodiments, a radioligand is actinium, lutetium, indium, radium, Pb-212, Cu-67, astatine, or thorium.

[0164] In some embodiments, an immune response potentiator is an anti-CD3 antibody, STING agonist, or TLR agonist. In some embodiments, a small molecule inhibitor is an androgen receptor (AR) inhibitor (e.g., enzalutamide). In some embodiments, a target agent is a chemotherapeutic (e.g., alkylating agents, antimetabolites, antitumor antibiotics, mitotic inhibitors, or nitrosoureas) or radiotherapeutic. A wide variety of chemotherapeutic agents may be used in accordance with the present disclosure. The term "chemotherapy" refers to the use of drugs to treat cancer. A "chemotherapeutic agent" is used to connote a compound or composition that is administered in the treatment of cancer. These agents or drugs are categorized by their mode of activity within a cell, for example, whether and at what stage they affect the cell cycle. Alternatively, an agent may be characterized based on its ability to directly cross-link DNA, to intercalate into DNA, or to induce chromosomal and mitotic aberrations by affecting nucleic acid synthesis.

[0165] Non-limiting examples of chemotherapeutic agents include alkylating agents (e.g., thiotepa and cyclosphosphamide), alkyl sulfonates (e.g., busulfan, improsulfan, and piposulfan), aziridines (e.g., such as benzodopa, carboquone, meturedopa, and uredopa), ethylenimines and methylamelamines (e.g., altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide, and trimethylolomelamine), acetogenins (e.g., bullatacin and bullatacinone), camptothecin (e.g., topotecan); bryostatin; callystatin, CC-1065 (e.g., adozelesin, carzelesin and bizelesin), cryptophycins (e.g., cryptophycin 1 and cryptophycin 8), dolastatin, duocarmycin (e.g., KW-2189 and CB1-TM1); eleutherobin, pancratistatin, sarcodictyin, spongistatin, nitrogen mustards (e.g., chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, and uracil mustard) nitrosureas (e.g., carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine), aclacinomysins, actinomycin, authrarnycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-

norleucine, doxorubicin (e.g., morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, such as mitomycin C, mycophenolic acid, nogalarnycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, and zorubicin, anti-metabolites (e.g., methotrexate and 5- fluorouracil (5-FU)), folic acid analogues (e.g., denopterin, pteropterin, and trimetrexate), purine analogs (e.g., fludarabine, 6-mercaptopurine, thiamiprine, and thioguanine) pyrimidine analogs (e.g., ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, and floxuridine); androgens (e.g., calusterone, dromostanolone propionate, epitiostanol, mepitiostane, and testolactone), anti-adrenals (e.g., as mitotane and trilostane), folic acid replenisher (e.g., frolinic acid; aceglatone; aldophosphamide glycoside), aminolevulinic acid, eniluracil, amsacrine, bestrabucil, bisantrene, edatrexate, defofamine, demecolcine, diaziquone, elformithine, elliptinium acetate, epothilone, etoglucid, gallium nitrate, hydroxyurea, lentinan, lonidainine, maytansinoids (e.g., such as maytansine and ansamitocins), mitoguazone, mitoxantrone, mopidanmol, nitraerine, pentostatin, phenamet, pirarubicin, losoxantrone, podophyllinic acid, 2-ethylhydrazide, procarbazine, PSKpolysaccharide complex, razoxane, rhizoxin, sizofiran, spirogermanium, tenuazonic acid, triaziquone, 2,2',2"-trichlorotriethylamine, trichothecenes (e.g., T-2 toxin, verracurin A, roridin A and anguidine), urethan, vindesine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, gacytosine, arabinoside (e.g., Ara-C), cyclophosphamide; toxoids (e.g., paclitaxel and docetaxel), gemcitabine, 6-thioguanine, mercaptopurine, platinum coordination complexes (cisplatin, oxaliplatin, and carboplatin), vinblastine, platinum, etoposide (e.g., VP-16), ifosfamide, mitoxantrone, vincristine, vinorelbine, novantrone, teniposide, edatrexate, daunomycin, aminopterin, xeloda, ibandronate, irinotecan (e.g., CPT-11), topoisomerase inhibitor, difluorometlhylornithine (DMFO), retinoids (retinoic acid), capecitabine, carboplatin, procarbazine, and plicamycin. Pharmaceutically acceptable salts, acids, or derivatives of any of the above are also chemotherapeutic agents described herein.

[0166] In some embodiments, a target agent comprises a radiotherapy. Other factors that cause DNA damage and have been used extensively include what are commonly known as γ-rays, X-rays, and/or the directed delivery of radioisotopes to tumor cells. Other forms of DNA damaging factors are also contemplated, such as microwaves, proton beam irradiation (U.S. Patents 5,760,395 and 4,870,287, each of which are hereby incorporated by reference in their entirety), and UV-irradiation. It is most likely that all of these factors affect a broad range of damage on DNA, on the precursors of DNA, on the replication and repair of DNA, and on the assembly and maintenance of chromosomes. Dosage ranges for X-rays range from daily doses of 50 to 200 roentgens for prolonged periods of time (3 to 4 wk), to single doses of 2000 to 6000 roentgens. Dosage ranges for radioisotopes vary widely, and depend on the half-life of the isotope, the strength and type of radiation emitted, and the uptake by the neoplastic cells.

[0167] In some embodiments, a target agent can be an amino acid sequence up to 200 amino acids, such as up to 50 amino acids. In some embodiments, a target agent comprises or is a peptide. In some embodiments, a peptide has a length of about 5 to about 10, about 10 to about 20 amino acids, about 20 to about 30, about 30 to about 40, or about 40 to about 50 residues.

[0168] In some embodiments, a target agent comprises an androgen receptor degrader, integrin inhibitor, EZH2, adenosine receptor inhibitors (CD73), WNT pathway inhibitor, AKT inhibitor, steroidogenesis inhibitor (e.g., ODM-208), PARP inhibitor, immune activator (e.g., TLR3 agonist), BET inhibitor, pyrrolobenzodiazepine (PBD), MYC pathway inhibitor, RAS pathway inhibitor, PI3K inhibitor, NRG1 inhibitor, SMARCA2 degrader, SMARCA2 inhibitor, SMARCA4 degrader, SMARCA4 inhibitor, farnesyl pyrophosphate synthase inhibitor, mTOR inhibitor, CDK4 inhibitor, CDK6 inhibitor, VEGFR2 inhibitor, MET inhibitor, tyrosine kinase inhibitor, histone deacetylase inhibitor, Janus kinase inhibitor, BCL-2 inhibitor, KRAS inhibitor, ALK5 inhibitor, pseudomonas exotoxin A (PEA), diphtheria toxin, or any combination thereof.

Conjugation

[0169] Various conjugates comprising an antibody or antigen-binding fragment thereof and one or more target agents are provided herein. Various conjugates comprising an antibody or antigen-binding fragment thereof and one or more target agents can be produced using the methods provided herein. In some embodiments, a conjugate comprises or is an antibody-drug conjugate (ADC).

[0170] Various conjugation technologies are known in the art. A target agent may be conjugated, e.g., associated with, an antibody or antigen-binding fragment thereof using any such conjugation technologies.

[0171] In some embodiments, one or more target agents are associated with an antibody or antigen-binding fragment thereof provided herein. In some embodiments, one or more target agents are associated with a bone-targeted antibody or antigen-binding fragment thereof provided herein.

[0172] In some embodiments, a target agent is directly associated with an antibody or antigen-binding fragment thereof. In some embodiments, a target agent is indirectly associated with an antibody or antigen-binding fragment thereof. In some embodiments, a target agent is covalently associated with (e.g., covalently linked to) an antibody or antigen-binding fragment thereof. In some embodiments, a target agent is directly covalently associated with (e.g., directly covalently linked to) an antibody or antigen-binding fragment thereof. In some embodiments, a target agent is indirectly covalently associated with (e.g., indirectly covalently linked to) an antibody or antigen-binding fragment thereof. In some embodiments, a target agent is noncovalently associated with an antibody or antigen-binding fragment thereof. In some embodiments, a target agent is associated with an antibody or antigen-binding fragment thereof via a linker. In some embodiments, a target agent is indirectly associated with an antibody or antigen-binding fragment

thereof via a linker. In some embodiments, a target agent is indirectly covalently associated with (e.g., indirectly covalently linked to) an antibody or antigen-binding fragment thereof via a linker.

[0173] Various suitable sites for conjugation of a target agent to an antibody or antigen-binding fragment thereof are known in the art. In some embodiments, a target agent is associated with an antibody or antigen-binding fragment thereof at one or more sites the antibody or antigen-binding fragment thereof. In some embodiments, a target agent is associated with an antibody or antigen-binding fragment thereof at one or more sites on a light chain of the antibody or antigen-binding fragment thereof. In some embodiments, a target agent is associated with an antibody or antigen-binding fragment thereof at one or more sites on a heavy chain of the antibody or antigen-binding fragment thereof. In some embodiments, a target agent is associated with an antibody or antigen-binding fragment thereof at one or more terminal sites of the antibody or antigen-binding fragment thereof. In some embodiments, a target agent is associated with an antibody or antigen-binding fragment thereof at one or more terminal sites of a light chain of the antibody or antigen-binding fragment thereof. In some embodiments, a target agent is associated with an antibody or antigen-binding fragment thereof at one or more terminal sites of a heavy chain of the antibody or antigen-binding fragment thereof. In some embodiments, a target agent is associated with an antibody or antigen-binding fragment thereof at one or more internal sites of the antibody or antigen-binding fragment thereof. In some embodiments, a target agent is associated with an antibody or antigen-binding fragment thereof at one or more internal sites of a light chain of the antibody or antigen-binding fragment thereof. In some embodiments, a target agent is associated with an antibody or antigen-binding fragment thereof at one or more internal sites of a heavy chain of the antibody or antigen-binding fragment thereof.

[0174] In some embodiments, one or more copies of a target agent are associated with an antibody or antigen-binding fragment thereof. In some embodiments, about 1 to 10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) copies of a target agent are associated with an antibody or antigen-binding fragment thereof. In some embodiments, one or more molecules of a target agent are associated with an antibody or antigen-binding fragment thereof. In some embodiments, about 1 to 10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) molecules of a target agent are associated with an antibody or antigen-binding fragment thereof.

[0175] In some embodiments, about 1 to 10 (e.g., about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10) target agents are associated with an antibody or antigen-binding fragment thereof. In some embodiments, about 1 to 5 (e.g., about 1, 2, 3, 4, or 5) target agents are associated with an antibody or antigen-binding fragment thereof.

[0176] Various conjugation methodologies are known in the art and can be used in a conjugate of the present disclosure and/or used to produce a conjugate of the present disclosure. In some embodiments, conjugation comprises chemical conjugation. In some embodiments, conjugation comprises lysine amide coupling. In some embodiments, conjugation comprises cysteine coupling. In some embodiments, conjugation comprises incorporation of non-natural amino acids into, e.g., an antibody or antigen-binding

fragment thereof. In some embodiments, conjugation comprises enzymatic conjugation. In some embodiments, conjugation comprises site-specific enzymatic conjugation. Various enzymatic conjugation methods are known in the art, including sortase-mediated conjugation, transglutamaniase-mediated conjugation, GalT-mediated conjugation, SialT-mediated conjugation, etc.

[0177] In some embodiments, conjugation comprises proximity-induced reactivity between a non-canonical amino acid (ncAA) and a nearby residue (e.g., a lysine or cysteine) of, e.g., an antibody or antigen-binding fragment thereof. In some embodiments, conjugation comprises proximity-induced, site-specific conjugation (e.g., pClick). Various pClick technologies are known in the art and may be used in combination with the technologies provided herein. See, e.g., Cao et al., Theranostics. 2021 Aug 27;11(18):9107-9117, which is hereby incorporated by reference in its entirety.

[0178] In some embodiments, conjugation comprises formation of one or more bonds between a target agent and an antibody or antigen-binding fragment thereof. In some embodiments, conjugation comprises formation of one or more bonds between a linker associated with, e.g., linked to, a target agent and an antibody or antigen-binding fragment thereof.

[0179] In some embodiments, conjugation of a target agent with an antibody or antigen-binding fragment thereof does not alter antigen binding by the antibody or antigen-binding fragment thereof. In some embodiments, conjugation of a target agent with an antibody or antigen-binding fragment thereof does not decrease antigen binding by the antibody or antigen-binding fragment thereof.

Cancers

[0180] Various conditions, disorders, and diseases can be treated with provided technologies (antibodies or antigen-binding fragments thereof, conjugates, compositions, methods, etc.). In some embodiments, a condition, disorder, or disease comprises or is a neoplastic condition, disorder, or disease. In some embodiments, a condition, disorder, or disease comprises or is a tumor. In some embodiments, a condition, disorder, or disease comprises or is a cancer. In some embodiments, a condition, disorder, or disease comprises or is a metastasis.

[0181] In some embodiments, a cancer is a cancer disclosed herein. In some embodiments, a cancer is a primary cancer. In some embodiments, a cancer is a secondary cancer. In some embodiments, a secondary cancer is a metastasis of a primary cancer.

[0182] Non-limiting examples of cancers include acute biphenotypic leukemia, acute eosinophilic leukemia, acute myeloid dendritic leukemia, acute myeloid leukemia, adenocarcinoma, adenocarcinoma of the lung, adrenocortical carcinoma, anal cancer, anaplastic large cell lymphoma, angioimmunoblastic T-cell lymphoma, angiosarcoma, appendix cancer, astrocytoma, B-cell prolymphocytic leukemia, basal cell carcinoma, basaloid squamous cell lung carcinoma, bladder cancer, brainstem glioma, breast cancer,

bronchial adenoma, bronchial carcinoid, Burkitt's lymphoma, cerebellar astrocytoma, cerebral astrocytoma, cervical cancer, cholangiocarcinoma, chondrosarcoma, chronic lymphocytic leukemia, chronic myelogenous leukemia, colon cancer, cutaneous T-cell lymphoma, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, ductal carcinoma, duodenal cancer, endometrial cancer, epithelioid hemangioendothelioma, esophageal cancer, ependymoma, Ewing's sarcoma, extragonadal germ cell tumor, extrahepatic bile duct cancer, fibrocartilaginous mesenchymoma, fibrosarcoma, follicular lymphoma, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gestational trophoblastic tumor, giant and spindle cell carcinoma, glioblastoma, glioma, gum cancer, hairy cell leukemia, head and neck cancer, hepatocarcinoma, hepatocellular cancer, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, hypopharyngeal cancer, intravascular large B-cell lymphoma, invasive lobular carcinoma, islet cell carcinoma, juxtacortical osteosarcoma, Kaposi sarcoma, keratoacanthoma, kidney cancer, large granular lymphocytic leukemia, laryngeal cancer, leiomyosarcoma, leukemia, liposarcoma, liver cancer, lung cancer, lymphoepithelial carcinoma, lymphoma, lymphoma of primary cutaneous origin, lymphomatoid granulomatosis, lymphoplasmacytic lymphoma, mammary secretory carcinoma, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal large B-cell lymphoma, medullary carcinoma, medulloblastoma, megakaryoblastic leukemia, melanoma, Merkel cell carcinoma, mesothelioma, monocytic leukemia, mucosa-associated lymphoid tissue lymphoma, multiple endocrine neoplasia syndrome, multiple myeloma, mycosis fungoides, myelodysplastic syndrome, myeloid sarcoma, myxosarcoma, nasal cavity cancer, nasopharyngeal carcinoma, nephroblastoma, neuroblastoma, nodal marginal zone B-cell lymphoma, non-Hodgkin lymphoma, non-small cell lung cancer, non-small cell lung carcinoma, oligodendroglioma, optic nerve glioma, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, ovarian epithelial cancer, ovarian germ cell tumor, pancreatic cancer, papillary carcinoma, paragranuloma, paranasal sinus cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, Phyllodes tumor, pilocytic astrocytoma, pilomatrix carcinoma, pineal astrocytoma, pituitary adenoma, plasma cell leukemia, plasmablastic lymphoma, pleuropulmonary blastoma, precursor B lymphoblastic leukemia, primary central nervous system lymphoma, primary cutaneous follicular lymphoma, primary cutaneous immunocytoma, primary effusion lymphoma, prostate acinar adenocarcinoma, prostate cancer, prostate ductal adenocarcinoma, prostate squamous cell carcinoma, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma of primary cutaneous origin, sebaceous carcinoma, Sezary syndrome, skin cancer, small cell carcinoma, small cell lung cancer, small cell prostate cancer small intestine cancer, soft tissue sarcoma, solid carcinoma, splenic marginal zone lymphoma, squamous cell carcinoma, squamous cell carcinoma of the lung, squamous cell lung cancer, squamous cell skin cancer, stomach cancer, T-cell prolymphocytic leukemia, testicular cancer, thymic carcinoma, thymoma, thyroid cancer, tongue cancer, trabecular

adenocarcinoma, transitional cell cancer, tubular carcinoma, undifferentiated pleomorphic sarcoma (UPS), urethral cancer, urothelial carcinoma, uterine sarcoma, uveal melanoma, vaginal cancer, vulvar cancer, Wilms tumor, or any variant or combination thereof.

[0183] In some embodiments, a sarcoma comprises or is chondrosarcoma, Ewing's sarcoma, osteosarcoma, soft tissue sarcoma, or undifferentiated pleomorphic sarcoma, or any variant or combination thereof. In some embodiments, a sarcoma comprises or is a sarcoma located near the skeleton of a subject.

[0184] In some embodiments, a tumor expresses one or more antigens associated with one or more tumors disclosed herein. In some embodiments, a tumor expresses one or more prostate cancer-associated antigens. In some embodiments, a cancer expresses one or more antigens associated with one or more cancers disclosed herein. In some embodiments, a cancer expresses one or more prostate cancer-associated antigens. In some embodiments, a metastasis expresses one or more prostate cancer-associated antigens.

[0185] In some embodiments, a tumor expresses one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2.

[0186] In some embodiments, a cancer expresses one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2.

[0187] In some embodiments, a metastasis expresses one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7,

ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2.

[0188] In some embodiments, a tumor is a PSMA-expressing tumor. In some embodiments, a tumor is associated with expression of PSMA. In some embodiments, a cancer is a PSMA-expressing cancer. In some embodiments, a cancer is associated with expression of PSMA. In some embodiments, a metastasis is a PSMA-expressing metastasis. In some embodiments, a metastasis is associated with expression of PSMA.

Characterization and Assessment

[0189] In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof can be characterized and/or assessed using various technologies available to those skilled in the art, e.g., biochemical assays, cell-based assays, animal models, clinical trials, etc. Certain useful technologies are described in the Examples. Those skilled in the art reading the present disclosure will readily appreciate that other technologies, e.g., in vitro models (e.g., cell lines) for various conditions, disorders, or diseases (e.g., cancer), animal models for various conditions, disorders, or diseases (e.g., cancer), clinical trials, etc. may be designed and/or utilized to assess provided technologies (e.g., agents, complexes, compounds, and compositions thereof, methods, etc.) in accordance with the present disclosure.

[0190] In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof are assayed using a hydroxyapatite-binding assay, e.g., a NanoHA binding assay. In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof are assayed using a hydroxyapatite-binding kinetics assay, e.g., to determine, e.g., association and/or dissociation constants. In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof are assayed using a hydroxyapatite-binding assay using x-ray photoelectron spectroscopy (XPS) or surface plasmon resonance (SPR). In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof are assayed using an in vivo biodistribution assay in a system, e.g., an animal, e.g., a mouse, a rat, or a monkey. In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof are assayed for in vivo bone biodistribution in a system, e.g., an animal, e.g., a mouse, a rat, or a monkey. A biodistribution assay, e.g., an in vivo biodistribution assay, e.g., an in vivo bone biodistribution assay may utilize an antibody or

antigen-binding fragment thereof provided herein that has been labeled with a detectable moiety, e.g., a luminescent moiety. In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof are assayed for in vivo pharmacokinetics (PK) in a system, e.g., an animal, e.g., a mouse, a rat, a monkey, or a human. In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof are assayed for binding to ex vivo bone slices. In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof are assayed for binding to ex vivo prostate metastatic bone slices. In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof are assayed for in vivo tumor killing in an appropriate model, e.g., a bone metastatic model, in a system, e.g., an animal, e.g., a mouse, a rat, or a monkey. In some embodiments, properties and/or activities of provided antibodies and antigen-binding fragments thereof, conjugates, and compositions thereof are assayed for in vivo tumor killing in an appropriate model, e.g., a primary tumor model, in a system, e.g., an animal, e.g., a mouse, a rat, or a monkey.

[0191] In some embodiments, an antibody or antigen-binding fragment thereof that comprises a bone-targeting moiety, e.g., a bone-targeting peptide, exhibits increased binding to hydroxyapatite as compared to a reference antibody or antigen-binding fragment thereof, e.g., an antibody or antigen-binding fragment thereof not comprising a bone-targeting moiety, e.g., a bone-targeting peptide.

[0192] In some embodiments, an antibody or antigen-binding fragment thereof that comprises a bone-targeting moiety, e.g., a bone-targeting peptide, exhibits similar stability, e.g., serum stability, thermal stability, as compared to a reference antibody or antigen-binding fragment thereof, e.g., an antibody or antigen-binding fragment thereof not comprising a bone-targeting moiety, e.g., a bone-targeting peptide.

[0193] In some embodiments, an antibody or antigen-binding fragment thereof that comprises a bone-targeting moiety, e.g., a bone-targeting peptide, exhibits decreased off-target binding as compared to a reference antibody or antigen-binding fragment thereof, e.g., an antibody or antigen-binding fragment thereof not comprising a bone-targeting moiety, e.g., a bone-targeting peptide. In some embodiments, an antibody or antigen-binding fragment thereof that comprises a bone-targeting moiety, e.g., a bone-targeting peptide, exhibits similar off-target binding as compared to a reference antibody or antigen-binding fragment thereof, e.g., an antibody or antigen-binding fragment thereof not comprising a bone-targeting moiety, e.g., a bone-targeting peptide.

[0194] In some embodiments, an antibody or antigen-binding fragment thereof that comprises a bone-targeting moiety, e.g., a bone-targeting peptide, exhibits an increased half-life, e.g., in vivo, as compared to a reference antibody or antigen-binding fragment thereof, e.g., an antibody or antigen-binding fragment thereof not comprising a bone-targeting moiety, e.g., a bone-targeting peptide. In some embodiments, an

antibody or antigen-binding fragment thereof that comprises a bone-targeting moiety, e.g., a bone-targeting peptide, exhibits a similar half-life, e.g., in vivo, as compared to a reference antibody or antigen-binding fragment thereof, e.g., an antibody or antigen-binding fragment thereof not comprising a bone-targeting moiety, e.g., a bone-targeting peptide. In some embodiments, an antibody or antigen-binding fragment thereof that comprises a bone-targeting moiety, e.g., a bone-targeting peptide, exhibits a decreased half-life, e.g., in vivo, as compared to a reference antibody or antigen-binding fragment thereof, e.g., an antibody or antigen-binding fragment thereof not comprising a bone-targeting moiety, e.g., a bone-targeting peptide.

Biological Applications

[0195] As appreciated by those skilled in the art, antibodies or antigen-binding fragments thereof, conjugates, and compositions thereof provided herein are useful for many purposes. In some embodiments, technologies (e.g., antibodies or antigen-binding fragments thereof, conjugates, compositions, methods) provided herein are useful for treating various conditions, disorders, or diseases, e.g., cancer, e.g., prostate cancer, in a subject. In some embodiments, provided technologies disclosed herein are useful for killing cancer cells, e.g., prostate cancer cells, in a system, e.g., a subject. In some embodiments, provided technologies disclosed herein are useful for targeting antibodies (e.g., anti-PSMA antibodies), conjugates (e.g., antibody-drug conjugates), or compositions thereof to bone. In some embodiments, provided technologies disclosed herein are useful for delivering target agents to cancer cells, e.g., prostate cancer cells, in a system, e.g., a subject.

[0196] In some embodiments, the present disclosure provides methods for killing a cancer cell in a system. In some embodiments, the present disclosure provides a method of killing a cancer cell in a system, comprising administering or delivering to the system an effective amount of an antibody or antigen-binding fragment thereof, conjugate, or composition thereof provided herein.

[0197] In some embodiments, the present disclosure provides methods for delivering a target agent to a cancer cell in a system. In some embodiments, the present disclosure provides a method of delivering a target agent to a cancer cell in a system, comprising administering or delivering to the system an effective amount of an antibody or antigen-binding fragment thereof, conjugate, or composition thereof provided herein.

[0198] In some embodiments, a system comprises PSMA. In some embodiments, a system expresses PSMA, e.g., PSMA polypeptides, e.g., PSMA proteins.

[0199] In some embodiments, a system comprises one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha

V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2.

[0200] In some embodiments, a system expresses one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2 polypeptides, e.g., PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2 proteins.

[0201] In some embodiments, a system comprises or is an in vitro system. In some embodiments, a system comprises or is an in vivo system.

[0202] In some embodiments, a system comprises a cell. In some embodiments, a system is a cell. In some embodiments, a system comprises a population of cells. In some embodiments, a system is a population of cells. In some embodiments, a cell is a tumor cell. In some embodiments, a cell is a prostate tumor cell. In some embodiments, a cell is a bone tumor cell. In some embodiments, a cell is a cancer cell. In some embodiments, a cell is a prostate cancer cell. In some embodiments, a cell is a bone cancer cell. In some embodiments, a cell comprises PSMA. In some embodiments, a cell is a PSMA-expressing cell. In some embodiments, a cell comprises one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5,

integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2. In some embodiments, a cell is a cell expressing one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2.

[0203] In some embodiments, a system comprises a tissue. In some embodiments, a system is a tissue. In some embodiments, a system comprises a tumor. In some embodiments, a system is a tumor. In some embodiments, a system comprises an organ. In some embodiments, a system is an organ. In some embodiments, a system comprises an organism. In some embodiments, a system is an organism. In some embodiments, a system comprises an animal. In some embodiments, a system is an animal. In some embodiments, a system comprises a mammal. In some embodiments, a system is a mammal. In some embodiments, a mammal is a mouse. In some embodiments, a mammal is a rat. In some embodiments, a mammal is a non-human primate, e.g., a monkey. In some embodiments, a system comprises a human. In some embodiments, a system is a human. In some embodiments, a system comprises a subject. In some embodiments, a system is a subject. In some embodiments, a system comprises a patient. In some embodiments, a system is a patient.

[0204] Various conditions, disorders, or diseases may be treated with provided technologies (e.g., antibodies or antigen-binding fragments thereof, conjugates, compositions, methods). In some embodiments, a condition, disorder, or disease comprises or is a tumor. In some embodiments, a condition, disorder, or disease comprises or is a cancer, e.g., a cancer described herein. In some embodiments, a condition, disorder, or disease comprises or is a prostate cancer. In some embodiments, a condition, disorder, or disease comprises or is a cancer associated with expression of PSMA. In some embodiments, a condition, disorder, or disease comprises or is a cancer associated with expression of one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-

3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2. In some embodiments, a condition, disorder, or disease comprises or is a bone metastasis, e.g., a prostate cancer bone metastasis.

[0205] In some embodiments, a condition, disorder, or disease that can be treated in accordance with the present disclosure is a condition, disorder, or disease described in WO 2019/191728.

[0206] In some embodiments, the present disclosure provides methods for treating a condition, disorder, or disease in a subject. In some embodiments, the present disclosure provides a method of treating a condition, disorder, or disease in a subject, comprising administering to the subject a therapeutically effective amount of an antibody or antigen-binding fragment thereof, conjugate, or composition thereof provided herein. In some embodiments, the present disclosure provides a method of treating a tumor in a subject, comprising administering to the subject a therapeutically effective amount of an antibody or antigen-binding fragment thereof, conjugate, or composition thereof provided herein. In some embodiments, the present disclosure provides a method of treating a cancer in a subject, comprising administering to the subject a therapeutically effective amount of an antibody or antigen-binding fragment thereof, conjugate, or composition thereof provided herein. In some embodiments, the present disclosure provides a method of treating a bone metastasis in a subject, comprising administering to the subject a therapeutically effective amount of an antibody or antigen-binding fragment thereof, conjugate, or composition thereof provided herein.

[0207] In some embodiments, a subject is an animal. In some embodiments, a subject is a mammal. In some embodiments, a subject is a mouse. In some embodiments, a subject is a rat. In some embodiments, a subject is a non-human primate, e.g., a monkey. In some embodiments, a subject is a human.

[0208] In some embodiments, a tumor is a prostate tumor. In some embodiments, a tumor is a bone tumor. In some embodiments, a tumor is a PSMA-expressing tumor. In some embodiments, a tumor expresses one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET,

ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2.

[0209] In some embodiments, a cancer is a cancer described herein. In some embodiments, a cancer is a prostate cancer. In some embodiments, a cancer is a bone cancer. In some embodiments, a cancer is a PSMA-expressing cancer. In some embodiments, a cancer is a cancer associated with PSMA. In some embodiments, a cancer is a cancer expressing one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2. In some embodiments, a cancer is a cancer associated with one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2.

[0210] In some embodiments, a bone metastasis is a prostate cancer bone metastasis. In some embodiments, a bone metastasis is a PSMA-expressing bone metastasis. In some embodiments, a bone metastasis is a bone metastasis expressing one or more of PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2,

TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2. In some embodiments, a bone metastasis is an osteoblastic bone metastasis. In some embodiments, a bone metastasis is an osteoclastic bone metastasis.

[0211] In some embodiments, the present disclosure provides a method of treating prostate cancer comprising administering or delivering to a subject suffering therefrom a therapeutically effective amount of an immune stimulating or immune checkpoint inhibiting antibody or antigen-binding fragment thereof, e.g., a bone-targeted antibody or antigen-binding fragment thereof.

[0212] In some embodiments, an antibody or antigen-binding fragment thereof or conjugate or composition thereof provided herein may be utilized in combination with another therapy, e.g., an additional therapeutic agent. In some embodiments, another therapy comprises or is a cell therapy, e.g., a stem cell therapy. In some embodiments, another therapy comprises or is a chemotherapy. In some embodiments, another therapy comprises or is a hormone therapy. In some embodiments, another therapy comprises or is an immunotherapy. In some embodiments, another therapy comprises or is a photodynamic therapy. In some embodiments, another therapy comprises or is a radiation therapy. In some embodiments, another therapy comprises or is surgery. In some embodiments, another therapy comprises or is a transplant, e.g., a stem cell transplant. In some embodiments, another therapy comprises or is administration or delivery of an additional therapeutic agent. In some embodiments, another therapy comprises or is administration or delivery of a target agent described herein. In some embodiments, another therapy comprises or is administration or delivery of an anti-cancer agent. In some embodiments, another therapy comprises or is administration or delivery of a chemotherapeutic agent.

[0213] In some embodiments, a method of treating provided herein further comprises administering to a subject a therapeutically effective amount of one or more additional therapeutic agents. In some embodiments, one or more additional therapeutic agents comprise one or more therapeutic agents described herein. In some embodiments, one or more additional therapeutic agents comprise one or more target agents described herein. In some embodiments, one or more additional therapeutic agents comprise one or more anti-cancer agents. In some embodiments, one or more additional therapeutic agents comprises one or more chemotherapeutic agents.

Pharmaceutical Compositions, Dosing, and Administration

[0214] In some embodiments, the present disclosure provides pharmaceutical compositions comprising an antibody or antigen-binding fragment thereof (e.g., a bone-targeted antibody or antigen-binding fragment thereof) or a conjugate (e.g., a conjugate comprising a bone-targeted antibody or antigen-binding fragment thereof and a target agent) provided herein and a pharmaceutically acceptable carrier. In some embodiments, for example, for therapeutic and/or clinical purposes, antibodies or antigen-binding fragments thereof or conjugates of the present disclosure are provided as pharmaceutical compositions.

[0215] When used as therapeutics, a provided antibody or antigen-binding fragment thereof or conjugate is typically administered as a pharmaceutical composition. In some embodiments, a pharmaceutical composition is suitable for administration or delivery of a provided antibody or antigen-binding fragment thereof or conjugate to an area or portion of a body affected by a condition, disorder, or disease. In some embodiments, a pharmaceutical composition is suitable for systemic administration or delivery of a provided antibody or antigen-binding fragment thereof or conjugate to a subject. In some embodiments, a pharmaceutical composition is comprises a therapeutically effective amount of a provided antibody or antigen-binding fragment thereof or conjugate, and a pharmaceutically acceptable carrier.

[0216] In some embodiments, a pharmaceutically acceptable carrier is a buffer. In some embodiments, a pharmaceutically acceptable carrier is a buffered saline. In some embodiments, a pharmaceutical composition is a liquid composition comprising dissolved antibodies or antigen-binding fragments thereof or conjugates.

[0217] In some embodiments, a pharmaceutical composition is formulated for intravenous administration, subcutaneous administration, intramuscular administration, intra-articular administration, intraosseous administration, or intra-tumoral administration. In some embodiments, a pharmaceutical composition is formulated for intravenous administration, e.g., intravenous injection. In some embodiments, a pharmaceutical composition is a liquid, a suspension, a solution, or a dispersion.

[0218] In some embodiments, antibodies or antigen-binding fragments thereof or conjugates or compositions thereof are formulated for a variety of modes of administration, including systemic and/or localized administration. Techniques and formulations generally may be found in Remington: The Science and Practice of Pharmacy (23rd Edition, 2020).

[0219] In some embodiments, an antibody or antigen-binding fragment thereof or a conjugate or a composition thereof, e.g., a pharmaceutical composition, is provided as a solid. In some embodiments, an antibody or antigen-binding fragment thereof or a conjugate or a composition thereof, e.g., a pharmaceutical composition, is lyophilized.

[0220] Various technologies for delivering antibodies or antigen-binding fragments thereof or conjugates or compositions thereof are known in the art and can be utilized in accordance with the present disclosure. In some embodiments, an antibody or antigen-binding fragment thereof is delivered using one or more of a cell therapy, extracellular vesicle, mRNA, lipid nanoparticle (LNP), or virus-like particle (VLP). In some embodiments, an antibody or antigen-binding fragment thereof is delivered using a cell therapy. In some embodiments, an antibody or antigen-binding fragment thereof is delivered using an extracellular vesicle. In some embodiments, an antibody or antigen-binding fragment thereof is delivered using a mRNA. In some embodiments, an antibody or antigen-binding fragment thereof is delivered using a LNP. In some embodiments, an antibody or antigen-binding fragment thereof is delivered using a VLP.

[0221] Provided antibodies or antigen-binding fragments thereof and conjugates and compositions thereof are effective over a wide dose range. Those skilled in the art will be able to determine, according to known methods, the appropriate amount, dose or dosage of an antibody or antigen-binding fragment thereof or conjugate or composition thereof, to administer to a patient, taking into account factors such as age, weight, general health, the route of administration, the nature of the symptom, disease or disorder requiring treatment, and the presence of other medications. For example, various dosing regimens for antibodies, e.g., monoclonal antibodies, are disclosed in Hendrikx J et al., Oncologist. 2017 Oct;22(10): 1212-1221, the entire contents of which is hereby incorporated by reference.

[0222] In some embodiments, an antibody or antigen-binding fragment thereof or conjugate or composition thereof is administered at a fixed dose, i.e., independent of body weight. In some embodiments, a fixed dose reduces interpatient variability, e.g., efficacy and/or PK/PD parameters.

[0223] In some embodiments, an antibody or antigen-binding fragment thereof or conjugate or composition thereof is administered at a fixed dose of about of 0.1 mg to about 2000mg. In some embodiments, an antibody or antigen-binding fragment thereof or conjugate is administered at a fixed dose of about 0.1 mg, about 0.2 mg, about 0.25mg, about 0.5mg, about 1mg, about 5mg, about 10mg, about 50mg, about 100mg, about 150mg, about 200mg, about 250mg, about 300mg, about 350mg, about 400mg, about 450mg, about 500mg, about 550mg, about 600mg, about 650mg, about 700mg, about 750mg, about 800mg, about 850mg, about 900mg, about 950mg, about 1000mg, about 1500mg, or about 2000mg. In some embodiments, an antibody or antigen-binding fragment thereof or conjugate is administered intravenously (IV) or subcutaneously (SC) at a fixed dose of about 0.25 mg to about 2000mg.

[0224] In some embodiments, an antibody or antigen-binding fragment thereof or conjugate or composition thereof administered at a fixed dose is administered daily, weekly, or monthly. In some embodiments, an antibody or antigen-binding fragment thereof or conjugate or composition thereof is administered at a fixed dose is administered once a week, once every 2 weeks, once every 3 weeks or once every 4 weeks.

[0225] In some embodiments, an antibody or antigen-binding fragment thereof or conjugate or composition thereof is administered based on body weight, e.g., in a mg/kg dosing. In some embodiments, an antibody or antigen-binding fragment thereof or conjugate is administered at a dose of about 0.025 mg/kg to about 20 mg/kg. In some embodiments, an antibody or antigen-binding fragment thereof or conjugate is administered at a dose of about 0.025 mg/kg, about 0.05 mg/kg, about 0.1 mg/kg, about 0.5 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, about 20

mg/kg. In some embodiments, an antibody or antigen-binding fragment thereof or conjugate is administered intravenously (IV) or subcutaneously (SC) at a dose of about 0.025 mg/kg to about 20 mg/kg.

[0226] In some embodiments, an antibody or antigen-binding fragment thereof or conjugate or composition thereof is administered at an initial dose. In some embodiments, an initial dose may be followed by one or more subsequent doses. In some embodiments, one or more subsequent dose may be administered daily, weekly, or monthly, or at other intervals in between. In some embodiments, a dosing regimen disclosed herein may be repeated for one or more times.

EXAMPLES

[0227] Certain examples of provided technologies (antibodies or antigen-binding fragments thereof, conjugates, compositions, methods, etc.) are presented herein. Those skilled in the art appreciate that many technologies can be utilized to prepare and/or assess properties and/or activities of provided technologies in accordance with the present disclosure.

Example 1. Design of and in silico analysis of bone-targeted anti-PSMA antibodies

[0228] Three anti-PSMA antibodies (OT-401B, OT-402B, OT-403B) comprising a bone-targeting peptide, Asp^6 at both CH1 (corresponding to A165 of the heavy chain) and CT (corresponding to the C-terminus of the heavy chain) locations were designed. Corresponding comparable anti-PSMA antibodies comprising no bone-targeting moieties were also selected. Sequences of the light chain and the heavy chain for each of the three bone-targeted anti-PSMA antibodies and each of the three corresponding comparable anti-PSMA antibodies comprising no bone-targeting moieties are provided below in Table 3.

TABLE 3

Antibody	Component	Component SEQ ID NO.	Component Sequence
OT-401	Light Chain	2	DIQMTQSPSSLSTSVGDRVTLTCKASQDVGTAVDWYQ QKPGPSPKLLIYWASTRHTGIPSRFSGSGSGTDFTLTISS LQPEDFADYYCQQYNSYPLTFGPGTKVDIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC
	Heavy Chain	18	EVQLVQSGPEVKKPGATVKISCKTSGYTFTEYTIHWV KQAPGKGLEWIGNINPNNGGTTYNQKFEDKATLTVD KSTDTAYMELSSLRSEDTAVYYCAAGWNFDYWGQG TLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK

			TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG K
OT-401B	Light Chain	2	DIQMTQSPSSLSTSVGDRVTLTCKASQDVGTAVDWYQ QKPGPSPKLLIYWASTRHTGIPSRFSGSGSGTDFTLTISS LQPEDFADYYCQQYNSYPLTFGPGTKVDIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC
	Heavy Chain	19	EVQLVQSGPEVKKPGATVKISCKTSGYTFTEYTIHWV KQAPGKGLEWIGNINPNNGGTTYNQKFEDKATLTVD KSTDTAYMELSSLRSEDTAVYYCAAGWNFDYWGQG TLLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGADDDDDDGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGDDDDDD
OT-402	Light Chain	3	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQ QKPGKAPKLLIYWASTRHTGVPSRFSGSGSGTEFTLTIS SLQPEDFATYYCQQYNSYPLTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC
	Heavy Chain	43	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHW VRQAPGQRLEWMGNINPNNGGTTYNQKFEDRVTITR DTSASTAYMELSSLRSEDTAVYYCAAGWNFDYWGQG TTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
OT-402B	Light Chain	3	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQ QKPGKAPKLLIYWASTRHTGVPSRFSGSGSGTEFTLTIS SLQPEDFATYYCQQYNSYPLTFGGGTKVEIKRTVAAPS

			VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC
	Heavy Chain	24	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHW VRQAPGQRLEWMGNINPNNGGTTYNQKFEDRVTITR DTSASTAYMELSSLRSEDTAVYYCAAGWNFDYWGQG TTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGADDDDDDGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGDDDDDD
OT-403	Light Chain	4	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQ QKPGKAPKLLIYWASTRHTGVPSRFSGSGSGTEFTLTIS SLQSEDFATYYCQQYNSYPLTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC
	Heavy Chain	43	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHW VRQAPGQRLEWMGNINPNNGGTTYNQKFEDRVTITR DTSASTAYMELSSLRSEDTAVYYCAAGWNFDYWGQG TTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKT HTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCV VVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGF YPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
OT-403B	Light Chain	4	DIQLTQSPSFLSASVGDRVTITCKASQDVGTAVDWYQ QKPGKAPKLLIYWASTRHTGVPSRFSGSGSGTEFTLTIS SLQSEDFATYYCQQYNSYPLTFGGGTKVEIKRTVAAPS VFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVD NALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKH KVYACEVTHQGLSSPVTKSFNRGEC
	Heavy Chain	24	QVQLVQSGAEVKKPGASVKVSCKASGYTFTEYTIHW VRQAPGQRLEWMGNINPNNGGTTYNQKFEDRVTITR DTSASTAYMELSSLRSEDTAVYYCAAGWNFDYWGQG TTLTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKD

			YFPEPVTVSWNSGADDDDDDGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC DKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQ YNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP IEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLV KGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSL SPGDDDDDD

[0229] In silico analysis was conducted to determine structural stability of the designed bone-targeted antibodies. AlphaFold2 was employed for predicting structures of designed bone-targeted antibodies using light chain and heavy chain amino-acid sequences as inputs. Following structure prediction, a software-based 100 ns molecular dynamics simulation was conducted.

[0230] An examination of root mean square deviation (RMSD) was used to measure the distance or dissimilarity between molecular conformations, and an assessment of root mean square fluctuation (RMSF), which is the time-averaged RMSD, was used to examine fluctuation patterns of various amino-acid residues during the simulation. Certain exemplary results are displayed in Figure 1 and Figure 2. Based on the RMSD data (including that shown in Figure 1), the bone-targeted antibody appears to undergo smaller structural changes in trajectory and thus, indicating greater stability than the antibody without any bone-targeting antibodies. As can be seen in Figure 2, RMSF values exhibited low values for residues 1-100 of both the heavy and light chains of the bone-targeted antibody ("MUT" in Figure 2) as compared to the antibody without any bone-targeting moieties ("wild" in Figure 2) – indicating orientation changes in this region. Meanwhile residues 100 to the end of the heavy chain exhibits greater stability in the bone-targeted antibody as compared to the antibody without any bone-targeting moieties, particularly in the region spanning residues 159-168 (where a bone-targeting moiety comprising Asp^6 is present). Without wishing to be bound by any particular theory, potential interactions between the inserted bone-targeting moiety (Asp^6) and the surrounding environment may contribute to increased stability.

[0231] As part of the molecular dynamics simulation, hydrogen bonding was also assessed, particularly in a region (CH1) wherein a bone-targeting moiety (Asp^6) was inserted in the heavy chain, using visualization software (VMD). Hydrogen bond analysis was conducted using the last 60 ns trajectory and a cutoff value of 3.5 angstroms for hydrogen bond distance and 120 degrees for hydrogen bond angle. The top five hydrogen bonds for both the bone-targeted antibody and the comparable antibody without any bone-targeting moieties were determined. Only a single relatively stable hydrogen bond formed in the antibody without any bone-targeting moieties, between V165 and T162. In contrast, the bone-targeted antibody exhibited stable hydrogen bonds (e.g., hydrogen bonds with occupancy rates exceeding 80%)

between D161 and D164 and V168 and D165. Further, other relatively stable hydrogen bonds (with occupancy rates between 50% and 75%) were noted between D164 and D161, D160 and D164, and D165 and D162. Accordingly, and without wishing to be bound by any particular theory, an introduced bone-targeting moiety (e.g., Asp^6) can stabilize the conformation of the region that the bone-targeting moiety is inserted into through hydrogen bonding.

[0232] Additionally, as part of the molecular dynamics simulation, a Molecular Mechanics Poisson-Boltzmann Surface Area (MMPBSA) approach was utilized to examine binding free energy between the heavy chain and light chain of the bone-targeted antibody and the comparable antibody without any bone-targeting moieties. In this approach, the heavy chain was considered as the receptor and the light chain was considered as the ligand. Binding free energy values between the heavy chain and the light chain was calculated. The total free energy calculated for the bone-targeting antibody heavy chain and light chain was lower than that calculated for the comparable antibody without any bone-targeting moieties – indicating that the addition of the bone-targeting moieties (e.g., Asp^6) is favorable for binding between the heavy chain and the light chain. Accordingly, and without wishing to be bound by any particular theory, introduction of bone-targeting moieties (e.g., Asp^6) can provide increased inter-chain stability, e.g., through formation of van Der Waals interactions and solvent solvation energy, and promote favorable binding between the heavy chain and the light chain.

[0233] In some embodiments, an antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties has a similar or greater stability than a comparable antibody or antigen-binding fragment thereof without one or more bone-targeting moieties, e.g., without any bone-targeting moieties. In some embodiments, an anti-PSMA antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties has a similar or greater stability than a comparable anti-PSMA antibody or antigen-binding fragment thereof without one or more bone-targeting moieties, e.g., without any bone-targeting moieties. In some embodiments, an antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties has a similar or greater inter-chain stability than a comparable antibody or antigen-binding fragment thereof without one or more bone-targeting moieties, e.g., without any bone-targeting moieties. In some embodiments, an anti-PSMA antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties has a similar or greater inter-chain stability than a comparable anti-PSMA antibody or antigen-binding fragment thereof without one or more bone-targeting moieties, e.g., without any bone-targeting moieties.

[0234] For each antibody, an isoelectric point (pI) was mathematically determined based on the light chain and heavy chain amino-acid sequences. Shown below in Table 4 are estimated molecular weights (MW) and isoelectric points (pI) for the assessed antibodies. In some embodiments, an antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties exhibits a PI about 1 to 3 units

(e.g., about 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, or 3 units) lower than the same or comparable antibody or antigen-binding fragment thereof missing one or more bone-targeting moieties, e.g., the same or comparable antibody or antigen-binding fragment comprising no bone-targeting moieties. In some embodiments, an anti-PSMA antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties exhibits a PI about 1 to 3 units (e.g., about 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, or 3 units) lower than the same or comparable anti-PSMA antibody or antigen-binding fragment thereof missing one or more bone-targeting moieties, e.g., the same or comparable anti-PSMA antibody or antigen-binding fragment comprising no bone-targeting moieties.

TABLE 4

Antibody	Estimated MW (kDa)	pI
OT-401	144.11	8.43
OT-401B	146.27	6.04
OT-402	144.20	8.43
OT-402B	146.36	6.17
OT-403	144.19	8.43
OT-403B	146.34	6.17

Example 2. Expression and purification of bone-targeted anti-PSMA antibodies

[0235] Genes encoding the designed bone-targeted anti-PSMA antibodies (OT-401B, OT-402B, OT-403B), and their corresponding non-bone-targeted anti-PSMA antibodies (OT-401, OT-402, OT-403) were expressed in CHO (Chinese hamster ovary) cells via transient transfection. In brief, cells were proliferated in appropriate medium, under agitation conditions and at 37 degrees Celsius, and supplemented with feed medium on identical schedules across antibodies to-be-expressed. On day 7 post-transfection, cells were harvested and the supernatant portion was separated from the pellet and further analyzed.

[0236] Supernatant was tested for titer via a standard high pressure liquid chromatography (HPLC) method, using an IgG-specific standard, and antibody expression titer was determined. Supernatant was further purified via standard affinity chromatography (AC) methods, using a MAbSelect Sure (MSS) column (Cytiva), and polished using a standard preparative size exclusion chromatography (SEC) method, using a Superdex 200 column (Cytiva). The resulting flow-through protein-containing buffer was exchanged in formulation buffer (200 mM His, 150 mM NaCl, pH 5.5) for long-term storage and further analysis. Final purity was measured. After the AC step, the MSS flow-through purity was analyzed via sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) in both non-reduced and reduced conditions as known in the art. Exemplary images of the resulting SDS-PAGE gels are shown in Figure 3. As seen in Table 5 and Figure 3, the bone-targeted antibody exhibits a similar level of expression as a comparable antibody comprising no bone-targeting moieties. After each purification step, the monomer purity was assessed via analytical SEC. Certain exemplary data are shown below in Table 5.

TABLE 5			
Antibody	Titer (g/L)	Purity after AC Step (%)	Final Purity (%)
OT-401	0.97	87.31	99.84
OT-401B	0.6	87.39	99.81
OT-402	1.35	78.58	99.12
OT-402B	0.91	86.18	99.85
OT-403	1.37	89.63	100
OT-403B	1.71	91.72	99.93

[0237] In some embodiments, an antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties exhibits a similar expression level as a comparable antibody or antigen-binding fragment thereof without one or more bone-targeting moieties, e.g., without any bone-targeting moieties. In some embodiments, an anti-PSMA antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties exhibits a similar expression level as a comparable anti-PSMA antibody or antigen-binding fragment thereof without one or more bone-targeting moieties, e.g., without any bone-targeting moieties. In some embodiments, an antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties can be produced at a similar purity level as a comparable antibody or antigen-binding fragment thereof without one or more bone-targeting moieties, e.g., without any bone-targeting moieties. In some embodiments, an anti-PSMA antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties can be produced at a similar purity level as a comparable anti-PSMA antibody or antigen-binding fragment thereof without one or more bone-targeting moieties, e.g., without any bone-targeting moieties.

Example 3. Characterization of bone-targeted anti-PSMA antibodies

[0238] The bone-targeted anti-PSMA antibodies designed in Example 1 and produced in Example 2 were analyzed for monomer stability after incubation. In brief, OT-402B antibody was incubated for 5 days at room temperature and examined by size-exclusion chromatography (SEC) after the incubation period. A sample of OT-402B which was maintained at 4 degrees Celsius was also examined to provide a baseline. Resulting data from the SEC analysis demonstrated that the room temperature-incubated OT-402B antibody was stable, as the main observed peak was 99.85% of the relative area of the corresponding main observed peak from the sample maintained at 4 degrees Celsius. Furthermore, no high-molecular weight aggregates or low-molecular weight fragments were observed under either condition.

[0239] In some embodiments, an antibody or antigen-binding fragment thereof comprising one or more bone-targeting moieties has a similar or greater stability than a comparable antibody or antigen-binding fragment thereof without one or more bone-targeting moieties, e.g., without any bone-targeting moieties. In some embodiments, an anti-PSMA antibody or antigen-binding fragment thereof comprising

one or more bone-targeting moieties has a similar or greater stability than a comparable anti-PSMA antibody or antigen-binding fragment thereof without one or more bone-targeting moieties, e.g., without any bone-targeting moieties.

[0240] Without wishing to be bound by any particular theory, an antibody conjugated to a target agent and comprising a bone-targeting moiety (e.g., comprising one or more bone targeting moieties comprising one or more Asp and/or one or more Glu residues) may have a normal or similar pK as compared to the same antibody conjugated to a target agent without a bone-targeting moiety. Such features may be critical for clinical use of an antibody described herein in targeting cancer lesions located outside of bone.

[0241] The bone-targeted anti-PSMA antibodies designed in Example 1 and produced in Example 2 were further analyzed by liquid chromatography-mass spectrometry (LC-MS) via electrospray ionization (ESI) to confirm the identity of the antibodies. As known in the art, LC-MS combines liquid chromatography (LC) – to separate analytes based on differential affinity between a solid stationary phase and a liquid mobile phase – and mass spectrometry (MS) to create and detect charged ions. MS was conducted using ESI as known in the art. Both non-reduced and reduced samples of OT-402 and OT-402B were analyzed using LC-MS via ESI and resulting data analyzed. Certain exemplary results are displayed in Table 6 (non-reduced) and Table 7 (reduced) and in Figure 4, Figure 5A, and Figure 5B. Modifications in Table 6 and Table 7 are shown in standard notation as known in the art.

TABLE 6

Antibody	Modification	Theoretical Mass (Da)	Measured Mass (Da)
OT-402	pE(Q)*2,Man5*2	146637.87	146646.75
	pE(Q)*2,G0F,G0	146948.23	146950.16
	pE(Q)*2,G0F*2	147094.37	147098.01
	pE(Q)*2,G0F,G1F	147256.51	147259.07
	pE(Q)*2,G1F*2	147418.66	147422.13
	pE(Q)*2,G1F,G2F	147580.80	147583.78
OT-402B	pE(Q)*2,Man5*2	148797.32	148801.85
	pE(Q)*2,G0F,G0	149107.67	149112.78
	pE(Q)*2,G0F*2	149253.81	149257.99
	pE(Q)*2,G0F,G1F	149415.95	149420.21
	pE(Q)*2,G1F*2	149578.10	149581.84
	pE(Q)*2,G1F,G2F	149740.24	149742.44

TABLE 7

Antibody Component	Modification	Theoretical Mass (Da)	Measured Mass (Da)
OT-402 Heavy Chain	pE(Q),Man5	49921.98	49919.24
	pE(Q),G0	50004.09	50002.34
	pE(Q),G0F	50150.23	50147.61
	pE(Q),G1F	50312.37	50309.86

	pE(Q),G2F	50474.52	50471.92
OT-402 Light Chain	-	23413.08	23413.44
OT-402B Heavy Chain	pE(Q),Man5	51001.70	51001.96
	pE(Q),G0	51083.81	51083.15
	pE(Q),G0F	51229.95	51229.69
	pE(Q),G1F	51392.09	51391.79
	pE(Q),G2F	51554.24	51553.87
OT-402B Light Chain	-	23413.08	23413.66

[0242] As shown by the data in Table 6 and the spectra shown and in Figure 4, the measured mass of both OT-402 and OT-402B under non-reduced conditions are consistent with the calculated theoretical mass. Further, the data in Table 7 and the spectra shown in Figure 5A and Figure 5B indicate that the measured mass for the light chain and the heavy chain of both OT-402 and OT-402B from the reduced samples were consistent with the theoretical mass for both chains for both antibodies. These results assist in confirming the identity of the produced antibodies as well as indicating that no additional modifications occurred in the bone-targeted antibody, OT-402B despite the introduction of the bone-targeting moieties (Asp^6 at CH1 and CT sites).

Example 4. PSMA binding affinity and kinetics of bone-targeted anti-PSMA antibodies

[0243] The bone-targeted anti-PSMA antibodies designed in Example 1 and produced in Example 2 were further assessed for PSMA binding affinity and kinetics using surface plasmon resonance (SPR). In brief, a Biacore T200 (Cytiva) with a CM5 sensor chip was used to perform the SPR assay. The immobilized ligand was an anti-human Fc and the assay buffer was HBS-EP+ (10 mM HEPES pH 7.4, 10 mM NaCl, 3 mM EDTA, 0.05% Tween 20). OT-401, OT-401B, OT-402, OT-402B, OT-403, or OT-403B were all examined. The assay was performed at 25 degrees Celsius. Capture was performed for 75 seconds at 10 ul/min; association was performed for 90 seconds at 30 ul/min; dissociation was performed for 300 seconds; and regeneration was performed using 3M $MgCl_2$ for 20 seconds (x2). Resulting data was analyzed using the manufacturer's software. Certain exemplary data are shown below in Table 8 and in Figure 6A and Figure 6B.

TABLE 8

Antibody	Antigen	Ka (1/s*M)	Kd (1/s)	KD (M)	Chi2	Rmax (RU)	t ½ (s)
OT-401	PSMA	$1.12 * 10^5$	$3.88 * 10^{-4}$	$3.46 * 10^{-9}$	2.71	73.2	1790
OT-401B		$1.13 * 10^5$	$5.57 * 10^{-4}$	$4.92 * 10^{-9}$	2.46	56.9	1250
OT-402		$1.03 * 10^5$	$3.31 * 10^{-4}$	$3.22 * 10^{-9}$	2.15	75.8	2090
OT-402B		$1.10 * 10^5$	$4.20 * 10^{-4}$	$3.82 * 10^{-9}$	1.73	58.9	1650
OT-403		$1.05 * 10^5$	$3.35 * 10^{-4}$	$3.17 * 10^{-9}$	1.45	76.4	2070
OT-403B		$1.28 * 10^5$	$5.41 * 10^{-4}$	$4.23 * 10^{-9}$	3.34	60.8	1280

[0244] As can be seen in Table 8 and Figure 6A and Figure 6B, the antibodies comprising bone-targeting moieties (OT-401B, OT-402B, OT-403B) demonstrated the same or similar Ka (association constant) for PSMA as the comparable antibodies without any bone-targeting moieties (OT-401, OT-402, OT-403, respectively) – indicating the introduction of the bone-targeting moieties (Asp^6 at CH1 and CT sites) did not disrupt the ability of the antibodies to bind to the prostate cancer antigen, PSMA. Furthermore, the exemplary SPR assay data presented in Table 6 also showed that the antibodies comprising bone-targeting moieties (OT-401B, OT-402B, OT-403B) exhibited a similar Kd (dissociation constant) as the comparable antibodies comprising no bone-targeting moieties (OT-401, OT-402, OT-403, respectively) – again suggesting that the introduction of the bone-targeting moieties (Asp^6 at CH1 and CT sites) did not disrupt binding to PSMA.

[0245] Without wishing to be bound by any particular theory, the incorporation of one or more bone-targeting moieties comprising, e.g., aspartate repeats, e.g., Asp^6, may lower the pI of an antibody as compared to the same or comparable antibody without one or more bone-targeting moieties. Such lowering of the pI of an antibody may result in a bone-targeted antibody having a pI outside of, e.g., lower than, the reported optimal range for therapeutic antibodies (Goyon et al., J Chromatogr B Analyt Technol Biomed Life Sci. 2017 Oct 15:1065-1066:119-128). An antibody with a pI outside of, e.g., lower than, the optimal range may exhibit decreased antigen binding, etc. Certain anti-PSMA antibodies reportedly have a lower pI than other certain antibodies, e.g., trastuzumab. This lower starting pI of certain anti-PSMA antibodies may increase risk of disrupting normal antibody structure and functionality when incorporating one or more bone-targeting moieties, e.g., bone-targeting peptides comprising poly-aspartate, e.g., Asp^6. Other factors that may negatively affect antibody antigen binding, etc. include the presence of a patch of negative residues, e.g., aspartate repeats, e.g., Asp^6, in an antibody and/or isomerization of aspartate residues in a bone-targeting moiety, e.g., Asp^6. These combined factors may disrupt the antibody confirmation that promotes epitope-paratope binding. In some embodiments, a bone-targeted anti-PSMA antibody has a similar or greater binding affinity for PSMA as compared to an anti-PSMA antibody without one or more bone-targeting moieties, e.g., without any bone-targeting moieties. In some embodiments, provided bone-targeted antibodies can provide a similar or greater binding affinity for PSMA as compared to a comparable anti-PSMA antibody without one or more bone-targeting moieties, e.g., without any bone-targeting moieties.

Example 5. Design and production of bone-targeted anti-PSMA antibodies.

[0246] Multiple anti-PSMA antibodies comprising various bone-targeting peptides at the CT location (corresponding to the C-terminus of the heavy chain) were designed. Sequences of the light chain and the heavy chain for each of these newly designed bone-targeted anti-PSMA antibodies are provided below in

Table 9.

TABLE 9					
Antibody	Component	Component SEQ ID NO.	Antibody	Component	Component SEQ ID NO.
OT10	Light Chain	3	OT33	Light Chain	3
	Heavy Chain	99		Heavy Chain	60
OT22	Light Chain	3	OT34	Light Chain	3
	Heavy Chain	23		Heavy Chain	61
OT23	Light Chain	3	OT35	Light Chain	3
	Heavy Chain	45		Heavy Chain	62
OT24	Light Chain	3	OT36	Light Chain	3
	Heavy Chain	83		Heavy Chain	63
OT25	Light Chain	3	OT37	Light Chain	3
	Heavy Chain	52		Heavy Chain	64
OT26	Light Chain	3	OT38	Light Chain	3
	Heavy Chain	53		Heavy Chain	65
OT27	Light Chain	3	OT39	Light Chain	3
	Heavy Chain	54		Heavy Chain	66
OT28	Light Chain	3	OT40	Light Chain	3
	Heavy Chain	55		Heavy Chain	67
OT29	Light Chain	3	OT41	Light Chain	3
	Heavy Chain	56		Heavy Chain	68
OT30	Light Chain	3	OT42	Light Chain	3
	Heavy Chain	57		Heavy Chain	69
OT31	Light Chain	3	OT43	Light Chain	3
	Heavy Chain	58		Heavy Chain	94
OT32	Light Chain	3			
	Heavy Chain	59			

[0247] The antibodies described above in Table 9 were produced as described in Example 2. Certain exemplary data are shown below in Table 10, including purity as measured following SEC-HPLC.

TABLE 10					
Antibody	Titer (mg/L)	Purity (%)	Antibody	Titer (mg/L)	Purity (%)
OT10	2288.86	99.81	OT33	1908.82	100
OT22	1988.34	99.87	OT34	1943.92	99.33
OT23	1946.07	100	OT35	1768.48	100
OT24	1824.43	99.78	OT36	1651.32	100
OT25	1914.30	100	OT37	2054.67	100
OT26	2089.40	100	OT38	1882.27	99.86
OT27	1867.13	100	OT39	1835.13	99.82
OT28	1862.30	100	OT40	1875.53	100
OT29	2099.21	100	OT41	1860.92	99.38

OT30	1896.44	100
OT31	1916.33	100
OT32	1910.00	100

OT42	976.55	100
OT43	2248.33	98.55

Example 6. Hydroxyapatite (HA) binding assay of bone-targeted anti-PSMA antibodies.

[0248] To evaluate the ability for bone-targeted anti-PSMA antibodies to bind to hydroxyapatite (HA) – crystals of which bones are partially comprised of – a HA-binding assay was conducted. For each antibody, a solution of 7.5 mg HA (BioRad Cat. 12002457) in 1 ml PBS (pH 7.4) was prepared and 0.5 mg of antibody was added. The solution was incubated at 37 degrees Celsius and the supernatant following centrifugation at 3000 rpm for 3 min was assessed for OD_{280} by Nanodrop at 0 min, 5 min, 10 min, 20 min, and 30 min, and optionally at 7 days. Percent binding to HA was calculated as $[(OD_{\text{without HA}} - OD_{\text{with HA}})/(OD_{\text{without HA}})] \times 100\%$. Certain exemplary data are reported in Figure 7 and in Table 12 and Table 13.

TABLE 12

Time	OT-401	OT-401B	OT-402	OT-402B	OT-403	OT-403B
0 min	4.17%	13.89%	8.45%	9.86%	7.14%	8.33%
5 min	11.11%	28.57%	20.00%	35.62%	15.71%	38.89%
10 min	27.78%	71.43%	36.62%	64.29%	26.76%	76.06%
20 min	28.17%	88.41%	37.50%	83.10%	30.00%	93.06%
30 min	29.58%	91.30%	25.35%	92.75%	24.64%	95.77%

TABLE 13

Time	OT22	OT23	OT24	OT25	OT26	OT27
0 min	9.72%	6.76%	7.04%	8.22%	8.11%	6.67%
5 min	34.72%	17.33%	26.03%	25.00%	19.44%	25.33%
10 min	49.30%	54.05%	55.56%	43.06%	33.78%	44.00%
20 min	77.78%	82.43%	76.39%	54.05%	45.95%	47.30%
30 min	94.44%	89.19%	81.94%	54.17%	45.95%	47.95%
7 days	81.01%	77.92%	65.82%	32.05%	16.46%	59.49%
Time	OT28	OT29	OT30	OT31	OT32	OT33
0 min	8.11%	9.21%	6.85%	9.46%	8.33%	8.11%
5 min	27.03%	26.32%	22.22%	20.27%	26.39%	24.32%
10 min	31.94%	42.11%	42.47%	35.14%	38.89%	41.89%
20 min	48.61%	54.05%	52.78%	44.59%	48.61%	55.41%
30 min	50.00%	52.63%	54.17%	48.00%	52.05%	50.68%
7 days	36.84%	59.21%	44.74%	62.34%	64.56%	49.35%
Time	OT34	OT35	OT36	OT37	OT38	OT39
0 min	8.11%	8.45%	5.63%	6.85%	6.76%	8.11%
5 min	23.61%	32.39%	22.54%	27.40%	17.57%	21.62%
10 min	27.03%	57.75%	40.28%	32.88%	30.14%	39.19%
20 min	49.32%	81.69%	50.00%	63.51%	40.54%	44.59%
30 min	48.65%	89.04%	48.61%	61.64%	36.99%	38.36%
7 days	37.18%	84.42%	37.66%	63.16%	31.58%	34.18%

Time	OT40	OT41	OT42	OT43	OT-402	OT-402B
0 min	7.89%	5.56%	5.48%	6.67%	8.00%	9.59%
5 min	31.58%	36.11%	28.77%	26.67%	28.77%	30.14%
10 min	45.33%	40.28%	45.95%	37.33%	27.40%	61.64%
20 min	49.33%	77.78%	68.49%	49.33%	29.73%	82.67%
30 min	44.74%	76.71%	63.38%	47.95%	28.77%	91.89%
7 days	37.97%	63.64%	53.33%	45.45%	28.38%	84.21%

Time	OT10
0 min	0.00%
5 min	31.43%
10 min	43.48%
20 min	47.83%
30 min	47.14%
7 days	-

In the table above, "-" represents no data reported.

[0249] As shown in Table 12 and Figure 7, bone-targeted anti-PSMA antibodies (OT-401B, OT-402B, OT-403B) exhibited increased levels of binding to HA as compared to the analogous anti-PSMA antibody without a bone-targeting moiety (OT-401, OT-402, OT-403). Further, bone-targeted anti-PSMA antibodies comprising various bone-targeting moieties exhibited binding to HA as displayed in Table 13. In some embodiments, a bone-targeted anti-PSMA antibody can provide increased binding to HA as compared to the analogous anti-PSMA antibody without a bone-targeting moiety.

Example 7. FcRn binding assay of bone-targeted anti-PSMA antibodies.

[0250] Exemplary bone-targeted anti-PSMA antibodies designed in Example 1 and produced in Example 2 were assessed in a FcRn binding assay. The neonatal Fc receptor (FcRn) is reportedly expressed in endosomal compartments of a variety of cell types, including antigen-presenting cells (APCs), and binds to the Fc region of immunoglobulin G (IgG) antibodies. This binding activity of FcRn modulates the half-life of IgG antibodies in vivo.

[0251] Assessment of FcRn binding by OT-401, OT-401B, OT-402, OT-402B, OT-403, and OT-403B was conducted using a Gator biolayer interferometry (BLI) system with a streptavidin (SA) probe according to manufacturer's instructions and using human FcRn (with a His tag and Strep II tag) as the immobilized ligand (0.25 ug/ml) and the anti-PSMA antibody (300 nM) as the analyte. The assay utilized a 70 capture phase, 120s association phase, and 120s dissociation phase. Certain exemplary results are displayed in Table 14.

TABLE 14					
Antibody	K_{off} (1/s)	K_{on} (1/Ms)	KD (M)	R_{max}	Full R^2
OT-401	$3.57 * 10^{-2}$	$1.68 * 10^{6}$	$2.13 * 10^{-8}$	0.247	0.994
OT-401B	$4.64 * 10^{-2}$	$1.18 * 10^{6}$	$3.69 * 10^{-8}$	0.158	0.991
OT-402	$4.64 * 10^{-2}$	$1.34 * 10^{6}$	$3.46 * 10^{-8}$	0.169	0.989
OT-402B	$6.84 * 10^{-2}$	$1.54 * 10^{6}$	$4.46 * 10^{-8}$	0.141	0.981
OT-403	$4.11 * 10^{-2}$	$1.32 * 10^{6}$	$3.11 * 10^{-8}$	0.149	0.974
OT-403B	$4.82 * 10^{-2}$	$1.53 * 10^{6}$	$3.16 * 10^{-8}$	0.152	0.975

[0252] As shown in Table 14, the antibodies comprising bone-targeting moieties (OT-401B, OT-402B, OT-403B) demonstrated similar binding kinetics to FcRn as the comparable antibodies without any bone-targeting moieties (OT-401, OT-402, OT-403, respectively) – indicating the introduction of the bone-targeting moieties (e.g., Asp^6 at CH1 and CT sites) did not alter binding to FcRn.

Example 8. FcgR binding assay of bone-targeted anti-PSMA antibodies.

[0253] Exemplary bone-targeted anti-PSMA antibodies designed in Example 1 and produced in Example 2 were assessed in a FcgR binding assay. FcgRs are reportedly Fc receptors for IgG that are expressed by a variety of cells of hematopoietic origin and contribute to various immune system functions and bind the Fc region of antibodies. The binding of antibodies by FcgRs mediate effector functions such as antibody-dependent cellular cytotoxicity (ADCC).

[0254] Assessment of FcgR binding by OT-401, OT-401B, OT-402, OT-402B, OT-403, and OT-403B was conducted using a Biacore T200 surface plasmon resonance (SPR) system with a CM5 sensor chip according to manufacturer's instructions and using an immobilized anti-His antibody on the CM5 sensor chip, His-tagged human FcgRIIIa (176V), and the anti-PSMA antibody as the analyte. The assay utilized a 50s, 10 ul/min capture phase; 90s, 30 ul/min association phase; a 450s dissociation phase, and a 2 x 20s regeneration phase with 3M $MgCl_2$. Certain exemplary results are displayed in Table 15.

TABLE 15						
Antibody	Ka (1/s*M)	Kd (1/s)	KD (M)	Chi^2	R_{max} (RU)	t ½ (s)
OT-401	$7.74 * 10^{4}$	$1.29 * 10^{-2}$	$1.67 * 10^{-7}$	4.44	86.5	53.7
OT-401B	$7.22 * 10^{4}$	$1.41 * 10^{-2}$	$1.96 * 10^{-7}$	3.44	67.7	49.0
OT-402	$1.03 * 10^{5}$	$1.23 * 10^{-2}$	$1.19 * 10^{-7}$	7.22	96.5	56.4
OT-402B	$1.12 * 10^{5}$	$1.56 * 10^{-2}$	$1.40 * 10^{-7}$	4.90	101.1	44.4
OT-403	$8.11 * 10^{4}$	$1.23 * 10^{-2}$	$1.52 * 10^{-7}$	4.25	76.6	56.4
OT-403B	$7.10 * 10^{4}$	$1.32 * 10^{-2}$	$1.86 * 10^{-7}$	3.95	80.0	52.4

[0255] As shown in Table 15, the antibodies comprising bone-targeting moieties (OT-401B, OT-402B, OT-403B) demonstrated similar binding kinetics to FcgRIIIa (176V) as the comparable antibodies without any bone-targeting moieties (OT-401, OT-402, OT-403, respectively) – indicating the introduction

of the bone-targeting moieties (e.g., Asp^6 at CH1 and CT sites) did not alter binding to FcgRIIIa (176V).

Example 9. Assessment of serum stability of bone-targeted anti-PSMA antibodies.

[0256] Exemplary bone-targeted anti-PSMA antibodies designed in Example 1 and produced in Example 2 were assessed for stability in mouse serum. In brief, anti-PSMA antibody (OT-401, OT-401B, OT-402, OT-402B, OT-403, OT-403B) was diluted to 0.1 mg/ml in mouse serum in a 96 well plate and incubated at 37 degrees Celsius for 0, 48, or 96 hours. Following incubation, protein samples were reduced and analyzed using liquid chromatography-mass spectrometry (LC-MS) for reduced intact mass. The measured intensity at 0 hours was set as the 100% level and percentage relative intensity change calculated by dividing the intensity at 48 hours or 96 hours by the intensity at 0 hours. Certain exemplary data are displayed in Table 16.

TABLE 16

Antibody	Component	Relative Intensity Change			Cleavage Detected
		0 hours	48 hours	96 hours	
OT-401	Heavy chain	100%	87%	33%	No
	Light chain	100%	87%	26%	No
OT-401B	Heavy chain	100%	93%	81%	No
	Light chain	100%	95%	81%	No
OT-402	Heavy chain	100%	88%	46%	No
	Light chain	100%	89%	41%	No
OT-402B	Heavy chain	100%	105%	105%	No
	Light chain	100%	104%	106%	No
OT-403	Heavy chain	100%	84%	93%	No
	Light chain	100%	83%	95%	No
OT-403B	Heavy chain	100%	96%	101%	No
	Light chain	100%	98%	99%	No

[0257] As shown in Table 16, the antibodies comprising bone-targeting moieties (OT-401B, OT-402B, OT-403B) demonstrated increased or similar serum stability as the comparable antibodies without any bone-targeting moieties (OT-401, OT-402, OT-403, respectively) – indicating the introduction of the bone-targeting moieties (e.g., Asp^6 at CH1 and CT sites) did not alter serum stability.

Example 10. Assessment of thermal stability of bone-targeted anti-PSMA antibodies.

[0258] Exemplary bone-targeted anti-PSMA antibodies designed in Example 1 and produced in Example 2 were assessed for thermal stability using a differential scanning fluorimetry (DSF) assay. In brief, anti-PSMA antibody (OT-401, OT-401B, OT-402, OT-402B, OT-403, OT-403B) was diluted to 0.1 mg/ml in PBS (pH 7.5) and 5x SYPRO Orange protein gel stain was added from a 5000x SYPRO Orange DMSO stock. Solutions were heated, relative fluorescence was measured, and melting temperatures were recorded. Certain exemplary data are displayed in Table 17.

TABLE 17		
Antibody	Tm1 (°C)	Tm2 (°C)
OT-401	68.50	-
OT-401B	67.00	-
OT-402	69.25	82.25
OT-402B	69.50	80.00
OT-403	69.25	82.00
OT-403B	69.50	79.50

In the table above, "-" indicates no second melting temperature was observed.

[0259] As shown in Table 17, the antibodies comprising bone-targeting moieties (OT-401B, OT-402B, OT-403B) demonstrated similar thermal stability as the comparable antibodies without any bone-targeting moieties (OT-401, OT-402, OT-403, respectively) – indicating the introduction of the bone-targeting moieties (e.g., Asp^6 at CH1 and CT sites) did not alter thermal stability.

Example 11. Assessment of off-target binding of bone-targeted anti-PSMA antibodies.

[0260] Exemplary bone-targeted anti-PSMA antibodies designed in Example 1 and produced in Example 2 were assessed for off-target binding using a baculovirus-based assay and a DNA-based assay. The baculovirus-based assay used an ELISA wherein baculovirus was coated onto plates at a concentration of 1%. Following coating, the plates were blocked with 0.5% BSA in PBS (pH 7.5). Samples of anti-PSMA antibodies (OT-401, OT-401B, OT-402, OT-402B, OT-403, OT-403B), negative control (panitumumab), or positive control (vesencumab) were added at various concentrations (250, 50, 10, 2, and 0.4 ug/ml) and incubated. Afterwards, secondary antibody (anti-human Fc HRP) was added. Addition of 3,3',5,5'-tetramethylbenzidine (TMB) substrate was used for indirect detection and quantification of binding by measurement of absorbance (OD450 - OD620). Plates were washed between steps and two replicates were conducted.

[0261] Certain exemplary data are shown in Table 18 and Figure 8A. Normalization factor was calculated as 1 / (blank sample OD450 - OD620). Normalized baculovirus score was calculated as (OD450 - OD620 for 250 ug/ml sample) * normalization factor.

TABLE 18			
Antibody	Normalization Factor	Normalized Baculovirus Score	Relative to Positive Control
OT-401	43.29	4.52	26.71
OT-401B	43.29	15.15	89.42
OT-402	45.56	8.92	52.65
OT-402B	52.49	17.09	100.90
OT-403	46.40	2.76	16.29
OT-403B	45.56	5.00	29.54
Negative control	36.63	2.41	14.25
Positive control	43.20	16.94	100.00

[0262] The DNA-based assay also used an ELISA wherein DNA was coated onto the plates at a concentration of 10 ug/ml. Following coating, the plates were blocked with 0.5% BSA in PBS (pH 7.5). Samples of anti-PSMA antibodies (OT-401, OT-401B, OT-402, OT-402B, OT-403, OT-403B), negative control (panitumumab), or positive control (vesencumab) were added at various concentrations (250, 50, 10, 2, and 0.4 ug/ml) and incubated. Afterwards, secondary antibody (anti-human Fc HRP) was added. Addition of 3,3',5,5'-tetramethylbenzidine (TMB) substrate was used for indirect detection and quantification of binding by measurement of absorbance (OD450 - OD620). Plates were washed between steps and two replicates were conducted.

[0263] Certain exemplary data are shown in Table 19 and Figure 8B. Normalization factor was calculated as 1 / (blank sample OD450 - OD620). Normalized baculovirus score was calculated as (OD450 - OD620 for 250 ug/ml sample) * normalization factor.

TABLE 19

Antibody	Normalization Factor	Normalized DNA Score	Relative to Positive Control
OT-401	67.11	15.34	45.08
OT-401B	66.67	27.30	80.23
OT-402	63.09	33.13	97.36
OT-402B	68.26	18.73	55.04
OT-403	65.15	4.28	12.58
OT-403B	64.52	1.57	4.62
Negative control	63.69	1.45	4.27
Positive control	65.15	34.03	100.00

[0264] Without wishing to be bound by theory, exemplary bone-targeted anti-PSMA antibodies may have a wide range of off-target binding. Exemplary bone-targeted anti-PSMA antibodies may have comparable off-target binding relative to the corresponding anti-PSMA antibody (e.g. non bone-targeted anti-PSMA antibody). Exemplary bone-targeted anti-PSMA antibodies may have increased off-target binding relative to the corresponding anti-PSMA antibody (e.g. non bone-targeted anti-PSMA antibody).

Example 12. Pharmacokinetics of bone-targeted anti-PSMA antibodies.

[0265] Exemplary bone-targeted anti-PSMA antibodies designed in Example 1 and produced in Example 2 were assessed in a single-dose pharmacokinetic (PK) study in mice. In brief, 6-8 weeks old male CB17 SCID mice (n=5 per treatment group) were intravenously administered a single dose of 1 mg/kg of certain exemplary antibodies from Example 1 in a volume of 10 ml/kg or a single dose of vehicle (PBS) as a control. Serum was collected on days 1, 3, 5, 7, 10, 14, and 21. Necropsies were conducted at study end-point (day 21) and tissues collected.

[0266] To quantify the concentration (ng/ml) of total antibody present in the collected mouse serum samples, an ELISA using goat anti-human IgG antibodies (Southern Biotech Cat. No. 2049-01; Novus

Biologicals, Cat. No. NBP1-74955) was implemented. A standard curve was produced by diluting antibody directly into naïve pooled mouse serum. Certain exemplary data are shown in Table 20 and Table 21.

TABLE 20

Day	Antibody W (ng/ml)		Bone-Targeted Antibody W (ng/ml)		Antibody X (ng/ml)		Bone-Targeted Antibody X (ng/ml)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	18640	1098	7982	296	10892	727	10640	216
3	16180	523	4454	177	8120	454	6072	185
5	12380	592	3056	228	6412	313	3312	124
7	10382	507	1866	198	5064	338	2044	147
10	9104	428	1132	148	3462	231	1134	67
14	7574	519	590	75	2134	164	516	51
21	4200	216	220	29	965	108	133	11

TABLE 21

	Antibody W	Bone-Targeted Antibody W	Antibody X	Bone-Targeted Antibody X
t ½ (h)	243	108	141.3	84
t ½ (d)	10.1	4.5	5.9	3.5

[0267] As depicted in Table 20 and Table 21, the antibodies comprising a Asp^6 bone-targeting moiety inserted at the CH1 and CT locations demonstrated shorter half-lives versus the comparable antibodies without any bone-targeting moieties.

[0268] Serum samples from days 14 and 21 were analyzed for a complete blood count (white blood cells, red blood cells, platelets, neutrophils, lymphocytes, monocytes, eosinophils). Certain exemplary results are shown in Figures 9A-9F for day 14 and in Figures 10A-10F for day 21. As displayed in the figures, mice administered a bone-targeted anti-PSMA antibody (BT Antibody X, BT Antibody W) exhibited similar complete blood count as mice administered the comparable anti-PSMA antibody without a bone-targeting moiety (Antibody X, Antibody W).

[0269] Serum samples from day 21 were also analyzed for levels of certain liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP)) and calcium levels. Certain exemplary results are shown in Figures 11A and 11B. As displayed in the figures, mice administered a bone-targeted anti-PSMA antibody (BT Antibody X, BT Antibody W) exhibited similar levels of liver enzymes and calcium as mice administered the comparable anti-PSMA antibody without a bone-targeting moiety (Antibody X, Antibody W).

Example 13. Pharmacokinetics of bone-targeted anti-PSMA antibodies.

[0270] Exemplary bone-targeted anti-PSMA antibodies designed in Example 1 and produced in Example 2 were assessed in a single-dose pharmacokinetic (PK) study in mice. In brief, 6-8 weeks old

male CB17 SCID mice (n=5 per treatment group) were intravenously administered a single dose of 1 mg/kg of certain exemplary antibodies from Example 1 in a volume of 10 ml/kg or a single dose of vehicle (PBS) as a control. Additionally, 7 month old male CB17 SCID mice (n=5 per treatment group) were intravenously administered a single dose of 1 mg/kg of certain exemplary antibodies from Example 1 in a volume of 10 ml/kg or a single dose of vehicle (PBS) as a control. Serum was collected on days 1, 3, 7, 14, and 21.

[0271] To quantify the concentration (ng/ml) of total antibody present in the collected mouse serum samples, an ELISA using goat anti-human IgG antibodies (Southern Biotech Cat. No. 2049-01; Novus Biologicals, Cat. No. NBP1-74955) was implemented. A standard curve was produced by diluting antibody directly into naïve pooled mouse serum. Certain exemplary data are shown for mice of age 6-8 weeks in Table 22 and Table 23 and for mice of age 7 months in Table 24 and Table 25 below.

TABLE 22

Day	Antibody Y (ng/ml)		Bone-Targeted Antibody Y (ng/ml)		Antibody Z (ng/ml)		Bone-Targeted Antibody Z (ng/ml)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	6070	519	5050	207	6060	371	3450	275
3	4810	301	3853	249	5547	279	2253	123
7	5040	568	2027	202	4123	575	656	18
14	3180	258	724	77	2637	106	194	11
21	2293	220	362	23	2057	141	67	0.3

TABLE 23

	Antibody Y	Bone-Targeted Antibody Y	Antibody Z	Bone-Targeted Antibody Z
t ½ (h)	302	129	350	102
t ½ (d)	12.6	5.4	14.6	4.3

TABLE 24

Day	Antibody Y (ng/ml)		Bone-Targeted Antibody Y (ng/ml)	
	Mean	SEM	Mean	SEM
1	5847	219	4243	371
3	4713	139	2950	197
7	3493	211	1617	95
14	2067	203	834	88
21	1613	139	509	81

TABLE 25

	Antibody Y	Bone-Targeted Antibody Y
t ½ (h)	265	201
t ½ (d)	11	8.4

[0272] As depicted in Tables 22-25, the antibodies comprising a Asp^6 bone-targeting moiety inserted at the CH1 and CT locations demonstrated shorter half-lives versus the comparable antibodies without any bone-targeting moieties.

Example 14. Pharmacokinetics of bone-targeted anti-PSMA antibodies.

[0273] Exemplary bone-targeted anti-PSMA antibodies designed and produced in Example 5 were also assessed in a single-dose pharmacokinetic (PK) study in mice described in Example 12. In brief, 6-8 weeks old male CB17 SCID mice (n=5 per treatment group) were intravenously administered a single dose of 1 mg/kg of certain exemplary antibodies from Example 5 in a volume of 10 ml/kg or a single dose of vehicle (PBS) as a control. Serum was collected on days 1, 3, 7, 14, and 21.

[0274] To quantify the concentration (ng/ml) of total antibody present in the collected mouse serum samples, an ELISA using goat anti-human IgG antibodies (Southern Biotech Cat. No. 2049-01; Novus Biologicals, Cat. No. NBP1-74955) was implemented. A standard curve was produced by diluting antibody directly into naïve pooled mouse serum. Certain exemplary data are shown in Table 26 and Table 27.

TABLE 26

Day	Antibody A (ng/ml)		Antibody B (ng/ml)		Antibody C (ng/ml)		Antibody D (ng/ml)	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
1	6397	107	5270	194	3707	90	3990	178
3	5587	102	4477	207	1477	131	3240	17
7	4727	390	3880	206	159	11	2473	44
14	3183	41	2453	197	35	1.8	1760	106
21	2537	38	1890	229	22	1.1	1227	88

Day	Antibody E (ng/ml)		Antibody F (ng/ml)	
	Mean	SEM	Mean	SEM
1	4973	88	4937	269
3	3907	281	3903	44
7	1873	82	3017	79
14	643	52	2173	50
21	329	34	1317	96

TABLE 27

	Antibody A	Antibody B	Antibody C	Antibody D
t ½ (h)	397	322	85.2	332
t ½ (d)	16.5	13.4	3.6	13.8

	Antibody E	Antibody F
t ½ (h)	119	282
t ½ (d)	5	11.8

[0275] Without wishing to be bound by theory, exemplary bone-targeted anti-PSMA antibodies may have a wide range of half-lives in vivo. As depicted in Tables 20-27, exemplary bone-targeted anti-PSMA antibodies may have shorter half-lives versus comparable antibodies without any bone-targeting moieties, exemplary bone-targeted anti-PSMA antibodies may have comparable half-lives versus the comparable antibodies without any bone-targeting moieties, or exemplary bone-targeted anti-PSMA antibodies may have longer half-lives versus the comparable antibodies without any bone-targeting moieties.

EQUIVALENTS

[0276] While various embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the functions and/or obtaining the results and/or one or more of the advantages described in the present disclosure, and each of such variations and/or modifications is deemed to be included. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be example and that the actual parameters, dimensions, materials, and/or configurations may depend upon the specific application or applications for which the teachings of the present disclosure is/are used. Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the embodiments of the present disclosure. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, claimed technologies may be practiced otherwise than as specifically described and claimed. In addition, any combination of two or more features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the scope of the present disclosure.

CLAIMS

1. An antibody or antigen-binding fragment thereof, wherein:

the antibody or antigen-binding fragment thereof binds to a prostate cancer-associated antigen, and

the antibody or antigen-binding fragment thereof comprises a bone-targeting moiety.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein the prostate cancer-associated antigen comprises or is PSMA, AKT, AXL, androgen receptor, B7-H3, CCL20, CCR5, CCR6, CD24, CD44, CD46, CD63, CD73, CD99, CD133, CD155, CD166, CDCP1, CDH1, CEACAM5, CHRNB2, CLDN3, CLDN4, CTLA-4, DLL-3, EGFR, Epcam, EphA2, EZH1, EZH2, FAP, FGFR1, FZD7, GPC3, GRPR, GSPT1, HER3, IGF-1R, IL-30, integrin alpha V, integrin alpha 5, integrin alpha 6, integrin alpha 9, integrin alpha II, integrin beta 2, integrin beta 7, ITGA3, KLK2, LAMP1, LGR5, LGALS3BP, LRP6, MCAM, MUC1, Myc, Nectin-4, Notch1, PARP, PD-1, PDL1, PROM1, PSCA, PTEN, PTPRZ1, RET, ROR1, SCARB1, SEZ6, SEZ6L, Siglec-7, Siglec-9, Siglec-15, SLC1A5, SLC39A6, SLC45A3, SLC7A5, SSTR2, STEAP1, STEAP2, TACSTD2, TGFb, TIM-3, TMEFF2, TMPRSS2, TNFRSF10B, TNFRSF21, TNFSF10, or TROP2.

3. The antibody or antigen-binding fragment thereof of claim 2, wherein the prostate cancer-associated antigen comprises or is PSMA.

4. The antibody or antigen-binding fragment thereof of any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises or is a monoclonal antibody or antigen-binding fragment thereof.

5. The antibody or antigen-binding fragment thereof of any one of the preceding claims, wherein the bone-targeting moiety comprises or is a bone-targeting peptide, optionally wherein the bone-targeting moiety is a negatively charged peptide and/or comprises one or more carboxylic peptides.

6. The antibody or antigen-binding fragment thereof of claim 5, wherein the bone-targeting peptide comprises or is Asp^3, Asp^4, Asp^5, Asp^6, Asp^7, Asp^8, Asp^9, Asp^{10}, Asp^{11}, Asp^{12}, Asp^{13}, Asp^{14}, or Asp^{15}.

7. The antibody or antigen-binding fragment thereof of claim 6, wherein the bone-targeting peptide comprises or is Asp^6.

8. The antibody or antigen-binding fragment thereof of claim 5, wherein the bone-targeting peptide comprises or is Glu^3, Glu^4, Glu^5, Glu^6, Glu^7, Glu^8, Glu^9, Glu^{10}, Glu^{11}, Glu^{12}, Glu^{13}, Glu^{14}, or Glu^{15}.

9. The antibody or antigen-binding fragment thereof of claim 5, wherein the bone-targeting peptide comprises or is $(Asp\text{-}Ser\text{-}Ser)_1$, $(Asp\text{-}Ser\text{-}Ser)_2$, $(Asp\text{-}Ser\text{-}Ser)_3$, $(Asp\text{-}Ser\text{-}Ser)_4$, $(Asp\text{-}Ser\text{-}Ser)_5$, $(Asp\text{-}Ser\text{-}Ser)_6$, $(Asp\text{-}Ser\text{-}Ser)_7$, $(Asp\text{-}Ser\text{-}Ser)_8$, $(Asp\text{-}Ser\text{-}Ser)_9$, or $(Asp\text{-}Ser\text{-}Ser)_{10}$.

10. The antibody or antigen-binding fragment thereof of claim 5, wherein the bone-targeting peptide

comprises or is KNFQSRSH, KRRTPVRE, KTYASMQW, VTKHLNQISQSY, IVQSKHTLSNQY, DHMDDMDDEDDDDHVDSQDSIDSNDSDDVDDTDDSH, SVSVGMKPSPRP, NNHYLPR, QPYHPTIPQSVH, CQYPTLKSC, HAPVQPQ, TMGFTAPRFPHY, PGEKADRAEKADRA, PGEKSHSASDRTA, PGYINLSYEKSHSQAINTDRTA, TMRNPITSLISV, LLADTTHRPWT, TVFLDHENANKILNQPKSYNSGKLAEPRREVAELEPRREVAEL, AEPRREVAELEPRREVAEL, AAFVSKQEGSEVVKQPRSYLYQWLGAPVPYPDPLAEPRREVAELEPRREVAELNPDCDELADHI GFQEAYRRFYGPV, KEIPPIPLLAPS, NNVSQKWQQRLI, NSMIAHNKTRMH, GIHVPWMPPVAF, QRSWTLDSALSM, SGHQLLLNKMPN, SSTLKTFFGFPD, DSSNPIFWRPSS, NYSHLRVKLPTP, ATWSHHLSSAGL, SYSQMDPPRSLP, TMRNPITSLISVGGGS, LLADTTHHRPWTGGGS, KEIPPIPLLAPSGGGS, NNVSQKWQQRLIGGGS, NSMIAHNKTRMHGGGS, GIHVPWMPPVAFGGGS, QRSWTLDSALSMGGGS, SGHQLLLNKMPNGGGS, SSTLKTFFGFPDGGGS, DSSNPIFWRPSSGGGS, NYSHLRVKLPTPGGGS, ATWSHHLSSAGLGGGS, or SYSQMDPPRSLPGGGS.

11. The antibody or antigen-binding fragment thereof of any one of claims 5-10, wherein the bone-targeting peptide is attached to a N-terminus or C-terminus of a light chain or a heavy chain of the antibody or antigen-binding fragment thereof.

12. The antibody or antigen-binding fragment thereof of any one of claims 5-10, wherein the bone-targeting peptide is inserted at an internal permissive site of the antibody or antigen-binding fragment thereof.

13. The antibody or antigen-binding fragment thereof of claim 12, wherein the internal permissive site is an internal permissive site of a light chain or an internal permissive site of a heavy chain.

14. The antibody or antigen-binding fragment thereof of claim 12, wherein the internal permissive site of the light chain is or corresponds to A153, optionally wherein the bone-targeting peptide is inserted following A153.

15. The antibody or antigen-binding fragment thereof of claim 12, wherein the internal permissive site of the heavy chain is or corresponds to G118, P123, A165, P243, D283, N344, or G361, optionally wherein the bone-targeting peptide is inserted following G118, P123, A165, P243, D283, N344, or G361.

16. The antibody or antigen-binding fragment thereof of claim 15, wherein the internal permissive site of the heavy chain is or corresponds to A165, optionally wherein the bone-targeting peptide is inserted following A165.

17. The antibody or antigen-binding fragment thereof of claim 12, wherein the internal permissive site is an internal permissive site in a loop region of a light chain or an internal permissive site in a loop region of a heavy chain.

18. The antibody or antigen-binding fragment thereof of claim 12, wherein the internal permissive

site is an internal permissive site that is an externally facing site of a light chain or an internal permissive site that is an externally facing site of a heavy chain.

19. The antibody or antigen-binding fragment thereof of claim 17 or 18, wherein the internal permissive site is an internal permissive site that is an externally facing site in a loop region of a light chain or an internal permissive site that is an externally facing site in a loop region of a heavy chain.

20. The antibody or antigen-binding fragment thereof of any one of claims 12-19, wherein 1 to (n + 15) amino-acid residues are deleted from the antibody or antigen-binding fragment thereof following the insertion of the bone-targeting peptide, wherein n is the number of amino-acid residues in the bone-targeting peptide.

21. The antibody or antigen-binding fragment thereof of any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises a second bone-targeting moiety.

22. The antibody or antigen-binding fragment thereof of claim 21, wherein the second bone-targeting moiety comprises or is a second bone-targeting peptide, optionally wherein the second bone-targeting moiety is a negatively charged peptide and/or comprises one or more carboxylic peptides.

23. The antibody or antigen-binding fragment thereof of claim 22, wherein the second bone-targeting peptide comprises or is Asp^{3}, Asp^{4}, Asp^{5}, Asp^{6}, Asp^{7}, Asp^{8}, Asp^{9}, Asp^{10}, Asp^{11}, Asp^{12}, Asp^{13}, Asp^{14}, or Asp^{15}.

24. The antibody or antigen-binding fragment thereof of claim 23, wherein the second bone-targeting peptide comprises or is Asp^{6}.

25. The antibody or antigen-binding fragment thereof of claim 22, wherein the second bone-targeting peptide comprises or is Glu^{3}, Glu^{4}, Glu^{5}, Glu^{6}, Glu^{7}, Glu^{8}, Glu^{9}, Glu^{10}, Glu^{11}, Glu^{12}, Glu^{13}, Glu^{14}, or Glu^{15}.

26. The antibody or antigen-binding fragment thereof of any one of claims 21-25, wherein the second bone-targeting peptide is attached to a N-terminus or C-terminus of a light chain or a heavy chain of the antibody or antigen-binding fragment thereof.

27. The antibody or antigen-binding fragment thereof of any one of claims 21-25, wherein the second bone-targeting peptide is inserted at an internal permissive site of the antibody or antigen-binding fragment thereof.

28. The antibody or antigen-binding fragment thereof of claim 27, wherein the internal permissive site is an internal permissive site of a light chain or an internal permissive site of a heavy chain.

29. The antibody or antigen-binding fragment thereof of claim 28, wherein the internal permissive site of the light chain is or corresponds to A153, wherein the bone-targeting peptide is inserted following A153.

30. The antibody or antigen-binding fragment thereof of claim 28, wherein the internal permissive site of the heavy chain is or corresponds to G118, P123, A165, P243, D283, N344, or G361, optionally

wherein the bone-targeting peptide is inserted following G118, P123, A165, P243, D283, N344, or G361.

31. The antibody or antigen-binding fragment thereof of claim 28, wherein the internal permissive site is an internal permissive site in a loop region of a light chain or an internal permissive site in a loop region of a heavy chain.

32. The antibody or antigen-binding fragment thereof of claim 28, wherein the internal permissive site is an internal permissive site that is an externally facing site of a light chain or an internal permissive site that is an externally facing site of a heavy chain.

33. The antibody or antigen-binding fragment thereof of claim 31 or 32, wherein the internal permissive site is an internal permissive site that is an externally facing site in a loop region of a light chain or an internal permissive site that is an externally facing site in a loop region of a heavy chain.

34. The antibody or antigen-binding fragment thereof of any one of claims 27-33, wherein 1 to (n + 15) amino-acid residues are deleted from the antibody or antigen-binding fragment thereof following the insertion of the second bone-targeting peptide, wherein n is the number of amino-acid residues in the second bone-targeting peptide.

35. The antibody or antigen-binding fragment thereof of any one of claims 21-34, wherein the antibody or antigen-binding fragment thereof comprises one or more additional bone-targeting moieties, optionally wherein the one or more additional bone-targeting moieties comprise 3, 4, or 5 inserted bone-targeting moieties.

36. The antibody or antigen-binding fragment thereof of any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises a light chain comprising a sequence selected from Table 1.

37. The antibody or antigen-binding fragment thereof of any one of claims 1-35, wherein the antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 2.

38. The antibody or antigen-binding fragment thereof of any one of claims 1-35, wherein the antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 3.

39. The antibody or antigen-binding fragment thereof of any one of claims 1-35, wherein the antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 4.

40. The antibody or antigen-binding fragment thereof of any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising a sequence selected from Table 2.

41. The antibody or antigen-binding fragment thereof of any one of claims 1-39, wherein the

antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence of SEQ ID NO: 19.

42. The antibody or antigen-binding fragment thereof of any one of claims 1-39, wherein the antibody or antigen-binding fragment thereof comprises a heavy chain comprising an amino-acid sequence of SEQ ID NO: 24.

43. The antibody or antigen-binding fragment thereof of any one of claims 1-35, wherein the antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 2 and a heavy chain comprising an amino-acid sequence of SEQ ID NO: 19.

44. The antibody or antigen-binding fragment thereof of any one of claims 1-35, wherein the antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 3 and a heavy chain comprising an amino-acid sequence of SEQ ID NO: 24.

45. The antibody or antigen-binding fragment thereof of any one of claims 1-35, wherein the antibody or antigen-binding fragment thereof comprises a light chain comprising an amino-acid sequence of SEQ ID NO: 4 and a heavy chain comprising an amino-acid sequence of SEQ ID NO: 24.

46. The antibody or antigen-binding fragment thereof of any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof is associated with a target agent.

47. The antibody or antigen-binding fragment thereof of claim 46, wherein the antibody or antigen-binding fragment thereof is conjugated to the target agent.

48. The antibody or antigen-binding fragment thereof of claim 46 or 47, wherein the target agent comprises an anti-cancer agent, an alkylating agent, an antitumor antibiotic, an antimetabolite, an antimitotic agent, a cytotoxic agent, a hormone, a nitrosourea, a plant alkaloid, a taxane, a radioligand, a chemotherapeutic agent, or any combination thereof.

49. The antibody or antigen-binding fragment thereof of claim 48, wherein the radioligand comprises an alpha emitter or a beta emitter.

50. The antibody or antigen-binding fragment thereof of claim 48, wherein the radioligand comprises actinium, lutetium, indium, radium, Pb-212, Cu-67, astatine, or thorium.

51. The antibody or antigen-binding fragment thereof of claim 48, wherein the target agent comprises calicheamicin, deruxtecan, govitecan SN-38, monomethyl auristatin E (MMAE), monomethyl auristatin F (MMAF), maytansinoid, SG3199, duocarmycin, exatecan, tubulysin, PNU-159682, TOP2 inhibitor, TLR agonist, STING agonist, amanitin, eribulin, MMAU, hemiasterlin, or any combination or derivative thereof.

52. The antibody or antigen-binding fragment thereof of claim 48, wherein the target agent comprises an androgen receptor degrader, integrin inhibitor, EZH2, adenosine receptor inhibitors (CD73), WNT pathway inhibitor, AKT inhibitor, steroidogenesis inhibitor (e.g., ODM-208), PARP inhibitor, immune

activator (e.g., TLR3 agonist), BET inhibitor, pyrrolobenzodiazepine (PBD), MYC pathway inhibitor, RAS pathway inhibitor, PI3K inhibitor, NRG1 inhibitor, SMARCA2 degrader, SMARCA2 inhibitor, SMARCA4 degrader, SMARCA4 inhibitor, farnesyl pyrophosphate synthase inhibitor, mTOR inhibitor, CDK4 inhibitor, CDK6 inhibitor, VEGFR2 inhibitor, MET inhibitor, tyrosine kinase inhibitor, histone deacetylase inhibitor, Janus kinase inhibitor, BCL-2 inhibitor, KRAS inhibitor, ALK5 inhibitor, pseudomonas exotoxin A (PEA), diphtheria toxin, or any combination thereof.

53. The antibody or antigen-binding fragment thereof of any one of the preceding claims, wherein the antibody or antigen-binding fragment thereof comprises one or more bone targeting moieties comprising a combination of one or more Asp residues and one or more Glu residues.

54. A method of delivering a target agent to a cancer cell in a system, comprising administering or delivering to the system an effective amount of the antibody or antigen-binding fragment thereof of any one of claims 46-53.

55. A method of killing a cancer cell in a system, comprising administering or delivering to the system an effective amount of the antibody or antigen-binding fragment thereof of any one of claims 1-53.

56. The method of claim 54 or 55, wherein the system comprises or is a population of cells.

57. The method of claim 54 or 55, wherein the system comprises or is an animal.

58. The method of claim 54 or 55, wherein the system comprises or is a human.

59. A method of treating a condition, disorder, or disease, comprising administering or delivering to a subject suffering therefrom a therapeutically effective amount of the antibody or antigen-binding fragment thereof of any one of claims 1-53.

60. The method of claim 59, wherein the condition, disorder, or disease comprises or is a cancer.

61. The method of claim 60, wherein the cancer comprises or is prostate cancer.

62. The method of any one of claims 59-61, wherein the condition, disorder, or disease comprises or is a bone metastasis.

63. The method of claim 59, wherein the condition, disorder, or disease comprises or is a tumor.

64. The method of claim 63, wherein the tumor is a prostate tumor.

65. The method of claim 63, wherein the tumor is a bone tumor.

66. The method of any one of claims 59-65, wherein the subject is a human.

67. The method of any one of claims 54-66, wherein the antibody or antigen-binding fragment thereof is delivered using one or more of a cell therapy, extracellular vesicle, mRNA, LNP, or VLP.

68. A method of treating prostate cancer comprising administering or delivering to a subject suffering therefrom a therapeutically effective amount of an immune stimulating or immune checkpoint inhibiting antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof

comprises a bone-targeting moiety.

69. The method of claim 68, wherein the antibody or antigen-binding fragment thereof is the antibody or antigen-binding fragment thereof of any one of claims 1-53.

70. Use of an antibody or antigen-binding fragment thereof of any one of claims 46-53 in a method of delivering a target agent to a cancer cell in a system.

71. Use of an antibody or antigen-binding fragment thereof of any one of claims 1-53 in a method of killing a cancer cell in a system.

72. The use of claim 70 or 71, wherein the system is a population of cells, an animal, or a human.

73. Use of an antibody or antigen-binding fragment thereof of any one of claims 1-53 in a method of treating a condition, disorder, or disease.

74. The use of claim 73, wherein the condition, disorder, or disease comprises or is a cancer, optionally prostate cancer.

75. The use of claim 73 or 74, wherein the condition, disorder, or disease comprises or is a bone metastasis.

76. The use of claim 73, wherein the condition, disorder, or disease comprises or is a tumor, optionally a prostate tumor or bone tumor.