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(54) Title: CHIMERIC ANTIGEN RECEPTORS TARGETING B-CELL MATURATION ANTIGEN AND METHODS OF USE THEREOF

(57) Abstract: Provided herein are BCMA CARs and CAR-T cells, methods of making, and using the same. In some embodiments, particular dosing regimens, redosing regimens, and combination regimens with lymphodepletion are provided, for the treatment and clinical management of multiple myeloma in subjects in need thereof.

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CHIMERIC ANTIGEN RECEPTORS TARGETING B-CELL MATURATION ANTIGEN AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

5 **[0001]** The present application claims the benefit of priority to U.S. Provisional Application No. 62/774,209, filed on December 1, 2018; U.S. Provisional Application No. 62/816,187, filed on March 10, 2019; and U.S. Provisional Application No. 62/931,487, filed on November 6, 2019, the contents of all of which are hereby incorporated by reference in their entireties.

10 ## SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on November 7, 2019, is named AT-022-04WO_SL and is 412,161 bytes in size.

15 ## BACKGROUND

[0003] Multiple myeloma (MM) is a malignancy characterized by an accumulation of clonal plasma cells. MM largely remains incurable, and most subjects develop resistance over time.

[0004] B-cell maturation antigen (BCMA, CD269, or TNFRSF17) is a member of the
20 tumor necrosis factor receptor (TNFR) superfamily and is involved in pro-survival signaling. BCMA was identified in a malignant human T cell lymphoma containing a t(4;16) translocation. BCMA is expressed at high levels on normal and malignant plasma cells at all stages of MM and some other plasma cell malignancies (e.g. DLBCL). BCMA is also expressed on most or all myeloma cells, and expression absent on non-B cell lineages

25 **[0005]** Adoptive transfer of T-cells genetically modified to recognize malignancy-associated antigens is showing promise as a new approach to treating cancer. T-cells can be genetically modified to express chimeric antigen receptors (CARs), which are fusion proteins comprised of an antigen recognition moiety and T-cell activation domains.

[0006] There is an unmet medical need for interventions that can effectively treat MM, including relapsed/refractory MM. Provided herein are methods and compositions that address this need.

SUMMARY

[0007] Chimeric antigen receptors (CARs) that bind to BCMA are provided herein; as well as dosing paradigms for use in the treatment of multiple (MM), including relapsed and/or refractory MM.

[0008] More specifically, in one aspect provided herein is a method of treating MM in a subject comprising administering to the subject at least one dose of allogeneic chimeric antigen receptor (CAR)-T cells comprising an anti-human BCMA CAR (BCMA CAR-T cells), wherein the at least one dose is about 7 x 10^6 cells/dose to about 480 x 10^6 cells/dose.

[0009] In some embodiments, the weight of the subject is ≥50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 20 x 10^6 cells/dose to about 480 x 10^6 cells/dose. In some embodiments, the at least one dose is about 20 x 10^6 cells/dose, about 40 x 10^6 cells/dose, about 120 x 10^6 cells/dose, about 360 x 10^6 cells/dose, or about 480 x 10^6 cells/dose. In some embodiments, the at least one dose is from about 20 x 10^6 cells/dose to about 40 x 10^6 cells/dose, from about 40 x 10^6 cells/dose to about 120 x 10^6 cells/dose, from about 120 x 10^6 cells/dose to about 360 x 10^6 cells/dose, or from about 360 x 10^6 cells/dose to about 480 x 10^6 cells/dose.

[0010] In some embodiments, the weight of the subject is >50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 20 x 10^6 cells/dose to about 480 x 10^6 cells/dose. In some embodiments, the at least one dose is about 20 x 10^6 cells/dose, about 40 x 10^6 cells/dose, about 160 x 10^6 cells/dose, about 240 x 10^6 cells/dose, about 320 x 10^6 cells/dose, or about 480 x 10^6 cells/dose. In some embodiments, the at least one dose is from about 20 x 10^6 cells/dose to about 40 x 10^6 cells/dose, from about 40 x 10^6 cells/dose to about 160 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 240 x 10^6 cells/dose, from about 240 x 10^6 cells/dose to about 320 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 320 x 10^6 cells/dose, or from about 320 x 10^6 cells/dose to about 480 x 10^6 cells/dose.

[0011] In some embodiments, the weight of the subject is <50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 7 x 10^6 cells/dose to about 360 x 10^6 cells/dose. In some embodiments, the at least one dose is about 7 x 10^6 cells/dose, about 14 x 10^6 cells/dose, about 20 x 10^6 cells/dose, about 80 x 10^6 cells/dose, about 240 x 10^6 cells/dose, or about 360 x 10^6 cells/dose. In some embodiments, the at least one dose is from about 7 x 10^6 or 14 x 10^6 cells/dose to about 20 x 10^6 cells/dose, from about 20 x 10^6 cells/dose to about 80 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 240 x 10^6 cells/dose, or from about 240 x 10^6 cells/dose to about 360 x 10^6 cells/dose.

[0012] In some embodiments, the weight of the subject is ≤50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 14 x 10^6 cells/dose to about 320 x 10^6 cells/dose. In some embodiments, the at least one dose is about 14 x 10^6 cells/dose, about 20 x 10^6 cells/dose, about 80 x 10^6 cells/dose, about 160 x 10^6 cells/dose about 200 x 10^6 cells/dose, or about 320 x 10^6 cells/dose. In some embodiments, the at least one dose is about 14 x 10^6 cells/dose to about 20 x 10^6 cells/dose, from about 20 x 10^6 cells/dose to about 80 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 200 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 160 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 200 x 10^6 cells/dose, or from about 200 x 10^6 cells/dose to about 320 x 10^6 cells/dose.

[0013] In some embodiments the subject has not received any prior therapy for multiple myeloma. In some embodiments the subject has received at least one, two, or three prior therapies for multiple myeloma. In some embodiments, the dosing regimens are a first line therapy. In some embodiments, the dosing regimens are a second line therapy. In some embodiments, the dosing regimens are a third line therapy. In some embodiments, the dosing regimens are a fourth line therapy.

[0014] In some embodiments the subject has received a prior chemotherapeutic regimen; a prior biologics-based regimen, and/or a prior autologous cell therapy-based regimen (e.g. stem cell therapy).

[0015] In some embodiments, the subject has relapsed MM. In some embodiments, the subject has refractory MM. In some embodiments, the subject has refractory and relapsed MM.

[0016] In some embodiments, the BCMA CAR-T cells comprise a CAR comprising an extracellular binding domain comprising a single chain Fv fragment (scFv), wherein the scFv comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH region comprises a VH complementary determining region 1 (VH CDR1), a VH complementary determining region 2 (VH CDR2), and a VH complementary determining region 3 (VH CDR3) and the VL region comprises a VL complementary determining region 1 (VL CDR1), a VL complementary determining region 2 (VL CDR2), and a VL complementary determining region 3 (VL CDR3), wherein: (a) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 153 or 154; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 209; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 222; (b) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 187 or 188; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 249; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 225; (c) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 165 or 166; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 226; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 227; (d) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 159 or 162; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 161; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 251; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 252; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 253; (e) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 190 or 191; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 161; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 262; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 252; and the VL CDR3 comprises the amino acid sequence

of SEQ ID NO: 263; (f) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 154 or 169; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 271; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 272; (g) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 129, 130, or 131; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 139 or 140; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 134; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 217; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 210; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 216; (h) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 158 or 159; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 209; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 225; or (i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 129, 130, or 131; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 132 or 133; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 137; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 377; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 210; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 214.

[0017] In some embodiments, the VH region of the scFv of a BCMA CAR comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 150, 151, or 152; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 153 or 154; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 155; and the VL region of the scFv comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 222.

[0018] In some embodiments, the VH region of the scFv of a BCMA CAR comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 151, 156, or 157; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 158 or 159; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 155; and the VL region of the scFv

comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 225.

[0019] In some embodiments, the BCMA CAR-T cells comprise a CAR comprising the amino acid sequence shown in SEQ ID NO: 344. In some of these embodiments, the CAR further comprises a CD20 epitope. In some of these embodiments, the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 397 or SEQ ID NO: 398.

[0020] In some embodiments, the BCMA CAR-T cells comprise a CAR comprising a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

[0021] In some embodiments, the BCMA CAR-T cells comprise a CAR comprising a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

[0022] In some embodiments, the BCMA CAR-T cells comprise a CAR comprising a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324

[0023] In some embodiments, the BCMA CAR-T cells comprise a CAR comprising a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

[0024] In some embodiments, the BCMA CAR-T cells comprise a CAR comprising an extracellular binding domain comprising a single chain Fv fragment (scFv), wherein the scFv comprises a VH region and a VL region, wherein the combination of VH and VL regions are chosen from the combinations presented in Table 1. In some embodiments, the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain. In some embodiments, the VH comprises SEQ ID NO: 33 and the VL comprises SEQ ID NO: 34. In some embodiments, the VH comprises SEQ ID NO: 112 and the VL comprises SEQ ID NO: 38.

[0025] In some embodiments, the CAR-T cells are deficient in CD52. In some embodiments, the CAR-T cells are deficient in TCRα and/or TCRβ. In some embodiments, the CAR-T cells do not express a safety switch. In some embodiments the genotype of the cells is $TCR\alpha\beta^{-}$and $CD52^{+/-}$.

[0026] In some embodiments, the subject receives a first lymphodepletion regimen prior to administration of the at least one dose. In some embodiments, the first lymphodepletion regimen comprises administering fludarabine and cyclophosphamide. In some embodiments, the first lymphodepletion regimen comprises administering fludarabine,

cyclophosphamide, and an anti-CD52 antibody. In some embodiments, the first lymphodepletion regimen comprises administering an anti-CD52 antibody. In some embodiments, the first lymphodepletion regimen comprises administering only an anti-CD52 antibody. In some embodiments, the fludarabine is administered at a dosage of about 30 mg/m2/day; cyclophosphamide is administered at a dosage of about 300 mg/m2/day; and CD52 antibody is administered at a dosage of about 10 to about 13 mg/day, about 13 to 20 mg/day, about 13 to 30 mg/day, or about 20 to 30 mg/day. In some embodiments, the first lymphodepletion regimen is initiated between about 1 to 15 days prior to administration of the at least one dose. In some embodiments, the first lymphodepletion regimen is administered over the course of 1, 2, 3, 4, or 5 days. In some embodiments, the first lymphodepletion regimen is administered 5 days prior to administration of the at least one dose in the course of 3 days. In some embodiments, the first lymphodepletion regimen is administered 7 days prior to administration of the at least one dose in the course of 3 days.

[0027] In some embodiments, the subject receives a subsequent dose of the CAR-T cells.

[0028] In another aspect provided herein is a formulation comprising BCMA CAR-T cells. In one embodiment the formulation comprises a solution comprising about 5% dimethyl sulfoxide (DMSO) and 14 × 10^6 cells /mL. In another embodiment the cells are formulated in a 1:1 mixture of CryoStor® Basal Solution and CryoStor® CS10 resulting in a 5% final concentration of dimethyl sulfoxide, wherein the dosage strength of the formulation is 14 × 10^6 cells /mL, wherein the genotype of the cells is BCMA-CAR+_TCRαβ-_CD52+/-, and wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, two rituximab-binding domains, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain.

BRIEF DESCRIPTION OF THE DRAWINGS

[0029] FIG. 1 shows a BCMA-containing CAR-T cell of the disclosure. The CAR has a functional off-switch activated by rituximab and an anti-BCMA scFv. The modified T-cell further has reduced expression of CD52 (to minimize rejection) and T-Cell receptor genes (TCRα, and/or TCRβ) (to avoid GvHD, graft versus host disease).

[0030] FIG. 2 shows the rituximab-mediated off switch enables detection and depletion (with a rituximab antibody) of the BCMA-containing CAR-T cells of the disclosure.

[0031] FIG. 3 shows that a BCMA scFV-containing CAR-T cell of the disclosure (BCMA-1), with its endogenous CD52 gene knocked down/knocked out, is resistant to a CD52 antibody treatment.

[0032] FIG. 4 shows expression of BCMA in target cells.

[0033] FIG. 5 shows that BCMA scFV-containing CAR-T cells of the disclosure (BCMA-1), show target-dependent expansion and maintains activity after repeated stimulation.

[0034] FIG. 6 shows that BCMA scFV-containing CAR-T cells of the disclosure (BCMA-1) show specific cytotoxic activity. The non-gene edited BCMA-1 refers to CAR-T cells not comprising the knockdown/knockout out of CD52 and/or TCRα and/or TCRβ.

[0035] FIG. 7 shows that BCMA scFV-containing CAR-T cells of the disclosure (BCMA-1) has dose-dependent cytotoxic activity that is not inhibited by soluble BCMA.

[0036] FIG. 8 - 11A and 11B BCMA scFV-containing CAR-T cells of the disclosure (BCMA-1) show anti-tumor efficacy in an orthotopic tumor model, and can be depleted with rituximab. **FIG. 8** shows activity of BCMA scFV-containing CAR-T cells of the disclosure (BCMA-1) in a MM.1S model. **FIG. 9** shows the effect of BCMA scFV-containing CAR-T cells of the disclosure (BCMA-1) on tumor eradication after a second dose. **FIG. 10** shows the long term antitumor effect of BCMA scFV-containing CAR-T cells of the disclosure (BCMA-1) in mice, supplemented with IL-7/IL-15. The MOLP-8 animal model was used. NSG mice (N=10) were administered with either 5 x 10^6 MM.1S cells or 2 x 10^6 MOLP-8 cells. Cytokines were provided via AAV-mediated gene delivery. Results were shown as mean ± SEM. **FIG. 11A - 11B** show that rituximab depletes BCMA

scFV-containing CAR-T cells of the disclosure (BCMA-1) in the model (**FIG. 11B**), and abrogates antitumor activity (**FIG. 11A**).

[0037] FIGS. 12- 15 depict the manufacturing processes of the BCMA CAR-T cells of the disclosure – specifically BCMA scFV-containing CAR-T cells of the disclosure (BCMA-1) can be manufactured under GMP-like conditions with preservation of antitumor activity. **FIG. 12** shows an exemplary allogeneic CAR-T manufacturing process for the BCMA CAR-T cells of the disclosure. **FIG. 13** shows the high viability and expansion of BCMA scFV-containing CAR-T cells of the disclosure (BCMA-1). **FIG. 14** shows efficient enrichment of TCRαβ-negative cells. MACS: Magnetic-activated Cell Sorting system (Miltenyi Biotec). **FIG. 15** shows the high antitumor effect of different doses of BCMA scFV-containing CAR-T cells of the disclosure (BCMA-1), in a MM.1S orthotopic tumor model.

[0038] FIG. 16 shows that the BCMA-1 scFv does not show off-target binding in tissue cross-reactivity studies, indicating the risk for off-target binding in a clinical setting to be low or non-existent.

[0039] FIG. 17 describes limitations of autologous CAR-T therapies.

[0040] FIG. 18 describes advantages of allogeneic CAR-T therapies.

[0041] FIG. 19 shows the schema for the Phase 1 (Design A or B) Study.

[0042] FIG. 20 shows the schema for the Phase 1, Design B Study.

[0043] FIG. 21 shows a schematic diagram of an exemplary vector element/construct of the disclosure.

DETAILED DESCRIPTION

[0044] The disclosure provides chimeric antigen receptors (CARs) and immune cells (e.g. T-cells) comprising CARs (CAR-T cells) that specifically bind to BCMA, and dosing regimens for use in the treatment of MM, including refractory/relapsed MM. The disclosure also provides polynucleotides encoding these CARs, compositions comprising these CAR-T cells, and methods of making and using these CARs and CAR-T cells.

[0045] The disclosure provides CARs that bind to BCMA (e.g., human BCMA, Uniprot accession number: Q02223-2). BCMA specific CARs provided herein include single chain CARS and multichain CARs. The CARs have the ability to redirect T cell specificity and reactivity toward BCMA in a non-MHC-restricted manner, exploiting the antigen-binding properties of monoclonal antibodies. The non-MHC-restricted antigen recognition gives T cells expressing CARs the ability to recognize an antigen independent of antigen processing, thus bypassing a major mechanism of tumor escape.

I. BCMA-Specific CARS

[0046] In some embodiments, CARs provided herein comprise an extracellular ligand-binding domain (e.g., a single chain variable fragment (scFv)), a transmembrane domain, and an intracellular signaling domain. In some embodiments, the extracellular ligand-binding domain, transmembrane domain, and intracellular signaling domain are in one polypeptide, i.e., in a single chain. Multichain CARs and polypeptides are also provided herein. In some embodiments, the mulitchain CARs comprise: a first polypeptide comprising a transmembrane domain and at least one extracellular ligand-binding domain, and a second polypeptide comprising a transmembrane domain and at least one intracellular signaling domain, wherein the polypeptides assemble together to form a multichain CAR.

[0047] In some embodiments, a BCMA specific multichain CAR is based on the high affinity receptor for IgE (FcεRI). The FcεRI expressed on mast cells and basophiles triggers allergic reactions. FcεRI is a tetrameric complex composed of a single α subunit, a single β subunit, and two disulfide-linked γ subunits. The α subunit contains the IgE-binding domain. The β and γ subunits contain ITAMs that mediate signal transduction. In some embodiments, the extracellular domain of the FcRα chain is deleted and replaced by a BCMA specific extracellular ligand-binding domain. In some embodiments, the multichain BCMA specific CAR comprises an scFv that binds specifically to BCMA, the CD8α hinge, and the ITAM of the FcRβ chain. In some embodiments, the CAR may or may not comprise the FcRγ chain. In some embodiments two copies of a rituximab mimotope (e.g., CPYSNPSLC (SEQ ID NO: 397); see also WO 2016/120216, incorporated herein by reference in its entirety) are present. An exemplary construct is show in FIG. 21.

[0048] As provided herein, the extracellular ligand-binding domain of the BCMA CAR comprises an scFv comprising the light chain variable (VL) region and the heavy chain

variable (VH) region of a target antigen specific monoclonal antibody joined by a flexible linker. Single chain variable region fragments are made by linking light and/or heavy chain variable regions by using a short linking peptide (Bird et al., Science 242:423-426, 1988). An example of a linking peptide is the GS linker having the amino acid sequence (GGGGS)3 (SEQ ID NO: 333), which bridges approximately 3.5 nm between the carboxy terminus of one variable region and the amino terminus of the other variable region. Linkers of other sequences have been designed and used (Bird et al., 1988, supra). In general, linkers can be short, flexible polypeptides and preferably comprised of about 20 or fewer amino acid residues. Linkers can in turn be modified for additional functions, such as attachment of drugs or attachment to solid supports. The single chain variants can be produced either recombinantly or synthetically. For synthetic production of scFv, an automated synthesizer can be used. For recombinant production of scFv, a suitable plasmid containing polynucleotide that encodes the scFv can be introduced into a suitable host cell, either eukaryotic, such as yeast, plant, insect or mammalian cells, or prokaryotic, such as E. coli. Polynucleotides encoding the scFv of interest can be made by routine manipulations such as ligation of polynucleotides. The resultant scFv can be isolated using standard protein purification techniques known in the art.

[0049] In some embodiments, provided herein is a BCMA CAR, wherein the CAR comprises an extracellular binding domain comprising a single chain Fv fragment (scFv), wherein the scFv comprises a heavy chain variable (VH) region and a light chain variable (VL) region, wherein the VH region comprises a VH complementary determining region 1 (VH CDR1), a VH complementary determining region 2 (VH CDR2), and a VH complementary determining region 3 (VH CDR3) and the VL region comprises a VL complementary determining region 1 (VL CDR1), a VL complementary determining region 2 (VL CDR2), and a VL complementary determining region 3 (VL CDR3), wherein: (a) the VH CDR1 comprises a sequence selected from the group consisting of: SEQ ID NOs.: 129, 130, 131, 150, 151, 152, 156, 157, 301, 302, 303, 381, 382, 386, 387, and 388; (b) the VH CDR2 comprises a sequence selected from the group consisting of: SEQ ID NOs.: 132, 133, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 153, 154, 158, 159, 160, 162, 163, 165, 166, 167, 168, 169, 171, 172, 174, 175, 176, 177, 178, 179, 180, 181, 183, 184, 185, 186, 187, 188, 190, 191, 192, 193, 194, 195, 196, 198, 199, 200, 201, 202, 203, 204, 206, 207, 208, 304, 305, 306, 383, 384, 389, and 390; (c) the VH CDR3 comprises a sequence selected from the group consisting of: SEQ ID NOs.: 134, 135, 136, 137, 148, 149, 155,

161, 164, 170, 173, 182, 189, 197, 205, 307, 308, 385, and 391; (d) the VL CDR1 comprises a sequence selected from the group consisting of: SEQ ID NOs.: 209, 212, 215, 217, 218, 219, 223, 226, 228, 230, 232, 235, 238, 239, 241, 243, 245, 246, 247, 249, 250, 251, 254, 257, 260, 262, 265, 266, 267, 269, 270, 271, 273, 275, 277, 279, 283, 285, 287, 290, 292, 295, 297, 299, 309, 377, 415, and 417; (e) the VL CDR2 comprises a sequence selected from the group consisting of: SEQ ID NOs.: 210, 221, 252, 310, 392, and 395; and (f) the VL CDR3 comprises a sequence selected from the group consisting of: SEQ ID NOs.: 211, 213, 214, 216, 220, 222, 224, 225, 227, 229, 231, 233, 234, 236, 237, 240, 242, 244, 248, 253, 255, 256, 258, 259, 261, 263, 264, 268, 272, 274, 276, 278, 280, 281, 282, 284, 286, 288, 289, 291, 293, 294, 296, 298, 300, 311, 312, 393, and 416.

[0050] In some embodiments, provided herein is a BCMA CAR, wherein the CAR comprises an extracellular ligand-binding domain comprising: a VH region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 2, 3, 7, 8, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 37, 39, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 83, 87, 92, 95, 97, 99, 101, 104, 106, 110, 112, 114, 76, 118, 120, 122, 125, 127, 313, 314 or 413; and/or a VL region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 1, 4, 5, 6, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 23, 34, 36, 38, 40, 41, 43, 45, 47, 49, 51, 53, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 317, 81, 82, 84, 85, 86, 88, 89, 90, 91, 93, 94, 96, 98, 100, 102, 103, 105, 107, 108, 109, 111, 113, 115, 116, 117, 119, 121, 123, 124, 126, 128, 315, 316, or 414. In some embodiments, the VH and VL are linked together by a flexible linker. In some embodiments a flexible linker comprises the amino acid sequence shown in SEQ ID NO: 333.

[0051] In some embodiments, a CAR of the disclosure comprises an extracellular ligand-binding domain having any one of partial light chain sequence as listed in Table 1 and/or any one of partial heavy chain sequence as listed in Table 1. In Table 1, the underlined sequences are CDR sequences according to Kabat and in bold according to Chothia, except for the following heavy chain CDR2 sequences, in which the Chothia CDR sequence is underlined and the Kabat CDR sequence is in bold: P5A2_VHVL, A02_Rd4_0.6nM_C06, A02_Rd4_0.6nM_C09, A02_Rd4_6nM_C16, A02_Rd4_6nM_C03, A02_Rd4_6nM_C01, A02_Rd4_6nM_C26, A02_Rd4_6nM_C25, A02_Rd4_6nM_C22, A02_Rd4_6nM_C19, A02_Rd4_0.6nM_C03, A02_Rd4_6nM_C07, A02_Rd4_6nM_C23,

A02_Rd4_0.6nM_C18, A02_Rd4_6nM_C10, A02_Rd4_6nM_C05, A02_Rd4_0.6nM_C10, A02_Rd4_6nM_C04, A02_Rd4_0.6nM_C26, A02_Rd4_0.6nM_C13, A02_Rd4_0.6nM_C01, A02_Rd4_6nM_C08, P5C1_VHVL, C01_Rd4_6nM_C24, C01_Rd4_6nM_C26, C01_Rd4_6nM_C10, C01_Rd4_0.6nM_C27, C01_Rd4_6nM_C20, C01_Rd4_6nM_C12, C01_Rd4_0.6nM_C16, C01_Rd4_0.6nM_C09, C01_Rd4_6nM_C09, C01_Rd4_0.6nM_C03, C01_Rd4_0.6nM_C06, C01_Rd4_6nM_C04, COMBO_Rd4_0.6nM_C22, COMBO_Rd4_6nM_C21, COMBO_Rd4_6nM_C10, COMBO_Rd4_0.6nM_C04, COMBO_Rd4_6nM_C25, COMBO_Rd4_0.6nM_C21, COMBO_Rd4_6nM_C11, COMBO_Rd4_0.6nM_C20, COMBO_Rd4_6nM_C09, COMBO_Rd4_6nM_C08, COMBO_Rd4_0.6nM_C19, COMBO_Rd4_0.6nM_C02, COMBO_Rd4_0.6nM_C23, COMBO_Rd4_0.6nM_C29, COMBO_Rd4_0.6nM_C09, COMBO_Rd4_6nM_C12, COMBO_Rd4_0.6nM_C30, COMBO_Rd4_0.6nM_C14, COMBO_Rd4_6nM_C07, COMBO_Rd4_6nM_C02, COMBO_Rd4_0.6nM_C05, COMBO_Rd4_0.6nM_C17, COMBO_Rd4_6nM_C22, and COMBO_Rd4_0.6nM_C11.

Table 1

Binding Domain	Light Chain	Heavy Chain
P6E01/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYGSPPSFT**F GQGTKVEIK (SEQ ID NO: 1)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
P6E01/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYGSPPSFT**F GQGTKVEIK (SEQ ID NO: 1)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L1.LGF/L3.KW/P6E01	EIVLTQSPGTLSLSPGERATLSC **RASQSLGSFYLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSGTD	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN

Binding Domain	Light Chain	Heavy Chain
	FTLTISRLEPEDFAVYYC**KHYGWP PSFT**FGQGTKVEIK (SEQ ID NO: 4)	TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L1.LGF/L3.NY/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS QSLGSFYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYNYPPSFT**F GQGTKVEIK (SEQ ID NO: 5)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L1.GDF/L3.NY/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS QSVGDFYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYNYPPSFT** FGQGTKVEIK (SEQ ID NO: 6)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L1.LGF/L3.KW/H3.AL	EIVLTQSPGTLSLSPGERATLSC**RAS QSLGSFYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KHYGWPPSFT**F GQGTKVEIK (SEQ ID NO: 4)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**ARVS PIAALMDY**WGQGTLVTVSS (SEQ ID NO: 7)
L1.LGF/L3.KW/H3.AP	EIVLTQSPGTLSLSPGERATLSC**RAS QSLGSFYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KHYGWPPSFT**F GQGTKVEIK (SEQ ID NO: 4)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA APMDY**WGQGTLVTVSS (SEQ ID NO: 8)
L1.LGF/L3.KW/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS QSLGSFYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KHYGWPPSFT**F GQGTKVEIK (SEQ ID NO: 4)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)

Binding Domain	Light Chain	Heavy Chain
L1.LGF/L3.PY/H3.AP	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSLGSFYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 9)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **APMDY**WGQGTLVTVSS (SEQ ID NO: 8)
L1.LGF/L3.PY/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSLGSFYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 9)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L1.LGF/L3.NY/H3.AL	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSLGSFYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYNYPPSFT**F GQGTKVEIK (SEQ ID NO: 10)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **ALMDY**WGQGTLVTVSS (SEQ ID NO: 412)
L1.LGF/L3.NY/H3.AP	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSLGSFYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYNYPPSFT**F GQGTKVEIK (SEQ ID NO: 10)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **APMDY**WGQGTLVTVSS (SEQ ID NO: 8)
L1.LGF/L3.NY/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSLGSFYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYNYPPSFT**F GQGTKVEIK (SEQ ID NO: 10)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L1.GDF/L3.KW/H3.AL	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVGDFYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA**

Binding Domain	Light Chain	Heavy Chain
	TISRLEPEDFAVYYC**KHYGWPPSF** **T**FGQGTKVEIK (SEQ ID NO: 11)	**ALMDY**WGQGTLVTVSS (SEQ ID NO: 7)
L1.GDF/L3.KW/H3.AP	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVGDFYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**KHYGWPPSF** **T**FGQGTKVEIK (SEQ ID NO: 11)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **APMDY**WGQGTLVTVSS (SEQ ID NO: 8)
L1.GDF/L3.KW/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVGDFYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**KHYGWPPSF** **T**FGQGTKVEIK (SEQ ID NO: 11)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L1.GDF/L3.PY/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVGDFYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYPYPPSFT** FGQGTKVEIK (SEQ ID NO: 12)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L1.GDF/L3.NY/H3.AL	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVGDFYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYNYPPSFT** FGQGTKVEIK (SEQ ID NO: 13)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **ALMDY**WGQGTLVTVSS (SEQ ID NO: 7)
L1.GDF/L3.NY/H3.AP	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVGDFYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYNYPPSFT** FGQGTKVEIK (SEQ ID NO: 13)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **APMDY**WGQGTLVTVSS (SEQ ID NO: 8)

Binding Domain	Light Chain	Heavy Chain
L1.GDF/L3.NY/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVGDFYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYNYPPSFT** FGQGTKVEIK (SEQ ID NO: 14)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L3.KW/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KHYGWPPSFT**F GQGTKVEIK (SEQ ID NO: 15)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L3.PY/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L3.NY/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYNYPPSFT**F GQGTKVEIK (SEQ ID NO: 17)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L3.PY/L1.PS/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYPS**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L3.PY/L1.AH/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAHYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA**

Binding Domain	Light Chain	Heavy Chain
	TISRLEPEDFAVYYC**QHYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	**SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L3.PY/L1.FF/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSFFLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L3.PY/L1.PH/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSPHYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L3.PY/L3.KY/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KYYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L3.PY/L3.KF/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KFYPYPPSFT**FG QGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L3.PY/H2.QR	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQRKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 24)
L3.PY/H2.DY	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI

Binding Domain	Light Chain	Heavy Chain
	GASSRATGIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	**DYSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 25)
L3.PY/H2 .YQ	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SYQGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 26)
L3.PY/H2 .LT	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SLTGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 27)
L3.PY/H2 .HA	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SHAGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 28)
L3.PY/H2 .QL	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQLKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 29)
L3.PY/H3 .YA	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIY AGMDY**WGQGTLVTVSS (SEQ ID NO: 30)

Binding Domain	Light Chain	Heavy Chain
L3.PY/H3.AE	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AEMDY**WGQGTLVTVSS (SEQ ID NO: 31)
L3.PY/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L3.PY/H3.TAQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCTR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 32)
L3.PY/P6E01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 2)
L3.PY/L1.PS/H2.QR	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYPS**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQRKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 24)
L3.PY/L1.PS/H2.DY	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYPS**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **DYSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA**

Binding Domain	Light Chain	Heavy Chain
	SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 18)	**SGMDY**WGQGTLVTVSS (SEQ ID NO: 25)
L3.PY/L1. PS/H2.YQ	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYPS**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SYQGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 26)
L3.PY/L1. PS/H2.LT	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYPS**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SLTGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 27)
L3.PY/L1. PS/H2.HA	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYPS**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SHAGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 28)
L3.PY/L1. PS/H2.QL	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYPS**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQLKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 29)
L3.PY/L1. PS/H3.YA	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYPS**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIY AGMDY**WGQGTLVTVSS (SEQ ID NO: 30)
L3.PY/L1. PS/H3.AE	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYPS**WYQQKPGQAPRLLIY	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI

Binding Domain	Light Chain	Heavy Chain
	GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QHYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	**SGSGGN**TFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**VSPIAAEMDY**WGQGTLVTVSS (SEQ ID NO: 31)
L3.PY/L1.PS/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYPS**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QHYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFGSY**AMTWVRQAPGKGLEWVSAI**SGSGGN**TFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**VSPIAAQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L3.PY/L1.PS/H3.TAQ	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYPS**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QHYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFGSY**AMTWVRQAPGKGLEWVSAI**SGSGGN**TFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTR**VSPIAAQMDY**WGQGTLVTVSS (SEQ ID NO: 32)
L3.PY/L1.AH/H2.QR	EIVLTQSPGTLSLSPGERATLSC**RASQSVSAHYLA**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QHYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFGSY**AMTWVRQAPGKGLEWVSAI**SGSGGN**TFYADQRKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**VSPIASGMDY**WGQGTLVTVSS (SEQ ID NO: 24)
L3.PY/L1.AH/H2.DY	EIVLTQSPGTLSLSPGERATLSC**RASQSVSAHYLA**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QHYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFGSY**AMTWVRQAPGKGLEWVSAI**DYSGGN**TFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**VSPIASGMDY**WGQGTLVTVSS (SEQ ID NO: 25)
L3.PY/L1.AH/H2.YQ	EIVLTQSPGTLSLSPGERATLSC**RASQSVSAHYLA**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QHYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFGSY**AMTWVRQAPGKGLEWVSAI**SYQGGN**TFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**VSPIASGMDY**WGQGTLVTVSS (SEQ ID NO: 26)

Binding Domain	Light Chain	Heavy Chain
L3.PY/L1.AH/H2.LT	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAHYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYPYPPSFT** FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SLTGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 27)
L3.PY/L1.AH/H2.HA	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAHYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYPYPPSFT** FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SHAGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 28)
L3.PY/L1.AH/H2.QL	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAHYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYPYPPSFT** FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQLKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 29)
L3.PY/L1.AH/H3.YA	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAHYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYPYPPSFT** FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIY** **AGMDY**WGQGTLVTVSS (SEQ ID NO: 30)
L3.PY/L1.AH/H3.AE	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAHYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYPYPPSFT** FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AEMDY**WGQGTLVTVSS (SEQ ID NO: 31)
L3.PY/L1.AH/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAHYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA**

Binding Domain	Light Chain	Heavy Chain
	TISRLEPEDFAVYYC**QHYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	**AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L3.PY/L1.AH/H3.TAQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAHYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QHYPYPPSFT** FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCTR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 32)
L3.PY/L1.FF/H2.QR	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSFFLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQRKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 24)
L3.PY/L1.FF/H2.DY	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSFFLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI DYSGGNTFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 25)
L3.PY/L1.FF/H2.YQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSFFLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SYQGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 26)
L3.PY/L1.FF/H2.LT	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSFFLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SLTGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 27)
L3.PY/L1.FF/H2.HA	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSFFLA**WYQQKPGQAPRLLIY	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI

Binding Domain	Light Chain	Heavy Chain
	GASSRATGIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	**SHAGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 28)
L3.PY/L1. FF/H2.QL	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSFFLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQLKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 29)
L3.PY/L1. FF/H3.YA	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSFFLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIY AGMDY**WGQGTLVTVSS (SEQ ID NO: 30)
L3.PY/L1. FF/H3.AE	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSFFLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA AEMDY**WGQGTLVTVSS (SEQ ID NO: 31)
L3.PY/L1. FF/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSFFLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L3.PY/L1. FF/H3.TA Q	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSFFLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCTR**VSPIA AQMDY**WGQGTLVTVSS (SEQ ID NO: 32)

Binding Domain	Light Chain	Heavy Chain
L3.PY/L1.PH/H2.QR	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSPHYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQRKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 24)
L3.PY/L1.PH/H2.HA	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSPHYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SHAGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 28)
L3.PY/L1.PH/H3.AE	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSPHYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AEMDY**WGQGTLVTVSS (SEQ ID NO: 31)
L3.PY/L1.PH/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSPHYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L3.PY/L1.PH/H3.TAQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSPHYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCTR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 32)
L3.PY/L3.KY/H2.QR	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQRKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA**

Binding Domain	Light Chain	Heavy Chain
	SRLEPEDFAVYYC**KYYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 22)	**SGMDY**WGQGTLVTVSS (SEQ ID NO: 24)
L3.PY/L3.KY/H2.DY	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KYYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **DYSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 25)
L3.PY/L3.KY/H2.YQ	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KYYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SYQGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 26)
L3.PY/L3.KY/H2.LT	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KYYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SLTGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 27)
L3.PY/L3.KY/H2.HA	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KYYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SHAGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 28)
L3.PY/L3.KY/H2.QL	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KYYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQLKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 29)

Binding Domain	Light Chain	Heavy Chain
L3.PY/L3.KY/H3.YA	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KYYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIY** **AGMDY**WGQGTLVTVSS (SEQ ID NO: 30)
L3.PY/L3.KY/H3.TAQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KYYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCTR**VSPIA** **AQMDY**WGQGTLVTVSS (SEQ ID NO: 32)
L3.PY/L3.KF/H2.DY	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KFYPYPPSFT**FG QGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **DYSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 25)
L3.PY/L3.KF/H2.YQ	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KFYPYPPSFT**FG QGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SYQGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 26)
L3.PY/L3.KF/H2.LT	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**KFYPYPPSFT**FG QGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SLTGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA** **SGMDY**WGQGTLVTVSS (SEQ ID NO: 27)
L3.PY/L3.KF/H2.QL	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADQLKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA**

Binding Domain	Light Chain	Heavy Chain
	SRLEPEDFAVYYC**KFYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	**SGMDY**WGQGTLVTVSS (SEQ ID NO: 29)
L3.PY/L3.KF/H3.YA	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**KFYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFGSY**AMTWVRQAPGKGLEWVSAI**SGSGGN**TFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**VSPIYAGMDY**WGQGTLVTVSS (SEQ ID NO: 30)
L3.PY/L3.KF/H3.AE	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**KFYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFGSY**AMTWVRQAPGKGLEWVSAI**SGSGGN**TFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**VSPIAAEMDY**WGQGTLVTVSS (SEQ ID NO: 31)
L3.PY/L3.KF/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**KFYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFGSY**AMTWVRQAPGKGLEWVSAI**SGSGGN**TFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**VSPIAAQMDY**WGQGTLVTVSS (SEQ ID NO: 3)
L3.PY/L3.KF/H3.TAQ	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAPRLLIY**GASSRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**KFYPYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFGSY**AMTWVRQAPGKGLEWVSAI**SGSGGN**TFYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTR**VSPIAAQMDY**WGQGTLVTVSS (SEQ ID NO: 32)
P5A2_VHVL	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYGSWPLT**FGQGTKVEIK (SEQ ID NO: 34)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSY**AMNWVRQAPGKGLEWVS**AISDSGGSTYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWPMDI**WGQGTLVTVSS (SEQ ID NO: 33)
A02_Rd4_0.6nM_C06	EIVLTQSPGTLSLSPGERATLSC**RASQSVSVIYLA**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTL	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSY**AMNWVRQAPGKGLEWVS**AISDSGGSAWYADSVKG**RFTISRDNSKN

Binding Domain	Light Chain	Heavy Chain
	TISRLEPEDFAVYYC**QQYQRWPLT** FGQGTKVEIK (SEQ ID NO: 36)	TLYLQMNSLRAEDTAVYYCAR**YWP** **MSL**WGQGTLVTVSS (SEQ ID NO: 35)
A02_Rd4_0.6nM_C09	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQSWPLT** FGQGTKVEIK (SEQ ID NO: 38)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **SDSGGSMWYADSVKG**RFTISRDNSK NTLYLQMNSLRAEDTAVYYCAR**YWP** **MSL**WGQGTLVTVSS (SEQ ID NO: 37)
A02_Rd4_6nM_C16 (P5AC16)	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSDIYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQTWPLT** FGQGTKVEIK (SEQ ID NO: 40)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **SdFGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MDI**WGQGTLVTVSS (SEQ ID NO: 39)
A02_Rd4_6nM_C03	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSNLYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQGWPLT** FGQGTKVEIK (SEQ ID NO: 41)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **SDSGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MDI**WGQGTLVTVSS (SEQ ID NO: 33)
A02_Rd4_6nM_C01	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAYYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYERWPLT** FGQGTKVEIK (SEQ ID NO: 43)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **TASGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MSL**WGQGTLVTVSS (SEQ ID NO: 42)
A02_Rd4_6nM_C26	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSLYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQVWPLT** FGQGTKVEIK (SEQ ID NO: 45)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **SDSGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MSL**WGQGTLVTVSS (SEQ ID NO: 44)
A02_Rd4_6nM_C25	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYLDWPLT** FGQGTKVEIK (SEQ ID NO: 47)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **SdSGGSRWYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MTP**WGQGTLVTVSS (SEQ ID NO: 46)

Binding Domain	Light Chain	Heavy Chain
A02_Rd4_6nM_C22	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQVWPLT** FGQGTKVEIK (SEQ ID NO: 49)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AV** **LdSGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MTP**WGQGTLVTVSS (SEQ ID NO: 48)
A02_Rd4_6nM_C19	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSVlYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYLAWPLT** FGQGTKVEIK (SEQ ID NO: 51)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **SdSGGSRWYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MSD**WGQGTLVTVSS (SEQ ID NO: 50)
A02_Rd4_0.6nM_C03	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYFTWPLT** FGQGTKVEIK (SEQ ID NO: 53)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **SdSGGSKWYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MSL**WGQGTLVTVSS (SEQ ID NO: 52)
A02_Rd4_6nM_C07	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSPyYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYERWPLT** FGQGTKVEIK (SEQ ID NO: 55)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **GGSGGSLPYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MDS**WGQGTLVTVSS (SEQ ID NO: 54)
A02_Rd4_6nM_C23	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSVEYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYARWPLT** FGQGTKVEIK (SEQ ID NO: 57)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **SdSGGSGWYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MSL**WGQGTLVTVSS (SEQ ID NO: 56)
A02_Rd4_0.6nM_C18	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSEIYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYFGWPLT** FGQGTKVEIK (SEQ ID NO: 59)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AV** **LdSGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MSL**WGQGTLVTVSS (SEQ ID NO: 58)
A02_Rd4_6nM_C10	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVEMSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **SdSGGSCWYADSVKG**RFTISRDNSKN

Binding Domain	Light Chain	Heavy Chain
	TISRLEPEDFAVYYC**QQYAHWPLT**FGQGTKVEIK (SEQ ID NO: 61)	TLYLQMNSLRAEDTAVYYCAR**YWP**MTPWGQGTLVTVSS (SEQ ID NO: 60)
A02_Rd4_6nM_C05	EIVLTQSPGTLSLSPGERATLSC**RAS**QSVSSSYLAWYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYQRWPLT**FGQGTKVEIK (SEQ ID NO: 63)	EVQLLESGGGLVQPGGSLRLSCAAS**G**FTFSSYAMNWVRQAPGKGLEWVS**AI**FaSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWP**MTPWGQGTLVTVSS (SEQ ID NO: 62)
A02_Rd4_0.6nM_C10	EIVLTQSPGTLSLSPGERATLSC**RAS**QSVSAQYLAWYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYQRWPLT**FGQGTKVEIK (SEQ ID NO: 65)	EVQLLESGGGLVQPGGSLRLSCAAS**G**FTFSSYAMNWVRQAPGKGLEWVS**AI**SgWGGSLPYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWP**MDSWGQGTLVTVSS (SEQ ID NO: 64)
A02_Rd4_6nM_C04	EIVLTQSPGTLSLSPGERATLSC**RAS**QSVSAlYLAWYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYQVWPLT**FGQGTKVEIK (SEQ ID NO: 67)	EVQLLESGGGLVQPGGSLRLSCAAS**G**FTFSSYAMNWVRQAPGKGLEWVS**AI**MsSGGPLYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWP**MALWGQGTLVTVSS (SEQ ID NO: 66)
A02_Rd4_0.6nM_C26	EIVLTQSPGTLSLSPGERATLSC**GPS**QSVSSSYLAWYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYQSWPLT**FGQGTKVEIK (SEQ ID NO: 69)	EVQLLESGGGLVQPGGSLRLSCAAS**G**FTFSSYAMNWVRQAPGKGLEWVS**AI**LmSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWP**MSLWGQGTLVTVSS (SEQ ID NO: 68)
A02_Rd4_0.6nM_C13	EIVLTQSPGTLSLSPGERATLSC**RAS**QSVSSSYWAWYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYESWPLT**FGQGTKVEIK (SEQ ID NO: 71)	EVQLLESGGGLVQPGGSLRLSCAAS**G**FTFSSYAMNWVRQAPGKGLEWVS**AI**SdSGGYRYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWP**MSLWGQGTLVTVSS (SEQ ID NO: 70)
A02_Rd4_0.6nM_C01 (P5AC1)	EIVLTQSPGTLSLSPGERATLSC**RG**GQSVSSSYLAWYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYQSWPL**TFGQGTKVEIK (SEQ ID NO: 73)	EVQLLESGGGLVQPGGSLRLSCAAS**G**FTFSSYAMNWVRQAPGKGLEWVS**AI**LsSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWPM**DIWGQGTLVTVSS (SEQ ID NO: 72)

Binding Domain	Light Chain	Heavy Chain
A02_Rd4_6nM_C08	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSFIYLA**WYQQKPGQAPRLLMY **DASIRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYGSWPLT**F GQGTKVEIK (SEQ ID NO: 75)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **LdSGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MSP**WGQGTLVTVSS (SEQ ID NO: 74)
P5C1_VHVL (PC1)	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSTYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYSTSPLT**FG QGTKVEIK (SEQ ID NO: 77)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSTYYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 76)
C01_Rd4_6nM_C24	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSPEYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYSVWPLT**FG QGTKVEIK (SEQ ID NO: 79)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSLPYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4_6nM_C26	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAIYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYSAWPLT**FG QGTKVEIK (SEQ ID NO: 317)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSLPYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4_6nM_C10	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSvYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYSTWPLT**FG QGTKVEIK (SEQ ID NO: 414)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSLPYADSVKG**RFTISRDNSKNTL YLQMNSLRAEDTAVYYCAR**YWPMD** **S**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4_0.6nM_C27	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSTYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYSRWPLT**FG QGTKVEIK (SEQ ID NO: 81)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSLPYADSVKG**RFTISRDNSKNTL YLQMNSLRAEDTAVYYCAR**YWPMD** **S**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4_6nM_C20	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSPIYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSLPYADSVKG**RFTISRDNSKNTL

Binding Domain	Light Chain	Heavy Chain
	SRLEPEDFAVYYC**QQYSAFPLT**FG QGTKVEIK (SEQ ID NO: 82)	YLQMNSLRAEDTAVYYCAR**YWPMD** **S**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4 _6nM_C1 2 (PC1C12)	EIVLTQSPGTLSLSPGERATLSC**WL** **SQSVSSTYLA**WYQQKPGQAPRLLI Y**DASSRAP**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYSEWPLT** FGQGTKVEIK (SEQ ID NO: 84)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGWSYYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 83)
C01_Rd4 _0.6nM_C 16	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSTYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYSSWPLT**FG QGTKVEIK (SEQ ID NO: 85)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSLPYADSVKG**RFTISRDNSKNTL YLQMNSLRAEDTAVYYCAR**YWPMD** **S**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4 _0.6nM_C 09	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSIFLA**WYQQKPGQAPRLLIY**D** **ASSRAP**GIPDRFSGSGSGTDFTLTIS RLEPEDFAVYYC**QQYSAWPLT**FG QGTKVEIK (SEQ ID NO: 86)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSLPYADSVKG**RFTISRDNSKNTL YLQMNSLRAEDTAVYYCAR**YWPMD** **S**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4 _6nM_C0 9	EIVLTQSPGTLSLSPGERATLSC**ACS** **QSVSSTYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYSAWPLT**FG QGTKVEIK (SEQ ID NO: 88)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AT** **VgSGGSIGYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 87)
C01_Rd4 _0.6nM_C 03	EIVLTQSPGTLSLSPGERATLSC**RAS** **CDVSSTYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYMRSPLT**FG QGTKVEIK (SEQ ID NO: 89)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSLPYADSVKG**RFTISRDNSKNTL YLQMNSLRAEDTAVYYCAR**YWPMD** **S**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4 _0.6nM_C 06	EIVLTQSPGTLSLSPGERATLSC**RAS** **EAVPSTYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYSAFPLT**FG QGTKVEIK (SEQ ID NO: 90)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSLPYADSVKG**TISRDNSKNTLY LQMNSLRAEDTAVYYCAR**YWPMDS** WGQGTLVTVSS (SEQ ID NO: 413)

Binding Domain	Light Chain	Heavy Chain
C01_Rd4_6nM_C04	EIVLTQSPGTLSLSPGERATLSC**CSS** **QSVSSTYLA**WYQQKPGQAPRLLIY **DASSRAP**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYSAFPLT**FG QGTKVEIK (SEQ ID NO: 91)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSLPYADSVKG**RFTISRDNSKNTL YLQMNSLRAEDTAVYYCAR**YWPMD** **S**WGQGTLVTVSS (SEQ ID NO: 78)
COMBO_Rd4_0.6nM_C22 (COM22)	EIVLTQSPGTLSLSPGERATLSC**RAS** **VRVSSTYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYMKWPL** **T**FGQGTKVEIK (SEQ ID NO: 93)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**AMNWVRQAPGKGLEWVS**AI** **SdSGGSRWYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCTR**YWPM** **DI**WGQGTLVTVSS (SEQ ID NO: 92)
COMBO_Rd4_6nM_C21	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAAYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYMCWPL** **T**FGQGTKVEIK (SEQ ID NO: 94)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSLPYADSVKG**RFTISRDNSKNTL YLQMNSLRAEDTAVYYCAR**YWPMD** **S**WGQGTLVTVSS (SEQ ID NO: 78)
COMBO_Rd4_6nM_C10	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYWG**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQCWPLT** FGQGTKVEIK (SEQ ID NO: 96)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSIHYADSVKG**RFTISRDNSKNTL YLQMNSLRAEDTAVYYCAR**YWPMD** **S**WGQGTLVTVSS (SEQ ID NO: 95)
COMBO_Rd4_0.6nM_C04	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSTYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQSWPLT** FGQGTKVEIK (SEQ ID NO: 98)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AHI** **gSGGSTYYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 97)
COMBO_Rd4_6nM_C25	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSpYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQSWPLT** FGQGTKVEIK (SEQ ID NO: 100)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSTYYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DP**WGQGTLVTVSS (SEQ ID NO: 99)
COMBO_Rd4_0.6nM_C21	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **gSGGSLPYADSVKG**RFTISRDNSKNTL

Binding Domain	Light Chain	Heavy Chain
	TISRLEPEDFAVYYC**QQYQSWPLT**FGQGTKVEIK (SEQ ID NO: 38)	YLQMNSLRAEDTAVYYCAR**YWPMD**SWGQGTLVTVSS (SEQ ID NO: 78)
COMBO_Rd4_6nM_C11	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSPIYLA**WYQQKPGQAPRLLMY **DASIRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QQYKAWPLT**F GQGTKVEIK (SEQ ID NO: 102)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSLGYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 101)
COMBO_Rd4_0.6nM_C20	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSYLYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYMEWPLT** FGQGTKVEIK (SEQ ID NO: 103)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSLPYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 78)
COMBO_Rd4_6nM_C09	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAQYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQAWPLT** FGQGTKVEIK (SEQ ID NO: 105)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIF** **ASGGSTYYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 104)
COMBO_Rd4_6nM_C08	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQKWPLT** FGQGTKVEIK (SEQ ID NO: 107)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGTWTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MDS**WGQGTLVTVSS (SEQ ID NO: 106)
COMBO_Rd4_0.6nM_C19	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSAVYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYRAWPLT** FGQGTKVEIK (SEQ ID NO: 108)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSLPYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 78)
COMBO_Rd4_0.6nM_C02	EIVLTQSPGTLSLSPGERATLSC**RAS** **IAVSSTYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYMVWPL** **T**FGQGTKVEIK (SEQ ID NO: 109)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSLPYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 78)

Binding Domain	Light Chain	Heavy Chain
COMBO_ Rd4_0.6nM_C23	EIVLTQSPGTLSLSPGERATLSC**RPR** **QSVSSSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQDWPLT** FGQGTKVEIK (SEQ ID NO: 111)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AL** **FGSGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MDS**WGQGTLVTVSS (SEQ ID NO: 110)
COMBO_ Rd4_0.6nM_C29	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQSWPLT** FGQGTKVEIK (SEQ ID NO: 38)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSLPYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DI**WGQGTLVTVSS (SEQ ID NO: 112)
COMBO_ Rd4_0.6nM_C09	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSSTYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQEWPLT** FGQGTKVEIK (SEQ ID NO: 113)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSLPYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DI**WGQGTLVTVSS (SEQ ID NO: 112)
COMBO_ Rd4_6nM_C12	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSASYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYMSWPLT** FGQGTKVEIK (SEQ ID NO: 115)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AA** **LGSGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP** **MDS**WGQGTLVTVSS (SEQ ID NO: 114)
COMBO_ Rd4_0.6nM_C30	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSYMYLA**WYQQKPGQAPRLLI Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYKSWPLT** FGQGTKVEIK (SEQ ID NO: 116)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSTYYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DS**WGQGTLVTVSS (SEQ ID NO: 76)
COMBO_ Rd4_0.6nM_C14	EIVLTQSPGTLSLSPGERATLSC**RAS** **QSVSALYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYYGWPLT** FGQGTKVEIK (SEQ ID NO: 117)	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSLPYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM** **DI**WGQGTLVTVSS (SEQ ID NO: 112)
COMBO_ Rd4_6nM_C07	EIVLTQSPGTLSLSPGERATLSC**RAS** **QPISSSYLA**WYQQKPGQAPRLLMY **DASIRAT**GIPDRFSGSGSGTDFTLTI	EVQLLESGGGLVQPGGSLRLSCAAS**G** **FTFSSY**PMSWVRQAPGKGLEWVS**AIG** **GSGGSLPYADSVKG**RFTISRDNSKNT

Binding Domain	Light Chain	Heavy Chain
	SRLEPEDFAVYYC**QQYQGWPLT**F GQGTKVEIK (SEQ ID NO: 119)	LYLQMNSLRAEDTAVYYCAR**YWPM AD**WGQGTLVTVSS (SEQ ID NO: 118)
COMBO_ Rd4_6nM _C02	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYEFWPLT** FGQGTKVEIK (SEQ ID NO: 121)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFSSY**AMNWVRQAPGKGLEWVS**AI SDSGGFVYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP MDS**WGQGTLVTVSS (SEQ ID NO: 120)
COMBO_ Rd4_0.6n M_C05	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSTYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYMSWPLT** FGQGTKVEIK (SEQ ID NO: 123)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFSSY**AMNWVRQAPGKGLEWVS**AI GGSGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP MSL**WGQGTLVTVSS (SEQ ID NO: 122)
COMBO_ Rd4_0.6n M_C17	EIVLTQSPGTLSLSPGERATLSC**RAS QGISSTYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYAYWPLT** FGQGTKVEIK (SEQ ID NO: 124)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFSSY**PMSWVRQAPGKGLEWVS**AIG GSGGSLPYADSVKG**RFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**YWPM DI**WGQGTLVTVSS (SEQ ID NO: 112)
COMBO_ Rd4_6nM _C22	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYQGWPLT** FGQGTKVEIK (SEQ ID NO: 126)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFSSY**AMNWVRQAPGKGLEWVS**AC LDSGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP MDS**WGQGTLVTVSS (SEQ ID NO: 125)
COMBO_ Rd4_0.6n M_C11	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSVRYLA**WYQQKPGQAPRLLM Y**DASIRAT**GIPDRFSGSGSGTDFTL TISRLEPEDFAVYYC**QQYGSWPIT**F GQGTKVEIK (SEQ ID NO: 128)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFSSY**PMSWVRQAPGKGLEWVS**AA LGSGGSTYYADSVKG**RFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**YWP MSL**WGQGTLVTVSS (SEQ ID NO: 127)
P6DY	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYPS**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYPYPPSFT**F GQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **DYSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA SGMDY**WGQGTLVTVSS (SEQ ID NO: 25)

Binding Domain	Light Chain	Heavy Chain
P6AP	EIVLTQSPGTLSLSPGERATLSC**RAS QLGSFYLA**WYQQKPGQAPRLLIY **GASSRAT**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYNYPPSFT**F GQGTKVEIK (SEQ ID NO: 80)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFGSY**AMTWVRQAPGKGLEWVSAI **SGSGGN**TFYADSVKGRFTISRDNSKN TLYLQMNSLRAEDTAVYYCAR**VSPIA APMDY**WGQGTLVTVSS (SEQ ID NO: 8)
Consensus	EIVLTQSPGTLSLSPGERATLSC $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$WYQ QKPGQAPRLLMY$X_{13}ASX_{14}RAX_{15}$GI PDRFSGSGSGTDFTLTISRLEPEDFA VYYC$X_{16}X_{17}$Y$X_{18}X_{19}$PPSFTFGQGTK VEIK, wherein X_1 is R, G, W, A, or C; X_2 is A, P, G, L, C, or S; X_3 is S, G, or R; X_4 is Q, C, E, V, or I; X_5 is S, P, G, A, R, or D; X_6 is V, G, I, or L; X_7 is S, E, D, P, or G; X_8 is S, P, F, A, M, E, V, N, D, or Y; X_9 is I, T, V, E, S, A, M, Q, Y, H, R, or F; X_{10} is Y or F; X_{11} is L, W, or P; X_{12} is A, S, or G, X_{13} is G or D; X_{14} is S or I; X_{15} is T or P; X_{16} is Q or K; X_{17} is H or Y; X_{18} is G, N, or P; and X_{19} is S, W, or Y (SEQ ID NO: 315); or EIVLTQSPGTLSLSPGERATLSC $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$WYQ QKPGQAPRLLMY$X_{13}ASX_{14}RAX_{15}$GI PDRFSGSGSGTDFTLTISRLEPEDFA VYYCQQY$X_{16}X_{17}X_{18}$PX_{19}FGQGTKV EIK, wherein X_1 is R, G, W, A, or C; X_2 is A, P, G, L, C, or S; X_3 is S, G, or R; X_4 is Q, C, E, V, or I; X_5 is S, L, P, G, A, R, or D; X_6 is V, G, or I; X_7 is S, E, D, or P; X_8 is S, P, F, A, M, E, V, N, D, or Y; X_9 is I, T, V, E, S, A, M, Q, Y, H,	EVQLLESGGGLVQPGGSLRLSCAASG FTFX$_1$SYX$_2$MX$_3$WVRQAPGKGLEWVS AX$_4X_5X_6X_7$GX$_8X_9X_{10}X_{11}$YADX$_{12}X_{13}$KGR FTISRDNSKNTLYLQMNSLRAEDTAV YYCARVSPIX$_{14}X_{15}X_{16}$MDYWGQGTLV TVSS, wherein X_1 is G or S, X_2 is A or P; X_3 is T, N, or S; X_4 is I, V, T, H, L, A, or C; X_5 is S, D, G, T, I, L, F, M, or V; X_6 is G, Y, L, H, D, A, S, or M; X_7 is S, Q, T, A, F, or W; X_8 is G or T; X_9 is N, S, P, Y, W, or F; X_{10} is S, T, I, L, T, A, R, V, K, G, or C; X_{11} is F, Y, P, W, H, or G; X_{12} is V, R, or L; X_{13} is G or T; X_{14} is A or Y; X_{15} is A or S; and X_{16} is G, Q, L, P, or E (SEQ ID NO: 313); or EVQLLESGGGLVQPGGSLRLSCAASG FTFX$_1$SYX$_2$MX$_3$WVRQAPGKGLEWVS AX$_4X_5X_6X_7$GX$_8X_9X_{10}X_{11}$YADX$_{12}X_{13}$KGR FTISRDNSKNTLYLQMNSLRAEDTAV YYCARYWPMX$_{14}X_{15}$WGQGTLVTVSS, wherein X_1 is G or S, X_2 is A or P; X_3 is T, N, or S; X_4 is I, V, T, H, L, A, or C; X_5 is S, D, G, T, I, L, F, M, or V; X_6 is G, Y, L, H, D, A, S, or M; X_7 is S, Q, T, A, F, or W; X_8 is G or T; X_9 is N, S, P, Y, W, or F; X_{10} is S, T, I, L, T, A, R, V, K, G, or C; X_{11} is F, Y, P, W, H, or G; X_{12} is V, R, or L; X_{13} is

Binding Domain	Light Chain	Heavy Chain
	or R; X_{10} is Y or F; X_{11} is L, W, or P; X_{12} is A, S, or G, X_{13} is G or D; X_{14} is S or I; X_{15} is T or P; X_{16} is G, Q, E, L, F, A, S, M, R, K, or Y; X_{17} is S, R, T, G, R, V, D, A, H, E, K, C, F, or Y; X_{18} is W, S, or F; and X_{19} is L or I (SEQ ID NO: 316)	G or T; X_{14} is D, S, T, or A; and X_{15} is I, S, L, P, or D (SEQ ID NO: 314)
P4G4	EIVLTQSPGTLSLSPGERATLSC**RAS QSVSSSYLA**WYQQKPGQAPRLLIY **GASSRAY**GIPDRFSGSGSGTDFTLTI SRLEPEDFAVYYC**QHYGSPPLFT**F GQGTKVEIK (SEQ ID NO: 401)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFSSY**AMSWVRQAPGKGLEWVSAI**S ASGGS**TYYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCAR**LSWSG AFDN**WGQGTLVTVSS (SEQ ID NO: 378)
P1A11	EIVLTQSPGTLSLSPGERATLSC**RAS QNVSSSYLA**WYQQKPGQAPRLLIY **GASYRAT**GIPDRFSGSGSGTDFTLT ISRLEPEDFAVYYC**QHYGSPPSFT**F GQGTKVEIK (SEQ ID NO: 379)	EVQLLESGGGLVQPGGSLRLSCAAS**G FTFRSY**AMSWVRQAPGKGLEWVSAI **SGSGGS**TFYADSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCAT**VGTSG AFGI**WGQGTLVTVSS (SEQ ID NO: 380)

[0052] Also provided herein are CDR portions of extracellular ligand-binding domains of CARs to BCMA (including Chothia, Kabat CDRs, and CDR contact regions). Determination of CDR regions is well within the skill of the art. It is understood that in some embodiments, CDRs can be a combination of the Kabat and Chothia CDR (also termed "combined CRs" or "extended CDRs"). In some embodiments, the CDRs are the Kabat CDRs. In other embodiments, the CDRs are the Chothia CDRs. In other words, in embodiments with more than one CDR, the CDRs may be any of Kabat, Chothia, combination CDRs, or combinations thereof. Table 2A and Table 2B provide examples of CDR sequences provided herein.

Table 2A

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
P6E01 For the following mAbs: P6E01/P6E01;L1.LGF/L3.KW/P6EO1; L1.LGF/L3.NY/P6E01; L1.GDF/L3.NY/P6E01; L3.KW/P6E01; L3.PY/P6E01; L3.NY/P6E01; L3.PY/L1.PS/P6E01; L3.PY/L1.AH/P6E01; L3.PY/L1.FF/P6E01; L3.PY/L1.PH/P6E01; L3.PY/L3.KY/P6E01; L3.PY/L3.KF/P6E01; and L3.PY/P6E01.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYADSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIASGMDY (SEQ ID NO: 134)
H3.AQ For the following mAbs: P6E01/H3.AQ; L1.LGF/L3.KW/H3.AQ; L1.LGF/L3.PY/H3.AQ	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYADSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIAAQMDY (SEQ ID NO: 135)
H3.AL For the following mAbs: L1.LGF/L3.KW/H3.AL; L1.LGF/L3.NY/H3.AL; and L1.GDF/L3.NY/H3.AL.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia);	AISGSGGNTFYADSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIAALMDY (SEQ ID NO: 136)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
	GFTFGSYAMT (SEQ ID NO: 131) (extended)		
H3.AP For the following mAbs: L1.LGF/L3.KW/H3.AP; L1.LGF/L3.PY/H3.AP; L1.LGF/L3NY/H3.AP; L1.GDF/L3.KW/H3.AP; L1.GDF/L3NY/H3.AP; P6AP.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYA DSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIAAPMDY (SEQ ID NO: 137)
H2.QR For the following mAbs: L3.PY/H2.QR; L3.PY/L1.PS/H2.QR; L3.PY/L1.AH/H2.QR; L3.PY/L1.FF/H2.QR; L3.PY/L1.PH/H2.QR; and L3.PY/L3.KY/H2.QR.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYA DQRKG (SEQ ID NO: 138) (Kabat) SGSGGN (SEQ ID NO:133) -(Chothia)	VSPIASGMDY (SEQ ID NO: 134)
H2.DY For the following mAbs: L3.PY/H2.DY; P6DY; L3.PY/L1.PS/H2.DY; L3.PY/L1.AH/H2.DY;	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia);	AIDYSGGNTFYA DSVKG (SEQ ID NO: 139) (Kabat)	VSPIASGMDY (SEQ ID NO: 134)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
L3.PY/L1.FF/H2.DY; L3.PY/L3.KY/H2.DY; and L3.PY/L3.KF/H2.DY.	GFTFGSYAMT (SEQ ID NO: 131) (extended)	DYSSGN (SEQ ID NO:140) -(Chothia)	
H2.YQ For the following mAbs: L3.PY/H2.YQ; L3.PY/L1.PS/H2.YQ; L3.PY/L1.AH/H2.YQ; L3.PY/L1.FF/H2.YQ; L3.PY/L3.KY/H2.YQ; and L3.PY/L3.KF/H2.YQ.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISYQGGNTFYA DSVKG (SEQ ID NO: 141) (Kabat) SYQGGN (SEQ ID NO:142) -(Chothia)	VSPIASGMDY (SEQ ID NO: 134)
H2.LT For the following mAbs: L3.PY/H2.LT; L3.PY/L1.PS/H2.LT; L3.PY/L1.AH/H2.LT; L3.PY/L1.FF/H2.LT; L3.PY/L3.KY/H2.LT; and L3.PY/L3.KF/H2.LT.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISLTGGNTFYA DSVKG (SEQ ID NO: 143) (Kabat) SLTGGN (SEQ ID NO:144) -(Chothia)	VSPIASGMDY (SEQ ID NO: 134)
H2.HA For the following mAbs: L3.PY/H2.HA; L3.PY/L1.AH/H2.HA; L3.PY/L1.FF/H2.HA; L3.PY/L1.PH/H2.HA; and L3.PY/L3.KY/H2.HA.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISHAGGNTFYA DSVKG (SEQ ID NO: 145) (Kabat) SHAGGN (SEQ ID NO:146) -(Chothia)	VSPIASGMDY (SEQ ID NO: 134)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
H2.QL For the following mAbs: L3.PY/H2.QL; L3.PY/L1.PS/H2.QL; L3.PY/L1.AH/H2.QL; L3.PY/L1.FF/H2.QL; L3.PY/L3.KY/H2.QL; and L3.PY/L3.KF/H2.QL.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYA DQLKG (SEQ ID NO: 147) (Kabat) SGSGGN (SEQ ID NO:133) -(Chothia)	VSPIASGMDY (SEQ ID NO: 134)
H3.YA For the following mAbs: L3.PY/H3.YA; L3.PY/L1.PS/H3.YA; L3.PY/L1.AH/H3.YA; L3.PY/L1.FF/H3.YA; L3.PY/L3.KY/H3.YA; and L3.PY/L3.KF/H3.YA.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYA DSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIYAGMDY (SEQ ID NO: 148)
H3.AE For the following mAbs: L3.PY/H3.AE; L3.PY/L1.AH/H3.AE; L3.PY/L1.FF/H3.AE; L3.PY/L1.PH/H3.AE; and L3.PY/L3.KF/H3.AE.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYA DSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIAAEMDY (SEQ ID NO: 149)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
H3.TAQ For the following mAbs: L3.PY/H3.TAQ; L3.PY/L1.PS/H3.TAQ; L3.PY/L1.AH/H3.TAQ; L3.PY/L1.FF/H3.TAQ; L3.PY/L1.PH/H3.TAQ; and L3.PY/L3.KF/H3.TAQ.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYA DSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIAAQMDY (SEQ ID NO: 135)
P5A2_VHVL and A02_Rd4_6nM_C03	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSTYYA DSVKG (SEQ ID NO: 153) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMDI (SEQ ID NO: 155)
COMBO_Rd4_0.6nM_C17; COMBO_Rd4_0.6nM_C14; COMBO_Rd4_0.6nM_C29; and COMBO_Rd4_0.6nM_C09	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLPYA DSVKG (SEQ ID NO: 158) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDI (SEQ ID NO: 155)
C01_Rd4_6nM_C04; C01_Rd4_0.6nM_C03; C01_Rd4_0.6nM_C06; COMBO_Rd4_0.6nM_C02; COMBO_Rd4_6nM_C21; C01_Rd4_6nM_C26; COMBO_Rd4_0.6nM_C19; C01_Rd4_6nM_C24; C01_Rd4_6nM_C20;	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLPYA DSVKG (SEQ ID NO: 158) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
C01_Rd4_0.6nM_C09; COMBO_Rd4_0.6nM_C21; C01_Rd4_0.6nM_C04_C27; C01_Rd4_0.6nM_C16; C01_Rd4_6nM_C10; COMBO_Rd4_0.6nM_C20			
P5C1_VHVL (PC1) and COMBO_Rd4_0.6nM_C30	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSTYYA DSVKG (SEQ ID NO: 162) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)
A02_Rd4_0.6nM_C06	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSAWYA DSVKG (SEQ ID NO: 163) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_0.6nM_C09	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSAWYA DSVKG (SEQ ID NO: 163) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_0.6nM_C16; A02_Rd4_6nM_C16 (P5A16)	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDFGGSTYYA DSVKG (SEQ ID NO: 165) (Kabat)	YWPMDI (SEQ ID NO: 155)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
		SDFGGS (SEQ ID NO: 166) (Chothia)	
A02_Rd4_6nM_C01	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AITASGGSTYYA DSVKG (SEQ ID NO: 167) (Kabat) TASGGS (SEQ ID NO: 168) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_6nM_C26	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSTYYA DSVKG (SEQ ID NO: 153) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_6nM_C25	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSRWYA DSVKG (SEQ ID NO: 169) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMTP (SEQ ID NO: 170)
A02_Rd4_6nM_C22	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AVLDSGGSTYY ADSVKG (SEQ ID NO: 171) (Kabat) LDSGGS (SEQ ID NO: 172) (Chothia)	YWPMTP (SEQ ID NO: 170)
A02_Rd4_6nM_C19	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia);	AISDSGGSRWYA DSVKG	YWPMSD (SEQ ID NO: 173)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
	GFTFSSYAMN (SEQ ID NO: 152) (extended)	(SEQ ID NO: 169) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	
A02_Rd4_0.6nM_C03	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSKWYA DSVKG (SEQ ID NO: 174) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_6nM_C07	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AIGGSGGSLPYA DSVKG(SEQ ID NO: 158) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)
A02_Rd4_6nM_C23	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSGWYA DSVKG (SEQ ID NO: 175)-(Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_0.6nM_C18	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AVLDSGGSTYY ADSVKG (SEQ ID NO: 171) (Kabat) LDSGGS (SEQ ID NO: 172) (Chothia)	YWPMSL (SEQ ID NO: 164)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
A02_Rd4_6nM_C10	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSCWYA DSVKG (SEQ ID NO: 176) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMTP (SEQ ID NO: 170)
A02_Rd4_6nM_C05	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AIFASGGSTYYA DSVKG (SEQ ID NO: 177) (Kabat) FASGGS (SEQ ID NO: 178) (Chothia)	YWPMTP (SEQ ID NO: 170)
A02_Rd4_0.6nM_C10	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISGWGGSLPYA DSVKG (SEQ ID NO: 304) (Kabat) SGWGGS (SEQ ID NO: 179) (Chothia)	YWPMDS (SEQ ID NO: 161)
A02_Rd4_6nM_C04	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AIMSSGGPLYYA DSVKG (SEQ ID NO: 180) (Kabat) MSSGGP (SEQ ID NO: 181) (Chothia)	YWPMAL (SEQ ID NO: 182)
A02_Rd4_0.6nM_C26	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AILMSGGSTYYA DSVKG (SEQ ID NO: 183) (Kabat) LMSGGS (SEQ ID NO: 184) (Chothia)	YWPMSL (SEQ ID NO: 164)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
A02_Rd4_0.6nM_C13	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGYRYYA DSVKG (SEQ ID NO: 185) (Kabat) SDSGGY (SEQ ID NO: 186) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_0.6nM_C01 (P5AC1)	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AILSSGGSTYYA DSVKG (SEQ ID NO: 187) (Kabat) LSSGGS (SEQ ID NO: 188) (Chothia)	YWPMDI (SEQ ID NO: 155)
A02_Rd4_6nM_C08	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AILDSGGSTYYA DSVKG (SEQ ID NO: 160) (Kabat) LDSGGS (SEQ ID NO: 172) (Chothia)	YWPMSP (SEQ ID NO: 189)
C01_Rd4_6nM_C12 (PC1C12)	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGWSYY ADSVKG (SEQ ID NO: 190) (Kabat) GGSGGW (SEQ ID NO: 191) (Chothia)	YWPMDS (SEQ ID NO: 161)
C01_Rd4_6nM_C09	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	ATVGSGGSIGYA DSVKG (SEQ ID NO: 192) (Kabat) VGSGGS (SEQ ID NO: 193) (Chothia)	YWPMDS (SEQ ID NO: 161)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
COMBO_Rd4_0.6nM_C22 (COM22)	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSRWYA DSVKG (SEQ ID NO: 169) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMDI (SEQ ID NO: 155)
COMBO_Rd4_0.6nM_C10	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSIHYA DSVKG (SEQ ID NO: 194) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_0.6nM_C04	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AHIGSGGSTYYA DSVKG (SEQ ID NO: 195) (Kabat) IGSGGS (SEQ ID NO: 196) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_0.6nM_C25	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSTYYA DSVKG (SEQ ID NO: 162) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDP (SEQ ID NO: 197)
COMBO_Rd4_6nM_C21	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLPYA DSVKG (SEQ ID NO: 158) (Kabat)	YWPMDS (SEQ ID NO: 161)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
		GGSGGS (SEQ ID NO: 159) (Chothia)	
COMBO_Rd4_6nM_C11	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLGYA DSVKG (SEQ ID NO: 198)(Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_6nM_C09	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIFASGGSTYYA DSVKG (SEQ ID NO: 177) (Kabat) FASGGS (SEQ ID NO: 178) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_6nM_C08	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGTWTYY ADSVKG (SEQ ID NO: 199) (Kabat) GGSGTW (SEQ ID NO: 200) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_0.6nM_C23	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	ALFGSGGSTYYA DSVKG (SEQ ID NO: 201) (Kabat) FGSGGS (SEQ ID NO: 202) (Chothia)	YWPMDS (SEQ ID NO: 161)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
COMBO_Rd4_0.6nM_C12	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AALGSGGSTYY ADSVKG (SEQ ID NO: 203) (Kabat) LGSGGS (SEQ ID NO: 204) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_6nM_C07	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLPYA DSVKG (SEQ ID NO: 158) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMAD (SEQ ID NO: 205)
COMBO_Rd4_6nM_C02	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGFVYYA DSVKG (SEQ ID NO: 206) (Kabat) SDSGGF (SEQ ID NO: 207) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_6nM_C05	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AIGGSGGSTYYA DSVKG (SEQ ID NO: 162) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMSL (SEQ ID NO: 164)
COMBO_Rd4_6nM_C22	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	ACLDSGGSTYYA DSVKG (SEQ ID NO: 208) (Kabat) LDSGGS (SEQ ID NO: 172) (Chothia)	YWPMDS (SEQ ID NO: 161)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
COMBO_Rd4_6nM_C11	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AALGSGGSTYY ADSVKG (SEQ ID NO: 203) (Chothia) LGSGGS (SEQ ID NO: 204) (Chothia)	YWPMSL (SEQ ID NO: 164)
Heavy chain consensus	SYX_1MX_2, wherein X_1 is A or P; and X_2 is T, N, or S (Kabat) (SEQ ID NO: 301) $GFTFX_1SY$, wherein X_1 is G or S (Chothia) (SEQ ID NO: 302) $GFTFX_1SYX_2MX_3$, wherein X_1 is G or S, X_2 is A or P; and X_3 is T, N, or S (SEQ ID NO: 303) (extended)	$AX_1X_2X_3X_4GX_5X_6X_7X_8YADX_9X_{10}KG$, wherein X_1 is I, V, T, H, L, A, or C; X_2 is S, D, G, T, I, L, F, M, or V; X_3 is G, Y, L, H, D, A, S, or M; X_4 is S, Q, T, A, F, or W; X_5 is G or T;X_6 is N, S, P, Y, W, or F; X_7 is S, T, I, L, T, A, R, V, K, G, or C; X_8 is F, Y, P, W, H, or G; X_9 is V, R, or L; and X_{10} is G or T (Kabat) (SEQ ID NO: 305) $X_1X_2X_3X_4X_5X_6$, wherein X_1 is S, V, I, D, G, T, L, F, or M; X_2 is G, Y, L, H, D, A, S, or M; X_3 is S, G, F, or W; X_4 is	$VSPIX_1X_2X_3MDY$, wherein X_1 is A or Y; X_2 is A or S; and X_3 is G, Q, L, P, or E (SEQ ID NO: 307) $YWPMX_1X_2$, wherein X_1 is D, S, T, or A; and X_2 is I, S, L, P, or D (SEQ ID NO: 308)

Heavy Chain			
Binding Domain	**CDRH1**	**CDRH2**	**CDRH3**
		G or S; X_5 is G or T; and X_6 is N, S, P, Y, or W (Chothia) (SEQ ID NO: 306)	
P4G4	SYAMS (SEQ ID NO: 381) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMS (SEQ ID NO: 382) (extended)	SASGGS (SEQ ID NO: 383) (Chothia) AISASGGSTYYA DSVKG (SEQ ID NO: 384) (Kabat)	LSWSGAFDN (SEQ ID NO: 385)
P1A11	SYAMS (SEQ ID NO: 386) (Kabat); GFTFRSY (SEQ ID NO: 387) GFTFRSYAMS (SEQ ID NO: 388)	SGSGGS (SEQ ID NO: 389) (Chothia) AISGSGGSTFYA DSVKG (SEQ ID NO: 390) (Kabat)	VGTSGAFGI (SEQ ID NO: 391)

Table 2B

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
P6E01 For the following mAbs: P6E01/P6E01; and P6E01/H3.AQ.	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	QHYGSPPSFT (SEQ ID NO: 211)
L1.LGF/L3.KW For the following mAbs: L1.LGF/L3.KW/P6E01; L1.LGF/L3.KW/H3.AL; L1.LGF/L3.KW/H3.AP; and L1.LGF/L3.KW/H3.AQ	RASQSLGSFYLA (SEQ ID NO: 212)	GASSRAT (SEQ ID NO: 210)	KHYGWPPSFT (SEQ ID NO: 213)
L1.LGF/L3.NY For the following mAbs: L1.LGF/L3.NY/P6E01; L1.LGF/L3.NY/H3.AL; L1.LGF/L3.NY/H3.AP; and L1.LGF/L3.NY/H3AQ	RASQSLGSFYLA (SEQ ID NO: 212)	GASSRAT (SEQ ID NO: 210)	QHYNYPPSFT (SEQ ID NO: 214)
L1.GDF/L3.NY For the following mAbs: L1.GDF/L3.NY/P6E01; L1.GDF/L3.NY/H3.AL; L1.GDF/L3.NY/H3.AP; and L1.GDF/L3.NY/H3.AQ	RASQSVGDFYLA (SEQ ID NO: 215)	GASSRAT (SEQ ID NO: 210)	QHYNYPPSFT (SEQ ID NO: 214)
L1.LGF/L3.PY For the following mAbs: L1.LGF/L3.PY/H3.AP; and L1.LGF/L3.PY/H3.AQ	RASQSLGSFYLA (SEQ ID NO: 212)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
L1.GDF /L3.KW For the following mAbs: L1.GDF /L3.KW/H3.AL; L1.GDF /L3.KW/H3.AP;	RASQSVGDFYLA (SEQ ID NO: 215)	GASSRAT (SEQ ID NO: 210)	KHYGWPPSFT (SEQ ID NO: 213)

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
and L1.GDF /L3.KW/H3.AQ			
L1.GDF /L3.PY/H3.AQ	RASQSVGDFYLA (SEQ ID NO: 215)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
L3.KW/P6E01	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	KHYGWPPSFT (SEQ ID NO: 213)
L3.PY For the following mAbs: L3.PY/P6E01; L3.PY/H2.QR; L3.PY/H2.DY; L3.PY/H2.YQ; L3.PY/H2.LT; L3.PY/H2.HA; L3.PY/H2.QL; L3.PY/H3.YA; L3.PY/H3.AE; L3.PY/H3.AQ; L3.PY/H3.TAQ	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
L3.NY/P6E01	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	QHYNYPPSFT (SEQ ID NO: 214)
L3.PY/L1.PS For the following mAbs: L3.PY/L1.PS/P6E01; P6DY; L3.PY/L1.PS/H2.QR; L3.PY/L1.PS/H2.DY;	RASQSVSSSYPS (SEQ ID NO: 217)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
L3.PY/L1.PS/H2.YQ; L3.PY/L1.PS/H2.LT; L3.PY/L1.PS/H2.HA; L3.PY/L1.PS/H2.QL; L3.PY/L1.PS/H3.YA; L3.PY/L1.PS/H3.AE; L3.PY/L1.PS/H3.AQ; L3.PY/L1.PS/H3.TAQ;			
L3.PY/L1.AH For the following mAbs: L3.PY/L1.AH/P6E01; L3.PY/L1.AH/H2.QR; L3.PY/L1.AH/H2.DY; L3.PY/L1.AH/H2.YQ; L3.PY/L1.AH/H2.LT; L3.PY/L1.AH/H2.HA; L3.PY/L1.AH/H2.QL; L3.PY/L1.AH/H3.YA; L3.PY/L1.AH/H3.AE; L3.PY/L1.AH/H3.AQ; L3.PY/L1.AH/H3.TAQ	RASQSVSAHYLA (SEQ ID NO: 218)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
L3.PY/L1.FF For the following mAbs: L3.PY/L1.FF/P6E01; L3.PY/L1.FF/H2.QR; L3.PY/L1.FF/H2.DY; L3.PY/L1.FF/H2.YQ; L3.PY/L1.FF/H2.LT; L3.PY/L1.FF/H2.HA;	RASQSVSSFFLA (SEQ ID NO: 219)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
L3.PY/L1.FF/H2.QL; L3.PY/L1.FF/H3.YA; L3.PY/L1.FF/H3.AE; L3.PY/L1.FF/H3.AQ; and L3.PY/L1.FF/H3.TAQ			
L3.PY/L1.PH For the following mAbs: L3.PY/L1.PH/P6E01; L3.PY/L1.PH/H2.QR; L3.PY/L1.PH/H2.HA; L3.PY/L1.PH/H3.AE; L3.PY/L1.PH/H3.AQ; and L3.PY/L1.PH/H3.TAQ	RASQSVSPHYLA (SEQ ID NO: 415)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
L3.PY/L3.KY For the following mAbs: L3.PY/L3.KY/P6E01; L3.PY/L3.KY/H2.QR; L3.PY/L3.KY/H2.DY; L3.PY/L3.KY/H2.YQ; L3.PY/L3.KY/H2.LT; L3.PY/L3.KY/H2.HA; L3.PY/L3.KY/H2.QL; L3.PY/L3.KY/H3.YA; and L3.PY/L3.KY/H3.TAQ	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	KYYPYPPSFT (SEQ ID NO: 220)
L3.PY/L3.KF For the following mAbs: L3.PY/L3.KF/H2.DY; L3.PY/L3.KF/H2.YQ; L3.PY/L3.KF/H2.LT;	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	KFYPYPPSFT (SEQ ID NO: 416)

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
L3.PY/L3.KF/H2.QL; L3.PY/L3.KF/H3.YA; L3.PY/L3.KF/H3.AE; L3.PY/L3.KF/H3.AQ; and L3.PY/L3.KF/H3.TAQ			
P5A2_VHVL (P5A)	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYGSWPLT (SEQ ID NO: 222)
A02_Rd4_0.6nM_C06	RASQSVSVlYLA (SEQ ID NO: 223)	DASIRAT (SEQ ID NO: 221)	QQYQRWPLT (SEQ ID NO: 224)
A02_Rd4_0.6nM_C09; COMBO_Rd_0.6nM_C29; and COMBO_Rd4_0.6nM_C21	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
A02_Rd4_6nM_C16 (P5AC16)	RASQSVSDlYLA (SEQ ID NO: 226)	DASIRAT (SEQ ID NO: 221)	QQYQTWPLT (SEQ ID NO: 227)
A02_Rd4_6nM_C03	RASQSVSNlYLA (SEQ ID NO: 228)	DASIRAT (SEQ ID NO: 221)	QQYQGWPLT (SEQ ID NO: 229)
A02_Rd4_6nM_C01	RASQSVSAYYLA (SEQ ID NO: 230)	DASIRAT (SEQ ID NO: 221)	QQYERWPLT (SEQ ID NO: 231)
A02_Rd4_6nM_C26	RASQSVSSlYLA (SEQ ID NO: 232)	DASIRAT (SEQ ID NO: 221)	QQYQVWPLT (SEQ ID NO: 233)
A02_Rd4_6nM_C25	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYLDWPLT

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
			(SEQ ID NO: 234)
A02_Rd4_6nM_C22	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQVWPLT (SEQ ID NO: 233)
A02_Rd4_6nM_C19	RASQSVSVlYLA (SEQ ID NO: 223)	DASIRAT (SEQ ID NO: 221)	QQYLAWPLT (SEQ ID NO: 236)
A02_Rd4_0.6nM_C03	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYFTWPLT (SEQ ID NO: 237)
A02_Rd4_6nM_C07	RASQSVSPYYLA (SEQ ID NO: 238)	DASIRAT (SEQ ID NO: 221)	QQYERWPLT (SEQ ID NO: 231)
A02_Rd4_6nM_C23	RASQSVSVEYLA (SEQ ID NO: 239)	DASIRAT (SEQ ID NO: 221)	QQYARWPLT (SEQ ID NO: 240)
A02_Rd4_0.6nM_C18	RASQSVSElYLA (SEQ ID NO: 241)	DASIRAT (SEQ ID NO: 221)	QQYFGWPLT (SEQ ID NO: 242)
A02_Rd4_6nM_C10	RASQSVEMSYLA (SEQ ID NO: 243)	DASIRAT (SEQ ID NO: 221)	QQYAHWPLT (SEQ ID NO: 244)
A02_Rd4_6nM_C05	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQRWPLT (SEQ ID NO: 224)
A02_Rd4_0.6nM_C10	RASQSVSAQYLA (SEQ ID NO: 245)	DASIRAT (SEQ ID NO: 221)	QQYQRWPLT (SEQ ID NO: 224)
A02_Rd4_6nM_C04	RASQSVSAlYLA	DASIRAT	QQYQVWPLT

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
	(SEQ ID NO: 235)	(SEQ ID NO: 221)	(SEQ ID NO: 233)
A02_Rd4_0.6nM_C26	GPSQSVSSSYLA (SEQ ID NO: 246)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
A02_Rd4_0.6nM_C13	RASQSVSSSYWA (SEQ ID NO: 247)	DASIRAT (SEQ ID NO: 221)	QQYESWPLT (SEQ ID NO: 248)
A02_Rd4_0.6nM_C01 (P5AC1)	RGGQSVSSSYLA (SEQ ID NO: 249)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
A02_Rd4_6nM_C08	RASQSVSFlYLA (SEQ ID NO: 250)	DASIRAT (SEQ ID NO: 221)	QQYGSWPLT (SEQ ID NO: 222)
P5C1_VHVL (PC1)	RASQSVSSTYLA (SEQ ID NO: 251)	DASSRAP (SEQ ID NO: 252)	QQYSTSPLT (SEQ ID NO: 253)
C01_Rd4_6nM_C24	RASQSVSPEYLA (SEQ ID NO: 254)	DASSRAP (SEQ ID NO: 252)	QQYSVWPLT (SEQ ID NO: 255)
C01_Rd4_6nM_C26	RASQSVSAlYLA (SEQ ID NO: 235)	DASSRAP (SEQ ID NO: 252)	QQYSAWPLT (SEQ ID NO: 256)
C01_Rd4_6nM_C10	RASQSVSSVYLA (SEQ ID NO: 257)	DASSRAP (SEQ ID NO: 252)	QQYSTWPLT (SEQ ID NO: 258)
C01_Rd4_0.6nM_C27	RASQSVSSTYLA (SEQ ID NO: 251)	DASSRAP (SEQ ID NO: 252)	QQYSRWPLT (SEQ ID NO: 259)
C01_Rd4_6nM_C20	RASQSVSPlYLA	DASSRAP	QQYSAFPLT

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
	(SEQ ID NO: 260)	(SEQ ID NO: 252)	(SEQ ID NO: 261)
C01_Rd4_6nM_C12 (PC1C12)	WLSQSVSSTYLA (SEQ ID NO: 262)	DASSRAP (SEQ ID NO: 252)	QQYSEWPLT (SEQ ID NO: 263)
C01_Rd4_0.6nM_C16	RASQSVSSTYLA (SEQ ID NO: 251)	DASSRAP (SEQ ID NO: 252)	QQYSSWPLT (SEQ ID NO: 264)
C01_Rd4_0.6nM_C09	RASQSVSSIFLA (SEQ ID NO: 265)	DASSRAP (SEQ ID NO: 252)	QQYSAWPLT (SEQ ID NO: 256)
C01_Rd4_6nM_C09	ACSQSVSSTYLA (SEQ ID NO: 266)	DASSRAP (SEQ ID NO: 252)	QQYSAWPLT (SEQ ID NO: 256)
C01_Rd4_0.6nM_C03	RASCDVSSTYLA (SEQ ID NO: 267)	DASSRAP (SEQ ID NO: 252)	QQYMRSPLT (SEQ ID NO: 268)
C01_Rd4_0.6nM_C06	RASEAVPSTYLA (SEQ ID NO: 269)	DASSRAP (SEQ ID NO: 252)	QQYSAFPLT (SEQ ID NO: 261)
C01_Rd4_0.6nM_C04	CSSQSVSSTYLA (SEQ ID NO: 270)	DASSRAP (SEQ ID NO: 252)	QQYSAFPLT (SEQ ID NO: 261)
COMBO_Rd4_0.6nM_C22 (COM22)	RASVRVSSTYLA (SEQ ID NO: 271)	DASIRAT (SEQ ID NO: 221)	QQYMKWPLT (SEQ ID NO: 272)
COMBO_Rd4_6nM_C21	RASQSVSAAYLA (SEQ ID NO: 273)	DASIRAT (SEQ ID NO: 221)	QQYMCWPLT (SEQ ID NO: 274)
COMBO_Rd4_6nM_C10	RASQSVSSSYWG	DASIRAT	QQYQCWPLT

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
	(SEQ ID NO: 275)	(SEQ ID NO: 221)	(SEQ ID NO: 276)
COMBO_Rd4_0.6nM_C04	RASQSVSSTYLA (SEQ ID NO: 251)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
COMBO_Rd4_6nM_C25	RASQSVSSPYLA (SEQ ID NO: 277)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
COMBO_Rd4_6nM_C11	RASQSVSPlYLA (SEQ ID NO: 260)	DASIRAT (SEQ ID NO: 221)	QQYKAWPLT (SEQ ID NO: 278)
COMBO_Rd4_0.6nM_C20	RASQSVSYLYLA (SEQ ID NO: 279)	DASIRAT (SEQ ID NO: 221)	QQYMEWPLT (SEQ ID NO: 280)
COMBO_Rd4_6nM_C09	RASQSVSAQYLA (SEQ ID NO: 245)	DASIRAT (SEQ ID NO: 221)	QQYQAWPLT (SEQ ID NO: 281)
COMBO_Rd4_6nM_C08	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQKWPLT (SEQ ID NO: 282)
COMBO_Rd4_0.6nM_C19	RASQSVSAVYLA (SEQ ID NO: 283)	DASIRAT (SEQ ID NO: 221)	QQYRAWPLT (SEQ ID NO: 284)
COMBO_Rd4_0.6nM_C02	RASIAVSSTYLA (SEQ ID NO: 285)	DASIRAT (SEQ ID NO: 221)	QQYMVWPLT (SEQ ID NO: 286)
COMBO_Rd4_0.6nM_C23	RPRQSVSSSYLA (SEQ ID NO: 287)	DASIRAT (SEQ ID NO: 221)	QQYQDWPLT (SEQ ID NO: 288)
COMBO_Rd4_0.6nM_C09	RASQSVSSTYLA	DASIRAT	QQYQEWPLT

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
	(SEQ ID NO: 251)	(SEQ ID NO: 221)	(SEQ ID NO: 289)
COMBO_Rd4_6nM_C12	RASQSVSASYLA (SEQ ID NO: 290)	DASIRAT (SEQ ID NO: 221)	QQYMSWPLT (SEQ ID NO: 291)
COMBO_Rd4_0.6nM_C30	RASQSVSYMYLA (SEQ ID NO: 292)	DASIRAT (SEQ ID NO: 221)	QQYKSWPLT (SEQ ID NO: 293)
COMBO_Rd4_0.6nM_C14	RASQSVSAlYLA (SEQ ID NO: 235)	DASIRAT (SEQ ID NO: 221)	QQYYGWPLT (SEQ ID NO: 294)
COMBO_Rd4_6nM_C07	RASQPISSSYLA (SEQ ID NO: 295)	DASIRAT (SEQ ID NO: 221)	QQYQGWPLT (SEQ ID NO: 229)
COMBO_Rd4_6nM_C02	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYEFWPLT (SEQ ID NO: 296)
COMBO_Rd4_0.6nM_C05	RASQSVSSTYLA (SEQ ID NO: 251)	DASIRAT (SEQ ID NO: 221)	QQYMSWPLT (SEQ ID NO: 291)
COMBO_Rd4_0.6nM_C17	RASQGISSTYLA (SEQ ID NO: 297)	DASIRAT (SEQ ID NO: 221)	QQYAYWPLT (SEQ ID NO: 298)
COMBO_Rd4_6nM_C22	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQGWPLT (SEQ ID NO: 229)
COMBO_Rd4_0.6nM_C11	RASQSVSVRYLA (SEQ ID NO: 299)	DASIRAT (SEQ ID NO: 221)	QQYGSWPIT (SEQ ID NO: 300)

Light Chain			
Binding Domain	**CDRL1**	**CDRL2**	**CDRL3**
Light chain consensus	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$, wherein X_1 is R, G, W, A, or C; X_2 is A, P, G, L, C, or S; X_3 is S, G, or R; X_4 is Q, C, E, V, or I; X_5 is S, P, G, A, R, or D; X_6 is V, G, I, or L; X_7 is S, E, D, P, or G; X_8 is S, P, F, A, M, E, V, N, D, or Y; X_9 is I, T, V, E, F S, A, M, Q, Y, H, or R; X_{10} is Y or F; X_{11} is L, W, or P; and X_{12} is A, S, or G (SEQ ID NO: 309)	$X_1ASX_2RAX_3$, wherein X_1 is G or D; X_2 is S or I; and X_3 is T or P (SEQ ID NO: 310)	$X_1X_2YX_3X_4PPSFT$, wherein X_1 is Q or K; X_2 is H or Y; X_3 is G, N, or P; and X_4 is S, W, or Y (SEQ ID NO: 311) $QQYX_1X_2X_3PX_4T$, wherein X_1 is G, Q, E, L, F, A, S, M, K, R, or Y; X_2 is S, R, T, G, V, F, Y, D, A, H, V, E, K, or C; X_3 is W, F, or S; and X_4 is L or I (SEQ ID NO: 312)
P4G4	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAY (SEQ ID NO: 392)	QHYGSPPLFT (SEQ ID NO: 393)
P1A11	RASQNVSSSYLA (SEQ ID NO: 417)	GASYRAT (SEQ ID NO: 395)	QHYGSPPSFT (SEQ ID NO: 211)
P6AP	RASQLGSFYLA (SEQ ID NO: 377)	GASSRAT (SEQ ID NO: 210)	QHYNYPPSFT (SEQ ID NO: 214)

[0053] In some embodiments, the BCMA CAR comprises an extracellular ligand-binding domain, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a single chain Fv fragment (scFv) comprising a heavy chain variable (VH) region comprising three complementarity determining regions (CDRs)

comprising the sequences shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising three CDRs comprising the sequences shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain.

[0054] In some embodiments, the extracellular binding region of the BCMA CAR comprises a VH region that comprises the amino acid sequence shown in SEQ ID NO: 112 and the VL region comprises the amino acid sequence shown in SEQ ID NO: 38.

[0055] In some embodiments, the extracellular binding region of the BCMA CAR comprises a VH region that comprises the amino acid sequence shown in SEQ ID NO: 33 and the VL region comprises the amino acid sequence shown in SEQ ID NO: 34.

[0056] In some embodiments, the extracellular binding region of the BCMA CAR comprises a VH region that comprises a VH CDR1 comprising the amino acid sequence shown in SEQ ID NO: 150, 151, or 152; a VH CDR2 comprising the amino acid sequence shown in SEQ ID NO: 153 or 154; and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 155; and comprises a VL region comprising a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 222.

[0057] In some embodiments, the extracellular binding region of the BCMA CAR comprises a VH region that comprises a VH CDR1 comprising the amino acid sequence shown in SEQ ID NO: 151, 156, or 157; a VH CDR2 comprising the amino acid sequence shown in SEQ ID NO: 158 or 159; and a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 155; and comprises a VL region comprising a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 225.

[0058] The binding affinity (K_D) of the BCMA specific CAR as described herein to BCMA (such as human BCMA (e.g., (SEQ ID NO: 354) can be about 0.002 to about 6500 nM. In

some embodiments, the binding affinity is about any of 6500 nm, 6000 nm, 5986 nm, 5567 nm, 5500 nm, 4500 nm, 4000 nm, 3500 nm, 3000 nm, 2500 nm, 2134 nm, 2000 nm, 1500 nm, 1000 nm, 750 nm, 500 nm, 400 nm, 300 nm, 250 nm, 200 nM, 193 nM, 100 nM, 90 nM, 50 nM, 45 nM, 40 nM, 35 nM, 30 nM, 25 nM, 20 nM, 19 nm, 18 nm, 17 nm, 16 nm, 15 nM, 10 nM, 8 nM, 7.5 nM, 7 nM, 6.5 nM, 6 nM, 5.5 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 0.5 nM, 0.3 nM, 0.1 nM, 0.01 nM, or 0.002 nM. In some embodiments, the binding affinity is less than about any of 6500 nm, 6000 nm, 5500 nm, 5000 nm, 4000 nm, 3000 nm, 2000 nm, 1000 nm, 900 nm, 800 nm, 250 nM, 200 nM, 100 nM, 50 nM, 30 nM, 20 nM, 10 nM, 7.5 nM, 7 nM, 6.5 nM, 6 nM, 5 nM, 4.5 nM, 4 nM, 3.5 nM, 3 nM, 2.5 nM, 2 nM, 1.5 nM, 1 nM, or 0.5 nM.

[0059] The intracellular signaling domain of a CAR according to the disclosure is responsible for intracellular signaling following the binding of extracellular ligand-binding domain to the target resulting in the activation of the immune cell and immune response. The intracellular signaling domain has the ability to activate of at least one of the normal effector functions of the immune cell in which the CAR is expressed. For example, the effector function of a T cell can be a cytolytic activity or helper activity including the secretion of cytokines.

[0060] In some embodiments, an intracellular signaling domain for use in a CAR can be the cytoplasmic sequences of, for example without limitation, the T cell receptor and co-receptors that act in concert to initiate signal transduction following antigen receptor engagement, as well as any derivative or variant of these sequences and any synthetic sequence that has the same functional capability. Intracellular signaling domains comprise two distinct classes of cytoplasmic signaling sequences: those that initiate antigen-dependent primary activation, and those that act in an antigen- independent manner to provide a secondary or co-stimulatory signal. Primary cytoplasmic signaling sequences can comprise signaling motifs which are known as immunoreceptor tyrosine-based activation motifs of ITAMs. ITAMs are well defined signaling motifs found in the intracytoplasmic tail of a variety of receptors that serve as binding sites for syk/zap70 class tyrosine kinases. Examples of ITAM used in the disclosure can include as non limiting examples those derived from TCRζ, FcRγ, FcRβ, FcRε, CD3γ, CD3δ, CD3ε, CD5, CD22, CD79a, CD79b and CD66d. In some embodiments, the intracellular signaling domain of the CAR can comprise the CD3ζ signaling domain which has amino acid sequence with at least about

70%, preferably at least 80%, more preferably at least 90%, 95%, 97%, or 99% sequence identity with an amino acid sequence shown in SEQ. ID NO: 324. In some embodiments the intracellular signaling domain of the CAR of the disclosure comprises a domain of a co-stimulatory molecule.

5 **[0061]** In some embodiments, the intracellular signaling domain of a CAR of the disclosure comprises a part of co-stimulatory molecule selected from the group consisting of fragment of 41BB (GenBank: AAA53133.) and CD28 (NP_006130.1). In some embodiments, the intracellular signaling domain of the CAR of the disclosure comprises amino acid sequence which comprises at least 70%, preferably at least 80%, more
10 preferably at least 90%, 95%, 97%, or 99% sequence identity with an amino acid sequence shown in SEQ. ID NO: 323 and SEQ. ID NO: 327.

[0062] CARs are expressed on the surface membrane of the cell. Thus, the CAR can comprise a transmembrane domain. Suitable transmembrane domains for a CAR disclosed herein have the ability to (a) be expressed at the surface of a cell, preferably an immune cell
15 such as, for example without limitation, lymphocyte cells or Natural killer (NK) cells, and (b) interact with the ligand-binding domain and intracellular signaling domain for directing cellular response of immune cell against a predefined target cell. The transmembrane domain can be derived either from a natural or from a synthetic source. The transmembrane domain can be derived from any membrane-bound or transmembrane protein. As non-
20 limiting examples, the transmembrane polypeptide can be a subunit of the T cell receptor such as α, β, γ or δ, polypeptide constituting CD3 complex, IL-2 receptor p55 (a chain), p75 (β chain) or γ chain, subunit chain of Fc receptors, in particular Fcγ receptor III or CD proteins. Alternatively, the transmembrane domain can be synthetic and can comprise predominantly hydrophobic residues such as leucine and valine. In some embodiments said
25 transmembrane domain is derived from the human CD8α chain (e.g., NP_001139345.1). The transmembrane domain can further comprise a stalk domain between the extracellular ligand-binding domain and said transmembrane domain. A stalk domain may comprise up to 300 amino acids, preferably 10 to 100 amino acids and most preferably 25 to 50 amino acids. Stalk region may be derived from all or part of naturally occurring molecules, such as
30 from all or part of the extracellular region of CD8, CD4, or CD28, or from all or part of an antibody constant region. Alternatively the stalk domain may be a synthetic sequence that corresponds to a naturally occurring stalk sequence, or may be an entirely synthetic stalk

sequence. In some embodiments said stalk domain is a part of human CD8α chain (e.g., NP_001139345.1). In another particular embodiment, said transmembrane and hinge domains comprise a part of human CD8α chain, preferably which comprises at least 70%, preferably at least 80%, more preferably at least 90%, 95% 97%, or 99% sequence identity with amino acid sequence selected from the group consisting of SEQ ID NO: 318. In some embodiments, CARs disclosed herein can comprise an extracellular ligand-binding domain that specifically binds BCMA, CD8α human hinge and transmembrane domains, the CD3ζ signaling domain, and 4-1BB signaling domain.

[0063] Table 3 provides exemplary sequences of domains which can be used in the CARs disclosed herein.

Table 3: Exemplary sequences of CAR Components

Domain	Amino Acid Sequence	SEQ ID NO:
CD8α signal peptide	MALPVTALLLPLALLLHAARP	318
FcγRIIIα hinge	GLAVSTISSFFPPGYQ	319
CD8α hinge	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD	320
IgG1 hinge	EPKSPDKTHTCPPCPAPPVAGPSVFLFPPKPKDTLMIARTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK	321
CD8α transmembrane (TM) domain	IYIWAPLAGTCGVLLLSLVITLYC	322
41BB intracellular signaling domain (ISD)	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL	323

Domain	Amino Acid Sequence	SEQ ID NO:
CD3ζ intracellular signaling domain (ISD)	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR	324
FcεRI α-TM-IC (FcεRI α chain transmembrane and intracellular domain)	FFIPLLVVILFAVDTGLFISTQQQVTFLLKIKRTRKGFRLLNPHPKPNPKNN	325
FcεRIβ-ΔITAM (FcεRI β chain without ITAM)	MDTESNRRANLALPQEPSSVPAFEVLEISPQEVSSGRLLKSASSPPLHTWLTVLKKEQEFLGVTQILTAMICLCFGTVVCSVLDISHIEGDIFSSFKAGYPFWGAIFFSISGMLSIISERRNATYLVRGSLGANTASSIAGGTGITILIINLKKSLAYIHIHSCQKFFETKCFMASFSTEIVVMMLFLTILGLGSAVSLTICGAGEELKGNKVPE	326
41BB-IC (41BB co-stimulatory domain)	KRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL	327
CD28-IC (CD28 co-stimulatory domain)	RSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS	328
FcεRIγ-SP (signal peptide)	MIPAVVLLLLLLVEQAAA	329
FcεRI γ-ΔITAM (FcεRI γ chain without ITAM)	LGEPQLCYILDAILFLYGIVLTLLYCRLKIQVRKAAITSYEKS	330
GSG-P2A (GSG-P2A ribosomal skip polypeptide)	GSGATNFSLLKQAGDVEENPGP	331

Domain	Amino Acid Sequence	SEQ ID NO:
GSG-T2A (GSG-T2A ribosomal skip polypeptide)	GSGEGRGSLLTCGDVEENPGP	332

[0064] In another aspect, the disclosure provides polynucleotides encoding any of the CARs and polypeptides described herein. Polynucleotides can be made and expressed by procedures known in the art.

[0065] In another aspect, the disclosure provides compositions (such as a pharmaceutical compositions) comprising any of the cells of the disclosure.

II. Engineered Immune Cells

[0066] The disclosure provides engineered immune cells comprising any of the BCMA CAR polynucleotides described herein. In some embodiments, the BCMA CAR is introduced into an immune cell with a lentiviral vector. In some embodiments, the lentiviral vector is a self-inactivating lentiviral vector that integrates into the recipient immune cell. In some embodiments, the BCMA CAR is introduced into an immune cell as a transgene via a plasmid vector. In some embodiments, the plasmid vector can also contain, for example, a selection marker which provides for identification and/or selection of cells which received the vector. In some embodiments the CAR can be introduced into the immune cell using non-viral methods.

[0067] An exemplary vector construct is show in FIG. 21.

[0068] Methods of generating engineered immune cells expressing any of the BCMA CARs provided herein is described in WO/2016/166630, incorporated by reference in its entirety.

[0069] Provided herein are isolated immune cells obtained according to any one of the methods described above. Any immune cell capable of expressing heterologous DNAs can be used for the purpose of expressing the CAR of interest. In some embodiments, the immune cell is a T cell. In some embodiments, an immune cell can be derived from, for

example without limitation, a stem cell. The stem cells can be adult stem cells, non-human embryonic stem cells, more particularly non-human stem cells, cord blood stem cells, progenitor cells, bone marrow stem cells, induced pluripotent stem cells, totipotent stem cells or hematopoietic stem cells. Representative human cells are CD34+ cells. The isolated cell can also be a dendritic cell, killer dendritic cell, a mast cell, a NK-cell, a B-cell or a T cell selected from the group consisting of inflammatory T-lymphocytes, cytotoxic T-lymphocytes, regulatory T-lymphocytes or helper T-lymphocytes. I n some embodiments, the cell can be derived from the group consisting of CD4+ T-lymphocytes and CD8+ T-lymphocytes.

[0070] In some embodiments, an isolated cell according to the present disclosure comprises one inactivated gene selected from the group consisting of CD52, GR, PD-1, CTLA-4, LAG3, Tim3, BTLA, BY55, TIGIT, B7H5, LAIR1, SIGLEC10, 2B4, HLA, TCRα and TCRβ and/or expresses a CAR, a multi-chain CAR and/or a pTα transgene. In some embodiments, an isolated cell comprises polynucleotides encoding polypeptides comprising a multi-chain CAR. In some embodiments, the isolated cell according to the present disclosure comprises two inactivated genes selected from the group consisting of: CD52 and GR, CD52 and TCRα, CDR52 and TCRβ, GR and TCRα, GR and TCRβ, TCRα and TCRβ, PD-1 and TCRα, PD-1 and TCRβ, CTLA-4 and TCRα, CTLA-4 and TCRβ, LAG3 and TCRα, LAG3 and TCRβ, Tim3 and TCRα, Tim3 and TCRβ, BTLA and TCRα, BTLA and TCRβ, BY55 and TCRα, BY55 and TCRβ, TIGIT and TCRα, TIGIT and TCRβ, B7H5 and TCRα, B7H5 and TCRβ, LAIR1 and TCRα, LAIR1 and TCRβ, SIGLEC10 and TCRα, SIGLEC10 and TCRβ, 2B4 and TCRα, 2B4 and TCRβ and/or expresses a CAR, a multi-chain CAR and a pTα transgene.

[0071] Gene inactivation can be carried out by methods practiced by those with skill in the art. The methods include, but are not limited to gene inactivation by use of zinc fingers, TALEN®s, and CRISPR/Cas-based system.

[0072] In some embodiments, the BCMA CAR containing immune cell has an inactivated CD52 gene. In some embodiments only one copy of the CD52 gene is inactivated.

[0073] In some embodiments, the BCMA CAR containing immune cell has an inactivated TCRα gene.

[0074] In some embodiments, the BCMA CAR containing immune cell has an inactivated TCRβ gene.

[0075] In some embodiments, TALEN® is used for gene inactivation. In such embodiments, the efficiency of gene inactivation with TALEN® is not 100%, and resulting TCRαβ-negative T-cells are enriched by depleting residual TCRαβ-positive T cells before cryopreservation. However, CD52-negative cells are not purified, resulting in a cell product with varying frequencies of CD52-negative cells, typically between 60-80%. Accordingly in some embodiments, the genotype of the BCMA CAR-T cells of the disclosure is BCMA-CAR+_TCRαβ-_CD52+/- T-cells

[0076] In some embodiments, TCR is rendered not functional in the cells according to the disclosure by inactivating TCRα gene and/or TCRβ gene(s). In some embodiments, a method to obtain modified cells derived from an individual is provided, wherein the cells can proliferate independently of the major histocompatibility complex (MHC) signaling pathway. Modified cells, which can proliferate independently of the MHC signaling pathway, susceptible to be obtained by this method are encompassed in the scope of the present disclosure. Modified cells disclosed herein can be used in for treating subjects in need thereof against Host versus Graft (HvG) rejection and Graft versus Host Disease (GvHD); therefore in the scope of the present disclosure is a method of treating subjects in need thereof against Host versus Graft (HvG) rejection and Graft versus Host Disease (GvHD) comprising treating said subject by administering to said subject an effective amount of modified cells comprising inactivated TCRα and/or TCRβ genes.

[0077] In some embodiments, the immune cells are engineered to be resistant to one or more chemotherapy drugs. The chemotherapy drug can be, for example, a purine nucleotide analogue (PNA), thus making the immune cell suitable for cancer treatment combining adoptive immunotherapy and chemotherapy. Exemplary PNAs include, for example, clofarabine, fludarabine, and cytarabine, alone or in combination. PNAs are metabolized by deoxycytidine kinase (dCK) into mono-, di-, and tri-phosphate PNA. Their tri-phosphate forms compete with ATP for DNA synthesis, act as pro-apoptotic agents, and are potent inhibitors of ribonucleotide reductase (RNR), which is involved in trinucleotide production. Provided herein are BCMA specific CAR-T cells comprising an inactivated dCK gene. In some embodiments, the dCK knockout cells are made by transfection of T

cells using polynucleotides encoding specific TAL-nuclease directed against dCK genes by, for example, electroporation of mRNA. The dCK knockout BCMA specific CAR-T cells are resistant to PNAs, including for example clorofarabine and/or fludarabine, and maintain T cell cytotoxic activity toward BCMA-expressing cells.

5 **[0078]** In some embodiments, isolated cells or cell lines of the disclosure can comprise a pTα or a functional variant thereof. In some embodiments, an isolated cell or cell line can be further genetically modified by inactivating the TCRα gene.

[0079] In some embodiments, the CAR-T cell comprises a polynucleotide encoding a safety switch, such as for example RQR8. See, e.g., WO2013153391A, which is hereby
10 incorporated by reference in its entirety. In CAR-T cells comprising the polynucleotide, the safety swtich polypeptide is expressed at the surface of a CAR-T cell. In some embodiments, the safety switch polypeptide comprises the amino acid sequence shown in SEQ ID NO: 342.

[0080] CPYSNPSLCSGGGGSELPTQGTFSNVSTNVSPAKPTTTACPYSNPSLCSGGGG
15 SP
APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL
S LVITLYCNHRNRRRVCKCPRPVV (SEQ ID NO: 342)

[0081] The safety switch polypeptide may also comprise a signal peptide at the amino terminus. In some embodiments, the safety switch polypeptide comprises the amino acid
20 sequence shown in SEQ ID NO: 400.

[0082] MGTSLLCWMALCLLGADHADACPYSNPSLCSGGGGSELPTQGTFSNVSTNV
SPAKPTTTACPYSNPSLCSGGGGSPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHT
RGLDFACDIYIWAPLAGTCGVLLLSLVITLYCNHRNRRRVCKCPRPVV (SEQ ID
NO: 400)

25 **[0083]** When the safety switch polypeptide is expressed at the surface of a CAR-T cell, binding of rituximab to the R epitopes of the polypeptide causes lysis of the cell. More than one molecule of rituximab may bind per polypeptide expressed at the cell surface. Each R epitope of the polypeptide may bind a separate molecule of rituximab. Deletion of BCMA specific CAR-T cells may occur in vivo, for example by administering rituximab to a
30 subject. The decision to delete the transferred cells may arise from undesirable effects

being detected in the subject which are attributable to the transferred cells, such as for example, when unacceptable levels of toxicity are detected.

[0084] In some embodiments, the CAR-T cell comprises a selected epitope within the scFv having a specificity to be recognized by a specific antibody. See, e.g., PCT application PCT/EP2016/051467, WO2016/120216, "mAb-DRIVEN CHIMERIC ANTIGEN RECEPTOR SYSTEMS FOR SORTING/DEPLETING ENGINEERED IMMUNE CELLS," filed on January 25, 2016, which is hereby incorporated by reference in its entirety. Such an epitope facilitates sorting and/or depleting the CAR-T cells. The epitope can be selected from any number of epitopes known in the art. In some embodiments, the epitope can be a target of a monoclonal antibody approved for medical use, such as, for example without limitation, the CD20 epitope recognized by rituximab. In some embodiments, the epitope comprises the amino acid sequence shown in SEQ ID NO: 397.

[0085] CPYSNPSLC (SEQ ID NO: 397)

[0086] In some embodiments, the epitope is located within the CAR. For example without limitation, the epitope can be located between the scFv and the hinge of a CAR. In some embodiments, two instances of the same epitope, separate by linkers, may be used in the CAR. For example, the polypeptide comprising the amino acid sequence shown in SEQ ID NO: 398 can be used within a CAR, located between the light chain variable region and the hinge.

[0087] GSGGGGSCPYSNPSLCSGGGGSCPYSNPSLCSGGGGS (SEQ ID NO: 398)

[0088] In some embodiments, the epitope-specific antibody may be conjugated with a cytotoxic drug. It is also possible to promote CDC cytotoxicity by using engineered antibodies on which are grafted component(s) of the complement system. In some embodiments, activation of the CAR-T cells can be modulated by depleting the cells using an antibody which recognizes the epitope.

III. Therapeutic Applications

[0089] Isolated cells obtained by the methods described above, or cell lines derived from such isolated cells, can be used as a medicament. In some embodiments, such a medicament can be used for treating MM. In some embodiments, the MM is refractory MM. In some

embodiments, the MM is relapsed MM. In some embodiments, the MM is refractory/relapsed MM.

[0090] In some embodiments the subject has not received any prior therapy for multiple myeloma. In some embodiments the subject has received at least one, two, or three prior therapies for multiple myeloma. In some embodiments, the dosing regimens provided herein are a first line therapy. In some embodiments, the dosing regimens provided herein are a second line therapy. In some embodiments, the dosing regimens provided herein are a third line therapy. In some embodiments, the dosing regimens provided herein are a fourth line therapy. In some embodiments, the subject has relapsed MM. In some embodiments, the subject has refractory MM. In some embodiments, the subject has refractory and relapsed MM.

[0091] In some embodiments, an isolated cell according to the disclosure, or cell line derived from the isolated cells, can be used in the manufacture of a medicament for treatment of a cancer in a subject in need thereof.

[0092] Also provided herein are methods for treating subjects. In some embodiments the method comprises providing an immune cell of the disclosure to a subject in need thereof. In some embodiments, the method comprises a step of administrating transformed immune cells of the disclosure to a subject in need thereof. The subject can be male or female, adult, adolescent, or pediatric. In some embodiments, the subject is a human subject.

[0093] In some embodiments, T cells of the disclosure can undergo in vivo T cell expansion and can persist for an extended amount of time.

[0094] Methods of treatment of the disclosure can be ameliorating, curative or prophylactic. The method of the disclosure may be either part of an autologous immunotherapy or part of an allogenic immunotherapy treatment. The disclosure is particularly suitable for allogeneic immunotherapy. T cells from donors can be transformed into non-alloreactive cells using standard protocols and reproduced as needed, thereby producing CAR-T cells which may be administered to one or several subjects. Such CAR-T cell therapy can be made available as an “off the shelf” therapeutic product. FIGS. 17 and 18 describe the limitations of autologous CAR-T therapies, and the advantages of allogeneic therapies.

[0095] Cells that can be used with the disclosed methods are described in the previous section. Treatment can be used to treat subjects diagnosed with MM. Adult tumors/cancers and pediatric tumors/cancers are also included. In some embodiments, the treatment can be in combination with one or more therapies against MM selected from the group of antibodies therapy, chemotherapy, cytokines therapy, dendritic cell therapy, gene therapy, hormone therapy, laser light therapy and radiation therapy.

[0096] In some embodiments, treatment can be administrated into subjects undergoing an immunosuppressive treatment. Indeed, the disclosure preferably relies on cells or population of cells, which have been made resistant to at least one immunosuppressive agent due to the inactivation of a gene encoding a receptor for such immunosuppressive agent. In this aspect, the immunosuppressive treatment should help the selection and expansion of the T cells according to the disclosure within the subject.

[0097] The administration of the cells or population of cells according to the disclosure may be carried out in any convenient manner, including by aerosol inhalation, injection, ingestion, transfusion, implantation or transplantation. The compositions described herein may be administered to a subject subcutaneously, intradermally, intratumorally, intranodally, intramedullary, intramuscularly, by intravenous or intralymphatic injection, or intraperitoneally. In one embodiment, the cell compositions of the disclosure are preferably administered by intravenous injection.

[0098] In some embodiments, the engineered BCMA CAR-expressing immune cells of the disclosure are formulated for infusion. In some embodiments, the cells are formulated in a solution comprising about 5% DMSO. In one embodiment 14 × 10^6 BCMA-CAR-T-cells/mL are formulated in a solution comprising about 5% DMSO. In a further embodiment the formulation comprises a 1:1 mixture of CryoStor® Basal Solution and CryoStor® CS10 resulting in a 5% final concentration of dimethyl sulfoxide. In some embodiments, the dosage strength of the formulation is 14 × 10^6 BCMA-CAR-T-cells/mL. In some embodiments this formulated drug product is supplied in a 2-mL closed-system vial with an integral stopper at a nominal volume of 1 mL.

[0099] In some embodiments, the BCMA CAR-T cells of the disclosure are BCMA-CAR+_TCRαβ-_CD52+/- T-cells and are formulated as a suspension for infusion. In some embodiments, the BCMA-CAR+_TCRαβ-_CD52+/- T-cells are formulated in a 1:1 mixture

of CryoStor® Basal Solution and CryoStor® CS10 resulting in a 5% final concentration of dimethyl sulfoxide. In some embodiments, the dosage strength of the formulation is 14 × 10^6 BCMA-CAR+_TCRαβ-_CD52+/- T-cells /mL.

IV. Lymphodepletion

5 **[00100]** In some embodiments, a lymphodepletion (LD) regimen is administered to the subject prior to a first and/or subsequent dose of the BCMA CAR-T cells. In some embodiments, the lymphodepletion regimen is administered to the subject concurrently with a first and/or subsequent dose of CAR-T cells. In some embodiments, the lymphodepletion regimen is administered before, during, and/or after a first and/or subsequent dose of
10 BCMA CAR-T cells.

[00101] Suitable LD regimens are described herein and/or known in the art. In some embodiments, LD starts prior to, concurrently with, or after a CAR-T infusion. Doses and timing of LD administration may be adapted with regard to the first or subsequent dosing of BCMA CAR-T. In some embodiments, the duration of LD is about 3 to 5 days. In some
15 embodiments, a time window between the end of LD and start of CAR-T administration is between about of 2 days to about 2 weeks. In some embodiments, LD is initiated about 15 to 7 days prior to administration of a dose of CAR-T cells. In some embodiments, LD is initiated about 19 to 5 days prior to administration of a dose of CAR-T cells. In some embodiments, LD is initiated about 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19,
20 or 20 days prior to administration of a dose of CAR-T cells. In some embodiments, duration of a LD regimen is about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days. In some embodiments, a dose of CAR-T cells is administered about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days after the end of LD.

[00102] In some embodiments, a LD regimen comprises administration of one or more
25 chemotherapeutic drugs.

[00103] In some embodiments, a LD regimen comprises administration of anti-CD52 antibody, such as an antibody that recognizes the human cluster of differentiation (CD) 52 antigen, a cell surface glycoprotein expressed on most lymphoid cells. As used herein a CD52 monoclonal antibody is one that is directed against the 21-28 kD cell surface
30 glycoprotein CD52. CD52 is an abundant molecule (approximately 5×10^5 antibody

binding sites per cell) present on at least 95% of all human peripheral blood lymphocytes and monocytes/macrophages. Exemplary CD52 antibodies for use in the methods and compositions described herein include, for example, alemtuzumab. In some embodiments, a CD52 antibody comprises the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 sequences as shown in Table 4 below.

Table 4: Exemplary CD52 antibody CDR sequences

CDR	Sequence (SEQ ID NO)
HCDR1	DFYMN (SEQ ID NO: 402)
HCDR2	FIRDKAKGYTTEYNPSVKG (SEQ ID NO: 403)
HCDR3	EGHTAAPFDY (SEQ ID NO: 404)
LCDR1	KASQNIDKYLN (SEQ ID NO: 405)
LCDR2	NTNNLQT (SEQ ID NO: 406)
LCDR3	LQHISRPRT (SEQ ID NO: 407)

[00104] In some embodiments, a CD52 antibody comprises a VH and/or a VL comprising the sequences shown in Table 5 below.

Table 5: Exemplary CD52 Antibody VH and VL sequences

VH/VL	Amino Acid Sequence	DNA Sequence
VH	QVQLQESGPGLVRPSQTLSLTCTVSGF TFTDFYMNWVRQPPGRGLEWIGFIRD KAKGYTTEYNPSVKGRVTMLVDTSK NQFSLRLSSVTAADTAVYYCAREGHT AAPFDYWGQGSLVTVSSASTKGPSVF PLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKKVEPKSCDKTHTCPPCPAP ELLGGPSVFLFPPKPKDTLMISRTPEV TCVVVDVSHEDPEVKFNWYVDGVEV HNAKTKPREEQYNSTYRVVSVLTVLH QDWLNGKEYKCKVSNKALPAPIEKTI SKAKGQPREPQVYTLPPSRDELTKNQ VSLTCLVKGFYPSDIAVEWESNGQPE NNYKTTPPVLDSDGSFFLYSKLTVDK SRWQQGNVFSCSVMHEALHNHYTQK SLSLSPGK (SEQ ID NO: 408)	caagtgcagcttcaagaatccggccctggtctggtccgcccct cccaaaccctctccctgacatgcaccgtgtcgggattcaccttt accgatttctacatgaactgggtccggcagccgcccggaaga ggtctggagtggatcggcttcattcgggacaaagccaaggg gtacaccaccgagtacaacccgtccgtgaagggacgcgtga ctatgctcgtggacacgtccaagaaccagttcagcttgaggct gagcagcgtgactgccgcggataccgcagtgtactactgtgc ccgggaagggcacactgccgctccattcgactattggggcca gggatcactggtcactgtgtcgtccgcctccaccaagggccc atcggtcttccccctggcaccctcctccaagagcacctctggg ggcacagcggccctgggctgcctggtcaaggactacttcccc gaaccggtgacggtgtcgtggaactcaggcgccctgaccag cggcgtgcacaccttcccggctgtcctacagtcctcaggactc tactccctcagcagcgtagtgaccgtgccctccagcagcttgg gcacccagacctacatctgcaacgtgaatcacaagcccagca acaccaaggtggacaagaaagttgagcccaaatcttgtgaca aaactcacacatgcccaccgtgcccagcacctgaactcctgg ggggaccgtcagtcttcctcttccccccaaaacccaaggaca

VH/VL	Amino Acid Sequence	DNA Sequence
		ccctcatgatctcccggacccctgaggtcacatgcgtggtggt ggacgtgagccacgaagaccctgaggtcaagttcaactggta cgtggacggcgtggaggtgcataatgccaagacaaagccgc gggaggagcagtacaacagcacgtaccgtgtggtcagcgtc ctcaccgtcctgcaccaggactggctgaatggcaaggagtac aagtgcaaggtctccaacaaagccctcccagcccccatcga gaaaaccatctccaaagccaaagggcagccccgagaacca caggtgtacaccctgcccccatcccgggacgagctgaccaa gaaccaggtcagcctgacctgcctggtcaaaggcttctatccc agcgacatcgccgtggagtgggagagcaatgggcagccgg agaacaactacaagaccacgcctcccgtgctggactccgac ggctccttcttcctctatagcaagctcaccgtggacaagagca ggtggcagcaggggaacgtcttctcatgctccgtgatgcatg aggctctgcacaaccactacacgcagaagagcctctccctgt ctccgggaaaa (SEQ ID NO: 409)
VL	DIQMTQSPSSLSASVGDRVTITCKASQ NIDKYLNWYQQKPGKAPKLLIYNTN NLQTGVPSRFSGSGSGTDFTFTISSLQP EDIATYYCLQHISRPRTFGQGTKVEIK RTVAAPSVFIFPPSDEQLKSGTASVVC LLNNFYPREAKVQWKVDNALQSGNS QESVTEQDSKDSTYSLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRG EC (SEQ ID NO: 410)	Atgggatggagctgtatcatcctcttcttggtagcaacagcta caggcgtgcactccgacatccaaatgacccaatccccatcct cactttccgcctccgtgggcgaccgcgtgactattacctgtaa agcgtcacagaatatcgacaagtacctgaactggtaccagca gaagcctggaaaggcccccaagctcctgatctacaacacca acaacttgcagactggagtgccgagcagattttccggctccg gctcggggactgatttcaccttcaccatctcgagcctgcagcc ggaggatattgctacctattactgcctgcaacacattagccgg cccaggacgttcggacagggtaccaaggtcgaaatcaagcg tacggtggctgcaccatctgtcttcatcttcccgccatctgatga gcagttgaaatctggaactgcctctgttgtgtgcctgctgaata acttctatcccagagaggccaaagtacagtggaaggtggata acgccctccaatcgggtaactcccaggagagtgtcacagag caggacagcaaggacagcacctacagcctcagcagcaccct gacgctgagcaaagcagactacgagaaacacaaagtctacg cctgcgaagtcacccatcagggcctgagctcgcccgtcacaa agagcttcaacaggggagagtgt (SEQ ID NO: 411)

[00105] In some embodiments, a CD52 antibody comprises a VH having the sequence of SEQ ID NO: 8, or a sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 408. In some embodiments, a CD52 antibody comprises a VL having the sequence of SEQ ID NO: 410, or a sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 410. In some embodiments, a CD52 antibody comprises a VH having the sequence of SEQ ID NO: 408 and a VL having the sequence of SEQ ID NO: 410. In some embodiments, a CD52 antibody comprises a VH

encoded by the DNA sequence of SEQ ID NO: 409 and a VL encoded by the DNA sequence of SEQ ID NO: 411.

[00106] In some embodiments, the anti-CD52 antibody is a recombinant humanized IgG1 kappa monoclonal antibody (mAb). In some embodiments, the anti-CD52 antibody is alemtuzumab. Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody directed against the 21-28 kD cell surface glycoprotein, CD52. See, e.g., Saif et al., *Pediatr Transplant* 2015 Mar;19(2):211-8. In some embodiments the anti-CD52 antibody comprises one or more CDR sequences isolated or derived from the CDRs of alemtuzumab. In some embodiments, the anti-CD52 antibody comprises the sequence of SEQ ID NO: 408, or a sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 408. In some embodiments, the anti-CD52 antibody comprises the sequence of SEQ ID NO: 410, or a sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 410. In some embodiments, the anti-CD52 antibody comprises an HCDR1 comprising the sequence of SEQ ID NO: 402, a HCDR2 comprising the sequence of SEQ ID NO: 403, a HCDR3 comprising the sequence of SEQ ID NO: 404, a LCDR1 comprising the sequence of SEQ ID NO: 405, a LCDR1 comprising the sequence of SEQ ID NO: 406, and/or a LCDR3 comprising the sequence of SEQ ID NO: 407. In some embodiments, the anti-CD52 antibody comprises an HCDR1 comprising the sequence of SEQ ID NO: 402, a HCDR2 comprising the sequence of SEQ ID NO: 403, a HCDR3 comprising the sequence of SEQ ID NO: 404, a LCDR1 comprising the sequence of SEQ ID NO: 405, a LCDR1 comprising the sequence of SEQ ID NO: 406, and a LCDR3 comprising the sequence of SEQ ID NO: 407; wherein the anti-CD52 antibody comprises the sequence of SEQ ID NO: 408 and/or SEQ ID NO: 410, or a sequence having at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% sequence identity to SEQ ID NO: 408 and/or SEQ ID NO: 410.

[00107] In some embodiments, LD comprises administering only a CD52 antibody.

[00108] In some embodiments, LD comprises administration of a combination of therapies. In some embodiments, the combination includes: fludarabine (range total dose about 90 to

150 mg/m^2) and cyclophosphamide (range total dose about 1000 to 4000 mg/m^2), with or without an anti-CD52 drug (*e.g.*, an anti-CD52 antibody such as an antibody comprising the sequence of SEQ ID NO: 408 and/or SEQ ID NO: 410) (total dose from about 0.3 to about 1 mg/kg, or a flat dose of from about 30 mg to about 40 mg, from about 25 to about 60 mg, from about 60 mg to about 90 mg, or from about 100 mg to about 120 mg). In some embodiments, the combination includes: fludarabine (about 30 mg/m^2) and cyclophosphamide (range total dose about 500 to 600 mg/m^2), with or without an anti-CD52 drug (*e.g.*, CD52 antibody) (total dose from about 0.3 to about 1 mg/kg, or a flat dose of from about 30 mg to about 40 mg, from about 25 to about 60 mg, from about 60 mg to about 90 mg, or from about 100 mg to about 120 mg). In some embodiments, the combination includes: fludarabine (about 30 mg/m^2) and cyclophosphamide (about 300 mg/m^2), with or without an anti-CD52 drug (*e.g.*, CD52 antibody) (total dose from about 0.3 to about 1 mg/kg, or a flat dose of from about 30 mg to about 40 mg, from about 20 mg to about 30 mg, from about 25 mg to about 60 mg, from about 60 mg to about 90 mg, or from about 100 mg to about 120 mg). In some embodiments, the combination includes: fludarabine (about 90 mg/m^2) and cyclophosphamide (about 900 mg/m^2), with or without an anti-CD52 drug (*e.g.*, CD52 antibody) (total dose from about 0.3 to about 1 mg/kg, or a flat dose of from about 30 mg to about 40 mg, from about 20 mg to about 30 mg, from about 25 mg to about 60 mg, from about 60 mg to about 90 mg, or from about 100 mg to about 120 mg). In some embodiments the combination includes: fludarabine (about 90mg/m^2), cyclophosphamide (about 1500 mg/m^2) and with or without an anti-CD52 drug (e.g. anti-CD52 antibody, about 1 mg/kg). In some embodiments the combination includes: fludarabine (about 150 g/m^2) and cyclophosphamide (about 130 mg/kg), with or without an anti-CD52 drug (e.g. anti-CD52 antibody, total dose from about 0.3 to about 1 mg/kg, or a flat dose of from about 30 mg to about 40 mg, from about 25 to about 60 mg, from about 60 mg to about 90 mg, or from about 100 mg to about 120 mg). In some embodiments the combination includes: fludarabine (about 150 g/m^2) and cyclophosphamide (about 120 mg/kg or about 130 mg/kg), with or without an anti-CD52 drug (e.g. an anti-CD52 antibody), total dose from about 0.3 to about 1 mg/kg, or a flat dose of from about 30 mg to about 40 mg, from about 25 to about 60 mg, or from about 100 mg to about 120 mg). In some embodiments, the combination includes: fludarabine (about 30 mg/m^2/day) and cyclophosphamide (about 300 mg/m^2/day), with or without an anti-CD52 drug (e.g. an anti-CD52 antibody, about 13 mg/day). In some embodiments, the combination includes:

fludarabine (about 30 mg/m^2/day) and cyclophosphamide (about 300 mg/m^2/day), with or without an anti-CD52 drug (e.g. an anti-CD52 antibody, about 10 mg/day). In some embodiments, the combination includes: cyclophosphamide and an anti-CD52 drug (e.g. an anti-CD52 antibody). In some embodiments, these above doses are administered during the course of one day. In some embodiments, these above doses are administered over multiple days.

[00109] In some embodiments, fludarabine and cyclophosphamide are administered on a first day, and the anti-CD52 antibody (e.g., an antibody comprising the sequence of SEQ ID NO: 408 and/or SEQ ID NO: 410) is administered on a second day. In some embodiments, fludarabine and cyclophosphamide are administered on a first day before administration of the CAR-T cells, and an anti-CD52 antibody (e.g., an antibody comprising the sequence of SEQ ID NO: 408 and/or SEQ ID NO: 410) is administered on a second day; wherein the second day is the same day that CAR-T cells are administered or the second day is after the CAR-T cells are administered. In some embodiments, fludarabine and cyclophosphamide are administered on a first day, CAR-T cells are administered on a second day, and an anti-CD52 antibody (e.g., an antibody comprising the sequence of SEQ ID NO: 408 and/or SEQ ID NO: 410) is administered at least about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, or about 12 weeks after the second day. In some embodiments, fludarabine and cyclophosphamide are administered before administration of CAR-T cells, and an anti-CD52 antibody (e.g., an antibody comprising the sequence of SEQ ID NO: 408 and/or SEQ ID NO: 410) is administered at least about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 11, or about 12 weeks after administration of the CAR-T cells.

[00110] In some embodiments, a lymphodepletion regimen comprises administration of fludarabine and cyclophosphamide (FC). In some embodiments, a lymphodepletion regimen comprises administration of fludarabine and anti-CD52 antibody (e.g., an antibody comprising the sequence of SEQ ID NO: 408 and/or SEQ ID NO: 410) (FA). In some embodiments, a lymphodepletion regimen comprises administration of cyclophosphamide and an anti-CD52 antibody (e.g., an antibody comprising the sequence of SEQ ID NO: 408 and/or SEQ ID NO: 410) (CA). In some embodiments, a lymphodepletion regimen comprises administration of fludarabine, cyclophosphamide, and an anti-CD52 antibody

(e.g., an antibody comprising the sequence of SEQ ID NO: 408 and/or SEQ ID NO: 410) (FCA).

[00111] The choice of specific lymphodepletion regimen drugs and dose before a first or second/subsequent dose of CAR-T cells may be determined based on hematological analysis and hematologic recovery of the patient. In the case of redosing, a second lymphodepletion regimen can be more or less intense compared to a first lymphodepletion regimen (for example, based on recovery of lymphocytes, neutrophils, and viral reactivation after a first dose). For example, at the time of redosing, if lymphocyte and neutrophil levels are high, a strong or aggressive lymphodepletion regimen may be used. Alternatively, at the time of redosing, if lymphocyte levels are low, a weaker or less aggressive lymphodepletion regimen may be used. In some embodiments, if the number of blasts at the time of redosing is high, a strong or aggressive lymphodepletion regimen is used. In some embodiments, if the number of blasts at the time of redosing is low, a weaker or less aggressive lymphodepletion regimen is used.

[00112] In some embodiments, an increased intensity of LD regimen may be applied at the time of redosing (with or without anti-CD52 drug). In some embodiments, a reduced intensity of LD regimen may be applied, for example, in case of grade 3-4 lymphopenia at time of redosing (with or without anti-CD52 drug).

[00113] In some embodiments, the components of the lymphodepletion regimen of fludarabine/cyclophosphamide (FC) or fludarabine/cyclophosphamide/anti-CD52 antibody (FCA) are administered simultaneously; in other embodiments, the components are administered serially. In some embodiments, the components of the lymphodepletion regimen of fludarabine/cyclophosphamide (FC) or fludarabine/cyclophosphamide/anti-CD52 antibody (FCA) are administered simultaneously on Day -5, Day -4 and Day -3. In some embodiments, the components of the lymphodepletion regimen of fludarabine/cyclophosphamide (FC) are administered prior to the administration of the anti-CD52 antibody. In some embodiments, the fludarabine/cyclophosphamide (FC) are administered on Day -7, Day -6 and Day -5, followed by the administration of the anti-CD52 antibody (A) on Day -4 and Day -3. In some embodiments, the fludarabine/cyclophosphamide (FC) are administered on Day -7, Day -6 and Day -5, followed by the administration of the anti-CD52 antibody (A) on Day -5, Day -4 and Day -

3. In some embodiments, the subject receives a FC regimen prior to the first dose of the CAR-T cell therapy; and a FCA regimen prior to a redosing of the CAR-T cell therapy. In some embodiments, the subject receives a FCA regimen prior to the first dose of the CAR-T cell therapy; and a second FCA regimen prior to a redosing of the CAR-T cell therapy.

[00114] Exemplary LD regimens are provided in Tables 6A, 6B, 6C, 6D, 6E, 6F and 6G. In Tables 6A-6G, the timing indicated under Schedule is relative to the timing of administration of a dose of CAR-T cells (D0), in days. Negative numbers indicate days prior to administration of CAR-T cells (at D0).

Table 6A

Lymphodepletion	**Dose**	**Total dose**
Fludarabine	30 mg/m^2/day	90 mg/m^2
Cyclophosphamide	500 mg/m^2/day	1500 mg/m^2
Anti-CD52 antibody (optional)	0.2 mg/kg/day	1 mg/kg

Table 6B

Lymphodepletion	**Dose**	**Route**
Fludarabine	30 mg/m^2/day	IV over 15-30 min
Cyclophosphamide	500 mg/m^2/day	IV over 1 hour
Anti-CD52 antibody	8 mg/day	IV

Table 6C

Lymphodepletion	**Dose**	**Route**
Fludarabine	30 mg/m^2/day	IV over 15-30 min
Cyclophosphamide	500 mg/m^2/day	IV over 1 hour
Anti-CD52 antibody	6 mg/day	IV

Table 6D

Lymphodepletion	**Dose**	**Total dose**
Fludarabine	30 mg/m^2/day	90 mg/m^2
Cyclophosphamide	300 mg/m^2/day	900 mg/m^2
Anti-CD52 antibody (optional)	13 mg/day	39 mg

Table 6E

Lymphodepletion	Dose	Total dose
Fludarabine	30 mg/m^2/day	90 mg/m^2
Cyclophosphamide	300 mg/m^2/day	900 mg/m^2
Anti-CD52 antibody (optional)	10 mg/day	30 mg

Table 6F

Lymphodepletion	Dose	Total dose
Fludarabine	30 mg/m^2/day	90 mg/m^2
Cyclophosphamide	300 mg/m^2/day	900 mg/m^2
Anti-CD52 antibody	30 mg/day	90 mg

Table 6G

Lymphodepletion	Dose	Total dose
Fludarabine	30 mg/m^2/day	90 mg/m^2
Cyclophosphamide	300 mg/m^2/day	900 mg/m^2
Anti-CD52 antibody	30 mg/day	60 mg

V. Dosing Regimens

[00115] In some embodiments, allogeneic BCMA CAR-T cells of the disclosure are administered using a flat dose. In other embodiments, allogeneic BCMA CAR-T cells are administered using dose-banding. For example, dose-banding may be used to avoid the risk of a wide range of CAR-T cell exposure. In some embodiments, a weight band may be used. For example, without limitation, subjects < 66 kg may be administered X dose, and subjects ≥ 66 kg may be administered about 1.33X dose. In some embodiments, subjects ≥50kg may be administered one dose, and subjects ≤50kg may be administered a different dose.

[00116] Exemplary dose levels for a first dose of allogeneic BCMA CAR-T cells are provided in Table 7A, for use in subjects with relapsed/refractory MM. The dose level designated as “-1” is administered only as needed.

Table 7A

Dose Level	Dose (x10^6 viable CAR-T cells) for subject whose weight ≥ 50 kg	Dose (x10^6 viable CAR-T cells) for subject whose weight <50 kg
1 (starting)	40	20
2	120	80
3	360	240
4	480	360
-1	20	7 or 14

[00117] In some embodiments, a subject whose weight is ≥50 kg is administered a dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 20 x 10^6 cells/dose to about 480 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells (described in Example 1).

[00118] In some embodiments, a subject whose weight is ≥50 kg is administered a dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 20 x 10^6 cells/dose to about 40 x 10^6 cells/dose, from about 40 x 10^6 cells/dose to about 120 x 10^6 cells/dose, from about 120 x 10^6 cells/dose to about 360 x 10^6 cells/dose, or from about 360 x 10^6 cells/dose to about 480 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00119] In some embodiments, a subject whose weight is <50 kg is administered a dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 7 x 10^6 cells/dose to about 360 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00120] In some embodiments, a subject whose weight is <50 kg is administered a dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 7 x 10^6 or 14 x 10^6 cells/dose to about 20 x 10^6 cells/dose, from about 20 x 10^6 cells/dose

to about 80 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 240 x 10^6 cells/dose, or from about 240 x 10^6 cells/dose to about 360 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00121] Alternative exemplary dose levels for a first dose of allogeneic BCMA CAR-T cells are provided in Table 7B, for use in subjects with relapsed/refractory MM. The Intermediate dose level, and the dose levels designated as "4" and "-1" are administered only as needed.

Table 7B

Dose Level	**Dose (x10^6 viable CAR-T cells) for subject whose weight > 50 kg**	**Dose (x10^6 viable CAR-T cells) for subject whose weight ≤50 kg**
1 (starting)	40	20
2	160	80
3	320	200
Intermediate	240	160
4	480	320
-1	20	14

[00122] In some embodiments, a subject whose weight is >50 kg is administered a dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 20 x 10^6 cells/dose to about 480 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells (described in Example 1).

[00123] In some embodiments, a subject whose weight is >50 kg is administered a dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 20 x 10^6 cells/dose to about 40 x 10^6 cells/dose, from about 40 x 10^6 cells/dose to about 160 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 320 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 240 x 10^6 cells/dose, from about 240 x 10^6 cells/dose to about 320 x 10^6 cells/dose, from about 240 x 10^6 cells/dose to about 480 x

10^6 cells/dose, or from about 320 x 10^6 cells/dose to about 480 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells.

[00124] In some embodiments, a subject whose weight is ≤50 kg is administered a dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 14 x 10^6 cells/dose to about 320 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00125] In some embodiments, a subject whose weight is ≤50 kg is administered a dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 14 x 10^6 cells/dose to about 20 x 10^6 cells/dose, from about 20 x 10^6 cells/dose to about 80 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 160 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 200 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 200 x 10^6 cells/dose, from about 200 x 10^6 cells/dose to about 320 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 320 x 10^6 cells/dose or from about 200 x 10^6 cells/dose to about 320 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00126] In some embodiments, a subject whose weight is >50kg is administered a dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose is about 40 x 10^6 cells/dose, 160 x 10^6 cells/dose, or 320 x 10^6 cells/dose. In some embodiments, an intermediate dose of about 240 x 10^6 cells/dose is administered (or another dose level between Dose Level 1 or Dose Level 3) if toxicity is observed with Dose level 3, or to determine a lower does that is efficacious. In some embodiments, a dose level of 480 x 10^6 cells/dose is administered (Dose level 4) if inadequate efficacy parameters are seen in Dose level 3. (FIG. 20). In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00127] The cells or population of cells can be administrated in one or more doses. In some embodiments, said effective amount of cells can be administrated as a single dose. In some embodiments, said effective amount of cells can be administrated as more than one dose

over a period time. Timing of administration is within the judgment of managing physician and depends on the clinical condition of the subject. The cells or population of cells may be obtained from any source, such as a blood bank or a donor. While individual needs vary, determination of optimal ranges of effective amounts of a given cell type for a particular disease or conditions within the skill of the art. An effective amount means an amount which provides a therapeutic or prophylactic benefit. The dosage administrated will generally be dependent upon the age, health and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment and the nature of the effect desired. In some embodiments, an effective amount of cells or composition comprising those cells are administrated parenterally. In some embodiments, administration can be an intravenous administration. In some embodiments, administration can be directly done by injection within a tumor.

[00128] In some embodiments of the disclosure, cells may be administered to a subject in conjunction with (e.g., before, simultaneously or following) any number of relevant treatment modalities, including but not limited to treatment with agents such as monoclonal antibody therapy, CCR2 antagonist (e.g., INC-8761), antiviral therapy, cidofovir and interleukin-2, Cytarabine (also known as ARA-C) or nataliziimab treatment for MS subjects or efaliztimab treatment for psoriasis subjects or other treatments for PML subjects. In some embodiments, BCMA specific CAR-T cells are administered to a subject in conjunction with one or more of the following: an anti-PD-1 antibody (e.g., nivolumab, pembrolizumab, or PF-06801591), an anti-PD-L1 antibody (e.g., avelumab, atezolizumab, or durvalumab), an anti-OX40 antibody (e.g., PF-04518600), an anti-4-1BB antibody (e.g., PF-05082566), an anti-MCSF antibody (e.g., PD-0360324), an anti-GITR antibody, and/or an anti-TIGIT antibody. In some embodiments, a BCMA specific CAR of the dislcosure is administered to a subject in conjunction with anti-PD-L1 antibody avelumab. In further embodiments, the T cells of the disclosure may be used in combination with chemotherapy, radiation, immunosuppressive agents, such as cyclosporin, azathioprine, methotrexate, mycophenolate, and FK506, antibodies, or other immunoablative agents such as CAMPATH, anti-CD3 antibodies or other antibody therapies, cytoxin, fludaribine, cyclosporin, FK506, rapamycin, mycoplienolic acid, steroids, FR901228, cytokines, and/or irradiation. These drugs inhibit either the calcium dependent phosphatase calcineurin (cyclosporine and FK506) or inhibit the p70S6 kinase that is important for growth factor induced signaling (rapamycin) (Henderson, Naya et al. 1991; Liu, Albers et al. 1992; Bierer,

Hollander et al. 1993). In a further embodiment, the cell compositions of the disclosure are administered to a subject in conjunction with (e.g., before, simultaneously or following) bone marrow transplantation, T cell ablative therapy using either chemotherapy agents such as, fludarabine, external-beam radiation therapy (XRT), cyclophosphamide, or antibodies such as OKT3 or CAMPATH, In some embodiments, the cell compositions of the disclosure are administered following B-cell ablative therapy such as agents that react with CD20, e.g., Rituxan. For example, in one embodiment, subjects may undergo standard treatment with high dose chemotherapy followed by peripheral blood stem cell transplantation. In certain embodiments, following the transplant, subjects receive an infusion of the expanded immune cells of the disclosure. In some embodiments, expanded cells are administered before or following surgery.

VI. Methods of Retreatment with CAR-T Cells

[00129] Also provided herein are methods for retreatment (redosing) with BCMA CAR-T cells. In particular, the methods involve administering one or more subsequent doses of cells to subjects having received a first dose, and/or administering the first and one or more subsequent doses. The doses generally are administered in particular amounts and according to particular timing parameters. In some embodiments, the methods generally involve administering a first dose of cells, thereby reducing disease burden, followed by a subsequent dose of cells, administered during a particular time window with respect to the first dose, or the administration of the subsequent dose to a subject having received such a first dose. In some embodiments, additional subsequent doses then are administered, for example, within the same or a similar window of time with respect to the subsequent dose. In some embodiments, the number of cells administered and timing of the multiple doses are designed to improve one or more outcomes, such as to reduce the likelihood or degree of toxicity to the subject, improve exposure of the subject to and/or persistence of the administered cells, and/or improve therapeutic efficacy. Also provided are articles of manufacture containing the cells and designed for administration following such dosing regimens.

[00130] In some retreatment (redosing) embodiments, a subject whose weight is >50 kg is administered a re-dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 20 x 10^6 cells/dose to about 480 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In

some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells (described in Example 1).

[00131] In some retreatment (redosing) embodiments, a subject whose weight is >50 kg is administered a re-dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 20 x 10^6 cells/dose to about 40 x 10^6 cells/dose, from about 40 x 10^6 cells/dose to about 160 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 320 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 240 x 10^6 cells/dose, from about 240 x 10^6 cells/dose to about 320 x 10^6 cells/dose, from about 240 x 10^6 cells/dose to about 480 x 10^6 cells/dose, or from about 320 x 10^6 cells/dose to about 480 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells.

[00132] In some retreatment (redosing) embodiments, a subject whose weight is >50 kg is administered a re-dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose is about 40 x 10^6 cells/dose, 160 x 10^6 cells/dose, or 320 x 10^6 cells/dose. In some embodiments, an intermediate dose of about 240 x 10^6 cells/dose is administered (or another dose level between Dose Level 1 or Dose Level 3) if toxicity is observed with Dose level 3, or to determine a lower does that is efficacious. In some embodiments, a dose level of 480 x 10^6 cells/dose is administered (Dose level 4) if inadequate efficacy parameters are seen in Dose level 3. (FIG. 20). In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00133] In some retreatment (redosing) embodiments, a subject whose weight is ≥50 kg is administered a re-dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 20 x 10^6 cells/dose to about 480 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells (described in Example 1).

[00134] In some retreatment (redosing) embodiments, a subject whose weight is ≥50 kg is administered a re-dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 20 x 10^6 cells/dose to about 40 x 10^6 cells/dose, from about 40 x

10^6 cells/dose to about 120 x 10^6 cells/dose, from about 120 x 10^6 cells/dose to about 360 x 10^6 cells/dose, or from about 360 x 10^6 cells/dose to about 480 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00135] In some retreatment (redosing) embodiments, a subject whose weight is ≤50 kg is administered a re-dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 14 x 10^6 cells/dose to about 320 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00136] In some retreatment (redosing) embodiments, a subject whose weight is ≤50 kg is administered a re-dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 14 x 10^6 cells/dose to about 20 x 10^6 cells/dose, from about 20 x 10^6 cells/dose to about 80 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 160 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 200 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 200 x 10^6 cells/dose, from about 200 x 10^6 cells/dose to about 320 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 320 x 10^6 cells/dose or from about 200 x 10^6 cells/dose to about 320 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00137] In some retreatment (redosing) embodiments, a subject whose weight is <50 kg is administered a re-dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 7 x 10^6 cells/dose to about 360 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

[00138] In some retreatment (redosing) embodiments, a subject whose weight is <50 kg is administered a re-dose of allogeneic BCMA CAR-T cells of the disclosure, wherein the dose ranges from about 7 x 10^6 or 14 x 10^6 cells/dose to about 20 x 10^6 cells/dose, from about 20 x 10^6 cells/dose to about 80 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 240 x 10^6 cells/dose, or from about 240 x 10^6 cells/dose to about 360 x 10^6 cells/dose. In some embodiments, the BCMA CAR-T cells are BCMA-CAR^{+}_TCRαβ^{-}

_CD52$^{+/-}$ T-cells. In some embodiments, the BCMA CAR-T cells are BCMA-1 CAR-T cells.

VII. Kits and Articles of Manufacture

[00139] The disclosure also provides kits and articles of manufacture for use in the disclosed methods. Kits of the disclosure include one or more containers (e.g. glass vials) comprising a polynucleotide encoding a BCMA specific CAR, or an engineered immune cell comprising a polynucleotide encoding a BCMA specific CAR as described herein (e.g. BCMA-1 CAR-T cells, e.g. BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$ T-cells), and instructions for use in accordance with any of the methods of the disclosure described herein. In some embodiments the engineered immune cells are formulated in a solution comprising about 5% DMSO. Further, the engineered immune cells can be provided in a frozen state.

[00140] In some embodiments, provided herein are additional vials comprising unit doses of a CD52 antibody (which can be provided in a frozen state or as a room temperature solution comprising a buffered medium), fludarabine, and/or cyclophosphamide.

[00141] Generally, these instructions provided herein comprise a description of administration of the engineered immune cell for the above described therapeutic treatments. The instructions relating to the use of the engineered immune cells as described herein generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (e.g., multi-dose packages) or sub-unit doses. Instructions supplied in the kits of the disclosure are typically written instructions on a label or package insert (e.g., a paper sheet included in the kit), but machine-readable instructions (e.g., instructions carried on a magnetic or optical storage disk) are also acceptable.

[00142] The kits of this disclosure are in suitable packaging. Suitable packaging includes, but is not limited to, vials, bottles, jars, flexible packaging (e.g., sealed Mylar or plastic bags), and the like. Also contemplated are packages for use in combination with a specific device, such as an infusion device such as a minipump. A kit may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The container may also have a sterile access port (for example the container may be an intravenous solution bag or a vial having a

stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a BCMA antibody. The container may further comprise a second pharmaceutically active agent.

[00143] Kits may optionally provide additional components such as buffers and interpretive information. Normally, the kit comprises a container and a label or package insert(s) on or associated with the container.

[00144] The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the disclosure in any way. Indeed, various modifications of the disclosure in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

EXAMPLES

Example 1: Production and Testing of BCMA-1

[00145] FIGS. 1- 16 depict the generation and testing of BCMA-1. BCMA-1 is an allogeneic T-cell containing an integrated self-inactivating third generation, recombinant lentiviral vector that expresses a BCMA CAR. The BCMA CAR comprises a scFv, wherein the scFV of the CAR is P5A2 of Table 1. The scFV comprises a VH and a VL, wherein the VH comprises the amino acid sequence shown in SEQ ID NO: 33 and the VL comprises the amino acid sequence shown in SEQ ID NO: 34 The extracellular region of the CAR also comprises 2 mimotopes that confer recognition by rituximab.

[00146] The genotype of the BCMA CAR-T-cells is BCMA-CAR^{+}_TCRαβ^{-}_CD52$^{+/-}$. The cells can be formulated in a solution comprising 5% DMSO. In one embodiment, the cells are formulated as a suspension for infusion in a 1:1 mixture of CryoStor® Basal Solution and CryoStor® CS10 resulting in a 5% final concentration of dimethyl sulfoxide, and the resulting dosage strength of the formulation is 14 × 10^6 BCMA-CAR+_TCRαβ-_CD52+/- T-cells /mL.

[00147] FIG. 2 shows the rituximab-mediated safety switch enables detection and depletion (with a rituximab antibody) of the BCMA-containing CAR-T cells of the disclosure. BCMA-1 cells were incubated with rabbit complement and rituximab. After 3

hours, cells were stained for CAR expression. The graph sows the percentage of live CAR+ cells (mean +/- SEM). (FIG. 2)

[00148] The cytotoxicity of BCMA-1 was tested against BCMA-expressing cell lines was assessed in vitro by co-culturing BCMA-1 effector cells with target cells stably expressing luciferase at increasing E:T ratios and measuring residual luciferase activity after 24 hours. BCMA-negative REH cells served as a control cell line. Compared to non-transduced control T cells (triangles), BCMA-1 (circles) exhibited dose-dependent cytotoxicity against BCMA-expressing cells but no apparent killing of control cells (REH). The killing activity of BCMA-1 and non-gene-edited BCMA-1 (open circles) was comparable. Graphs represent percentage of cell lysis relative to target cells cultured alone (FIG. 6). Results shown are mean +/- SEM of 3 donors. Negative cytotoxicity values (resulting from target cell growth or enhanced luciferase signal during the assay) were plotted as 0% lysis.

[00149] FIG. 16 shows that the scFV of BCMA-1 does not show off-target binding in tissue cross-reactivity studies, indicating the risk for off-target binding in a clinical setting to be low or non-existent. Testing was done in 13 human tissues. The extracellular domain of the CAR was fused to human IgG2dA D265A (mutation to prevent Fc binding). The method was developed for optimal staining on cell lines overexpressing BCMA. No staining observed in human tissues

[00150] Result of immunohistochemistry staining in 9 human tissues – a triple signal amplification was carried out to increase signal. There was detection of expected signal in tonsil, lymph nodes, spleen tissues. There was no epithelial binding in breast, pancreas, fallopian tube, prostate, bladder tissues. Accordingly, the risk for unexpected binding is considered low or non-existent.

Example 2: Phase 1 Study, Design A

[00151] FIG. 19 shows the outline for the Phase 1 Study (Design A) for treatment of refractory/relapsed MM. The design of Design A includes a lymphodepletion phase of: fludarabine (flu) 30 mg/m2/day IV; cyclophosphamide (cy) 300 mg/m2/day IV; and CD52 antibody 13 mg/day IV, from 3 to 5 days prior to treatment; and a treatment phase (on day 0) which includes escalating doses from 20-80x10^6 cells IV (for subjects ≥50kg) or 7-360 x 10^6 cells IV (for subjects <50kg).

[00152] Criteria for inclusion may include one or more of the following:

- Measurable MM after ≥3 prior MM regimens
  - Induction +/- ASCT +/- maintenance is 1 regimen
  - Received prior PI, IMiD and CD38 inhibition (unless contraindicated) with at least 2 continuous cycles of each regimen unless PD was best response
  - Refractory to most recent prior regimen
- ECOG PS 0-1
- Adequate organ function
- 5 elimination half lives washout prior to LD
  - 4 weeks for mAb
- BCMA expression may be used for patient selection.

[00153] The dose-banded levels for BCMA-1 Escalation in Phase 1 Design A is provided in Table 8.

Table 8

Dose Level	**Dose (x10^6 viable CAR-T cells) for subject whose weight ≥ 50 kg**	**Dose (x10^6 viable CAR-T cells) for subject whose weight <50 kg**
1 (starting)	40	20
2	120	80
3	360	240
4	480	360
-1	20	7 or 14

[00154] Dose escalation will generally be governed by the 3+3 design; each dose level can receive cells from at least two different donors; up to five dose levels can be tested. The

starting dose is noted as Dose Level 1 in Table 8, in some embodiments, a subject may receive a Dose level of -1 if indicated.

[00155] Redosing may be carried out, using BCMA CAR-T cells from a different donor, in a relapsed patient, using conditioning with, for example, 20mg CD52 antibody conditioning.

Example 3: Phase 1 Study, Design B

[00156] FIG. 19 shows the outline for the Phase 1 Study, Design B, for treatment of refractory/relapsed MM. The design of Design B includes a lymphodepletion phase of: fludarabine (flu) 30 mg/m2/day IV; cyclophosphamide (cy) 300 mg/m2/day IV; and CD52 antibody 13 mg/day IV, from 3 to 5 days prior to treatment; and a treatment phase (on day 0) which includes escalating doses from 20-80x10^6 cells IV (for subjects ≥50kg) or 7-360 x 10^6 cells IV (for subjects <50kg).

[00157] Criteria for inclusion may include one or more of the following:

[00158] 1. Documented diagnosis of relapsed/refractory multiple myeloma (R/R MM) as defined by the IMWG consensus criteria for response and minimal residual disease assessment in multiple myeloma.

[00159] 2. Subjects have measurable disease including one or more of the following criteria:

a. Serum M-protein ≥0.5 g/dL

b. Urine M-protein ≥200 mg/24 hours,

c. Involved serum free light chain (FLC) level ≥10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal.

[00160] 3. Patients have received at least ≥3 prior MM regimens:

a. Induction with or without hematopoietic stem cell transplant and with or without maintenance therapy is considered a single regimen.

b. Received prior proteasome inhibitor, immunomodulatory agent, and an anti-CD38 antibody (unless contraindicated) with at least 2 consecutive cycles of each regimen unless progressive disease was the best response to the regimen.

c. Refractory to the last treatment regimen.

5 **[00161]** 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

[00162] A cycle of treatment is considered as the combination of 1 lymphodepletion and 1 treatment period.

[00163] One goal of this study is to evaluate the MTD of BCMA-1, and/or establish its RP2D

10 **[00164]** In some embodiments, the study includes 2 parts: dose escalation and dose expansion.

[00165] In the dose escalation part successive cohorts of patients may receive escalating doses of BCMA-1 in a 3+3 design. At each dose level, the first patient can be treated and observed for 28 days prior to treating subsequent patients with BCMA-1. All patients will
15 generally be monitored closely for dose limiting toxicities (DLTs) during the first 28 days after BCMA-1 infusion. The target DLT rate for BCMA-1 is <33%. An intermediate dose level can be explored between DL1 and DL3 (Table 9). A dosing strategy using 2 different weight bands based on the variations in weight observed in the general population can be implemented. Patients weighing ≤50 kg can receive a dose 33% to 50% lower than that
20 administered to patients weighing >50 kg. The provisional dose levels in BCMA-1 Escalation in Phase 1, Design B is provided in Table 9. Intermediate Dose level, Dose level 4, and Dose Level -1 can be administered as needed.

Table 9

Dose Level	Dose (x10^6 viable CAR-T cells) for subject whose weight > 50 kg	Dose (x10^6 viable CAR-T cells) for subject whose weight ≤50 kg
1 (starting)	40	20
2	160	80
3	320	200
Intermediate	240	160
4	480	320
-1	20	14

[00166] Dose escalation will generally be governed by the 3+3 design; each dose level can receive cells from at least two different donors; up to five dose levels can be tested. The starting dose is noted as Dose Level 1 in Table 9, in some embodiments, a subject may receive a Dose level of -1, a Dose level of 4, or an Intermediate Dose level (as displayed in Table 9) if indicated.

[00167] Accordingly, in Design B, BCMA-1 can be administered on Day 0 by intravenous (IV) infusion for approximately 5 minutes. Escalating doses of 40 x 10^6, 160 x 10^6, and 320 x 10^6 allogeneic CAR T cells can be studied for patients weighing >50 kg. The corresponding doses for patients weighing ≤50 kg are 20 x 10^6, 80 x 10^6, and 200 x 10^6.

[00168] An anti-CD52 human IgG1 monoclonal antibody that recognizes the human CD52 antigen and can be used as a part of lymphodepletion regimen.

[00169] The anti-CD52 antibody can be administered on Day -5, Day -4, and Day -3 by IV infusion over 4 hours at a dose of 13 mg/day concomitantly with fludarabine (30 mg/m2/day) and/or cyclophosphamide (300 mg/m2/day), or the antibody alone. A lower dose at 10 mg/day is planned in case of toxicity. Fludarabine (30 mg/m2/day) can be administered for 3 days.

[00170] The overall duration of this Phase 1 study is approximately 48 months from first patient enrolled to last patient completed.

[00171] The dose expansion part can include additional cohorts added to the protocol, to characterize R2PD with the appropriate conditioning regimens of BCMA-1. Up to 3 cohorts of 12 patients in each cohort can be evaluated at the dose levels and conditioning regimens chosen based on the findings from the dose escalation.

[00172] The study can end when all patients treated with BCMA-1 have been followed for at least 24 months from the initial BCMA-1 infusion, have withdrawn consent for any further contact, been lost to follow-up, or died, unless the study is terminated by the sponsor earlier.

[00173] Redosing may be carried out, using BCMA CAR-T cells from a different donor, in a relapsed patient, using conditioning with, for example, 20mg CD52 antibody conditioning.

Example 4: Phase 2 Study

[00174] Phase 2 can involve testing an addition cohort of 6-12 subjects using the highest dose with acceptable toxicity from Phase 1 Design A or Design B (either RP2D - the dose level producing around 20% of dose-limiting toxicity from Phase 1; or the dose level above the RP2D dose). Subjects may receive a CD52 antibody without flu/cy; the CD52 antibody may be administered at a dose of ~ 40mg (13mg/day x 3days) before the CAR-T cell treatment and repeated at 13mg/day on Day 7, 14, and 21 after CAR-T cell treatment.

[00175] Although the disclosed teachings have been described with reference to various applications, methods, and compositions, it will be appreciated that various changes and modifications can be made without departing from the teachings herein and the claims below. The foregoing examples are provided to better illustrate the disclosed teachings and are not intended to limit the scope of the teachings presented herein. While the present teachings have been described in terms of these exemplary embodiments, the skilled artisan will readily understand that numerous variations and modifications of these exemplary embodiments are possible without undue experimentation. All such variations and modifications are within the scope of the current teachings.

[00176] All references cited herein, including patents, patent applications, papers, text books, and the like, and the references cited therein, to the extent that they are not already, are hereby incorporated by reference in their entirety. In the event that one or more of the

incorporated literature and similar materials differs from or contradicts this application, including but not limited to defined terms, term usage, described techniques, or the like, this application controls.

[00177] The foregoing description and Examples detail certain specific embodiments of the invention and describes the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the invention may be practiced in many ways and the invention should be construed in accordance with the appended claims and any equivalents thereof.

WHAT IS CLAIMED IS:

1. A method of treating multiple myeloma in a subject comprising administering to the subject at least one dose of allogeneic chimeric antigen receptor (CAR)-T cells comprising an anti-human BCMA CAR (BCMA CAR-T cells), wherein the at least one dose is about 7 x 10^6 cells/dose to about 480 x 10^6 cells/dose.

2. The method of claim 1, wherein the weight of the subject is ≥50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 20 x 10^6 cells/dose to about 480 x 10^6 cells/dose.

3. The method of claim 2, wherein the at least one dose is about 20 x 10^6 cells/dose, about 40 x 10^6 cells/dose, about 120 x 10^6 cells/dose, about 360 x 10^6 cells/dose, or about 480 x 10^6 cells/dose.

4. The method of claim 2, wherein the at least one dose is from about 20 x 10^6 cells/dose to about 40 x 10^6 cells/dose, from about 40 x 10^6 cells/dose to about 120 x 10^6 cells/dose, from about 120 x 10^6 cells/dose to about 360 x 10^6 cells/dose, or from about 360 x 10^6 cells/dose to about 480 x 10^6 cells/dose.

5. The method of claim 1, wherein the weight of the subject is <50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 7 x 10^6 cells/dose to about 360 x 10^6 cells/dose.

6. The method of claim 5, where in the at least one dose is about 7 x 10^6 cells/dose, about 14 x 10^6 cells/dose, about 20 x 10^6 cells/dose, about 80 x 10^6 cells/dose, about 240 x 10^6 cells/dose, or about 360 x 10^6 cells/dose.

7. The method of claim 5, where in the at least one dose is from about 7 x 10^6 or 14 x 10^6 cells/dose to about 20 x 10^6 cells/dose, from about 20 x 10^6 cells/dose to about 80 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 240 x 10^6 cells/dose, or from about 240 x 10^6 cells/dose to about 360 x 10^6 cells/dose.

8. The method of claim 1, wherein the weight of the subject is >50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 20 x 10^6 cells/dose to about 480 x 10^6 cells/dose.

9. The method of claim 8, wherein the at least one dose is about 20 x 10^6 cells/dose, about 40 x 10^6 cells/dose, about 160 x 10^6 cells/dose, about 240 x 10^6 cells/dose, about

320 x 10^6 cells/dose, or about 480 x 10^6 cells/dose.

10. The method of claim 8, wherein the at least one dose is from about 20 x 10^6 cells/dose to about 40 x 10^6 cells/dose, from about 40 x 10^6 cells/dose to about 160 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 240 x 10^6 cells/dose, from about 240 x 10^6 cells/dose to about 320 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 320 x 10^6 cells/dose, or from about 320 x 10^6 cells/dose to about 480 x 10^6 cells/dose.

11. The method of claim 1, wherein the weight of the subject is ≤50 kg, and the method comprises administering at least one dose of BCMA CAR-T cells, wherein the dose ranges from about 14 x 10^6 cells/dose to about 320 x 10^6 cells/dose.

12. The method of claim 11, where in the at least one dose is about 14 x 10^6 cells/dose, about 20 x 10^6 cells/dose, about 80 x 10^6 cells/dose, about 160 x 10^6 cells/dose, about 200 x 10^6 cells/dose, or about 320 x 10^6 cells/dose.

13. The method of claim 12, where in the at least one dose is from about 14 x 10^6 cells/dose to about 20 x 10^6 cells/dose, from about 20 x 10^6 cells/dose to about 80 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 200 x 10^6 cells/dose, from about 80 x 10^6 cells/dose to about 160 x 10^6 cells/dose, from about 160 x 10^6 cells/dose to about 200 x 10^6 cells/dose, or from about 200 x 10^6 cells/dose to about 320 x 10^6 cells/dose.

14. The method of any one of claims 1 to 13, wherein the multiple myeloma is refractory multiple myeloma.

15. The method of any one of claims 1 to 14, wherein the multiple myeloma is relapsed multiple myeloma.

16. The method of any one of claims 1 to 13, wherein the multiple myeloma is refractory and relapsed multiple myeloma.

17. The method of any one of claims 1 to 13, wherein the subject has not received any prior therapy for multiple myeloma.

18. The method of any one of claims 1 to 13, wherein the subject has received at least one, two, or three prior therapies for multiple myeloma.

19. The method of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular binding domain comprising a single chain Fv fragment (scFv), wherein the scFv comprises a heavy chain variable (VH) region and a light chain

variable (VL) region, wherein the VH region comprises a VH complementary determining region 1 (VH CDR1), a VH complementary determining region 2 (VH CDR2), and a VH complementary determining region 3 (VH CDR3) and the VL region comprises a VL complementary determining region 1 (VL CDR1), a VL complementary determining region 2 (VL CDR2), and a VL complementary determining region 3 (VL CDR3), wherein:

(a) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 153 or 154; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 209; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 222;

(b) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 187 or 188; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 249; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 225;

(c) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 165 or 166; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 226; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 227;

(d) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 159 or 162; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 161; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 251; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 252; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 253;

(e) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 190 or 191; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 161; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 262; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 252; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 263;

(f) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 150, 151, or 152; the

VH CDR2 comprises the amino acid sequence of SEQ ID NO: 154 or 169; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 271; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 272;

(g) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 129, 130, or 131; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 139 or 140; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 134; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 217; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 210; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 216;

(h) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 151, 156, or 157; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 158 or 159; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 155; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 209; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 221; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 225; or

(i) the VH CDR1 comprises the amino acid sequence of SEQ ID NO: 129, 130, or 131; the VH CDR2 comprises the amino acid sequence of SEQ ID NO: 132 or 133; the VH CDR3 comprises the amino acid sequence of SEQ ID NO: 137; the VL CDR1 comprises the amino acid sequence of SEQ ID NO: 377; the VL CDR2 comprises the amino acid sequence of SEQ ID NO: 210; and the VL CDR3 comprises the amino acid sequence of SEQ ID NO: 214

20. The method of claim 19, wherein the VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 150, 151, or 152; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 153 or 154; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 155; and the VL region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 222.

21. The method of claim 19, wherein the VH region comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 151, 156, or 157; a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 158 or 159; and a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 155; and the VL region comprises a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 209; a VL CDR2 comprising the amino acid sequence

of SEQ ID NO: 221; and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 225.

22. The method of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular binding domain comprising a single chain Fv fragment (scFv), wherein the scFv comprises a VH region and a VL region, wherein the combination of VH and VL regions are chosen from the combinations presented in Table 1.

23. The method of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain.

24. The method of claim 23, wherein the VH comprises SEQ ID NO: 33 and the VL comprises SEQ ID NO: 34.

25. The method of claim 23, wherein the VH comprises SEQ ID NO: 112 and the VL comprises SEQ ID NO: 38.

26. The method of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising the amino acid sequence shown in SEQ ID NO: 344.

27. The method of claim 26, wherein the CAR further comprises a CD20 epitope.

28. The method of claim 27, wherein the CD20 epitope comprises the amino acid sequence shown in SEQ ID NO: 397 or SEQ ID NO: 398.

29. The method of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO:

323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

30. The method of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 112; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 38; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

31. The method of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

32. The method of any one of claims 1 to 18, wherein the BCMA CAR-T cells comprise a CAR comprising a CD8α signal peptide having the sequence of SEQ ID NO: 318; a VH region having the sequence of SEQ ID NO: 33; a GS linker having the sequence of SEQ ID NO: 333; a VL region having the sequence of SEQ ID NO: 34; a CD20 epitope having the sequence of SEQ ID NO: 398; a CD8α hinge having the sequence of SEQ ID NO: 320; a CD8α transmembrane domain having the sequence of SEQ ID NO: 322; a 4-1BB intracellular signaling domain having the sequence of SEQ ID NO: 323; and a CD3ζ intracellular signaling domain having the sequence of SEQ ID NO: 324.

33. The method of any one of claims 1 to 32, wherein the CAR-T cells are deficient in CD52.

34. The method of any one of claims 1 to 32, wherein the CAR-T cells are deficient in TCRα and/or TCRβ.

35. The method of any one of claims 1 to 34, wherein the genotype of the cells is $TCR\alpha\beta^{-}$ and $CD52^{+/-}$.

36. The method of any one of claims 1 to 32, wherein the CAR-T cells do not express a

safety switch.

37. The method of any one of claims 1 to 32, wherein the CAR-T cells express a rituximab epitope.

38. The method of any one of claims 1 to 37, wherein the subject receives a first lymphodepletion regimen prior to administration of the at least one dose.

39. The method of claim 38, wherein the first lymphodepletion regimen comprises administering fludarabine and cyclophosphamide.

40. The method of claim 38, wherein the first lymphodepletion regimen comprises administering fludarabine, cyclophosphamide, and an anti-CD52 antibody.

41. The method of claim 38, wherein the first lymphodepletion regimen comprises administering an anti-CD52 antibody.

42. The method of claim 38, wherein the first lymphodepletion regimen comprises administering only an anti-CD52 antibody.

43. The method of claim 38, wherein fludarabine is administered at a dosage of about 30 $mg/m^2/day$; cyclophosphamide is administered at a dosage of about 300 $mg/m^2/day$; and the CD52 antibody is administered at a dosage of about 10 to about 13 mg/day.

44. The method of claim 40, wherein fludarabine is administered at a dosage of about 30 $mg/m^2/day$; cyclophosphamide is administered at a dosage of about 300 $mg/m^2/day$; and the CD52 antibody is administered at a dosage of about 13 to about 30 mg/day, about 13 to 20 mg/day, about 13 to 30 mg/day, or about 20 to 30 mg/day.

45. The method of claim 44, wherein the CD52 antibody is administered at a dosage of about 13 mg/day, about 20 mg/day or about 30 mg/day.

46. The method of any one of claims 36 to 45, wherein the first lymphodepletion regimen is initiated between about 1 to 15 days prior to administration of the at least one dose.

47. The method of any one of claims 36 to 46, wherein the first lymphodepletion regimen is administered over the course of 1, 2, 3, 4, or 5 days.

48. The method of any one of claims 36-47, wherein the first lymphodepletion regimen is administered 5 days prior to administration of the at lease one dose in the course of 3 days.

49. The method of any one of claims 1 to 48, wherein the subject receives a subsequent

dose of the CAR-T cells.

50. A formulation comprising BCMA CAR-T cells, wherein the cells are formulated in a solution comprising about 5% dimethyl sulfoxide, wherein the dosage strength of the formulation is 14 × 10^6 cells /mL, wherein the genotype of the cells is BCMA-CAR+_TCRαβ-_CD52+/-, and wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, two rituximab-binding domains, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain.

51. A formulation comprising BCMA CAR-T cells, wherein the cells are formulated in a 1:1 mixture of CryoStor® Basal Solution and CryoStor® CS10 resulting in a 5% final concentration of dimethyl sulfoxide, wherein the dosage strength of the formulation is 14 × 10^6 cells /mL, wherein the genotype of the cells is BCMA-CAR+_TCRαβ-_CD52+/-, and wherein the BCMA CAR-T cells comprise a CAR comprising an extracellular ligand-binding domain, two rituximab-binding domains, a first transmembrane domain, and an intracellular signaling domain, wherein the extracellular domain comprises a scFv comprising a heavy chain variable (VH) region comprising a sequence shown in SEQ ID NO: 33, 72, 39, 76, 83, 92, 25, 112, or 8 of Table 1; and a light chain variable (VL) region comprising a sequence shown in SEQ ID NO: 34, 73, 40, 77, 84, 93, 18, 38, or 80 of Table 1, wherein the first transmembrane domain comprises a CD8α chain transmembrane domain, and wherein the intracellular signaling domain comprises a CD3ζ signaling domain and/or a 4-1BB signaling domain.

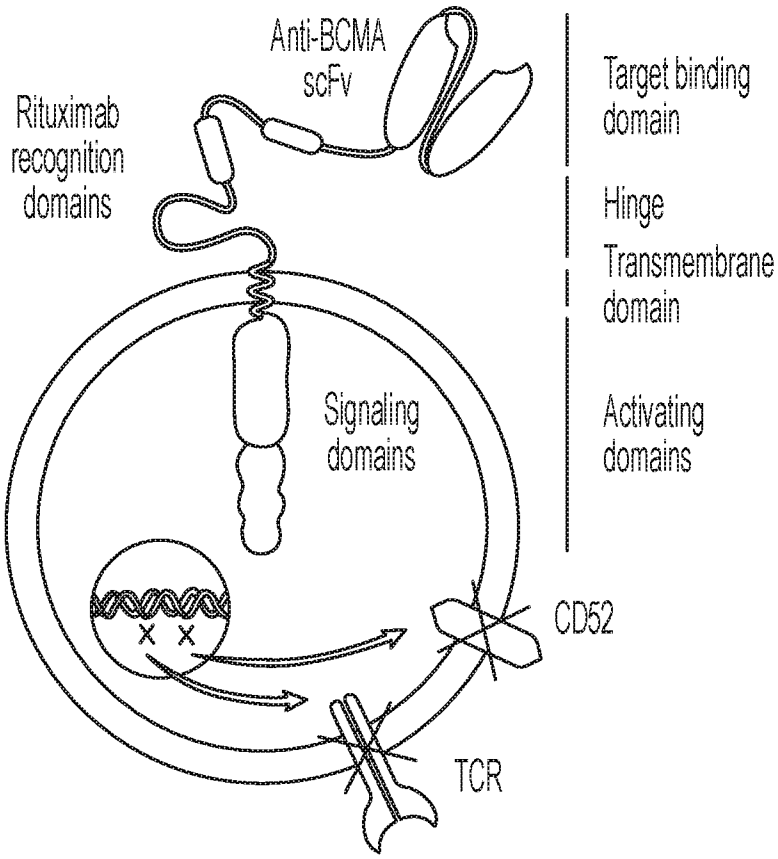

Anti-BCMA
scFv
Rituximab
recognition
domains
Target binding
domain
Hinge
Transmembrane
domain
Signaling
domains
Activating
domains
CD52
TCR

FIG. 1

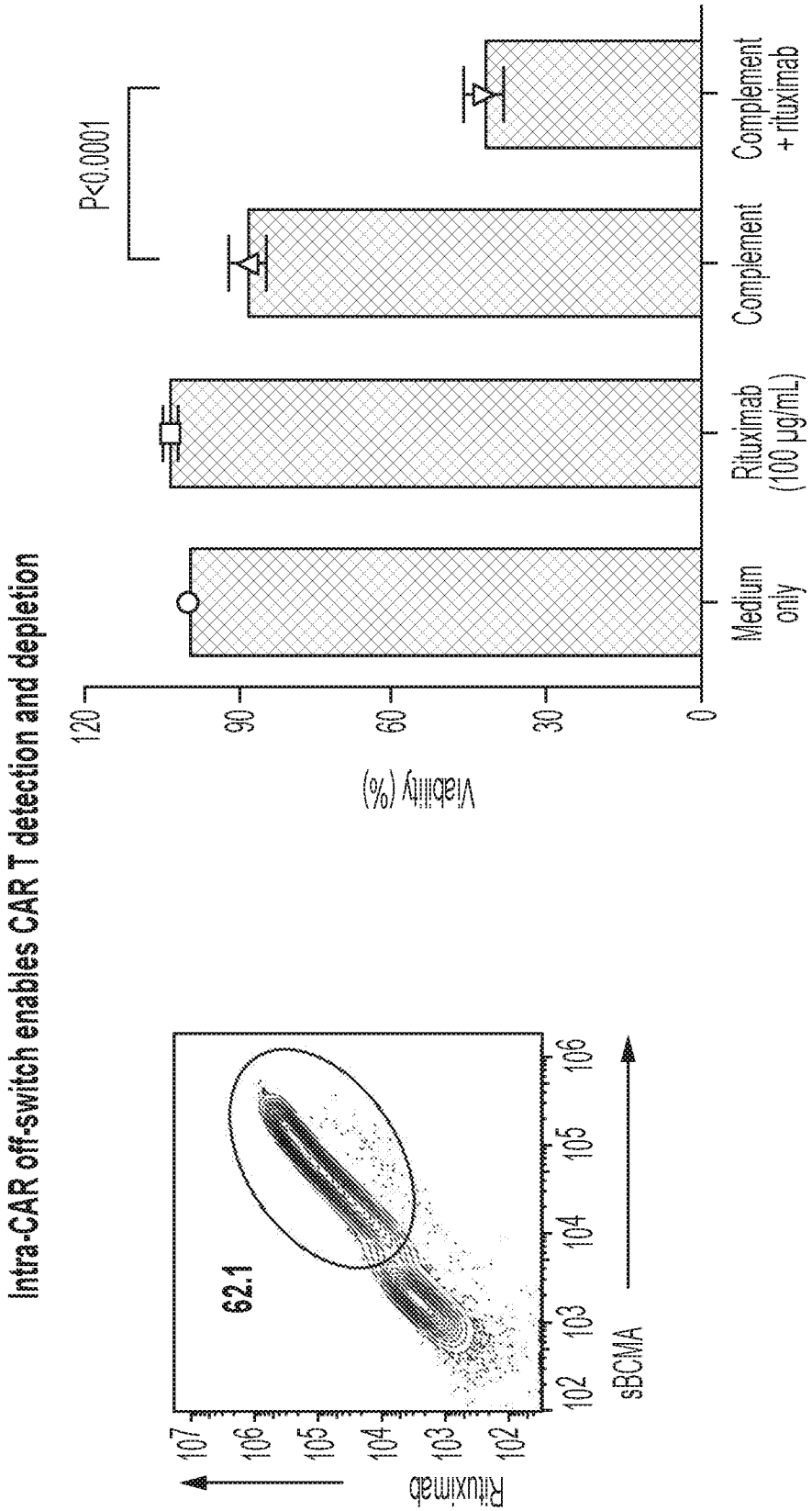

Intra-CAR off-switch enables CAR T detection and depletion
62.1
Rituximab
sBCMA
Viability (%)
P<0.0001
Medium only
Rituximab (100 µg/mL)
Complement
Complement + rituximab

FIG. 2

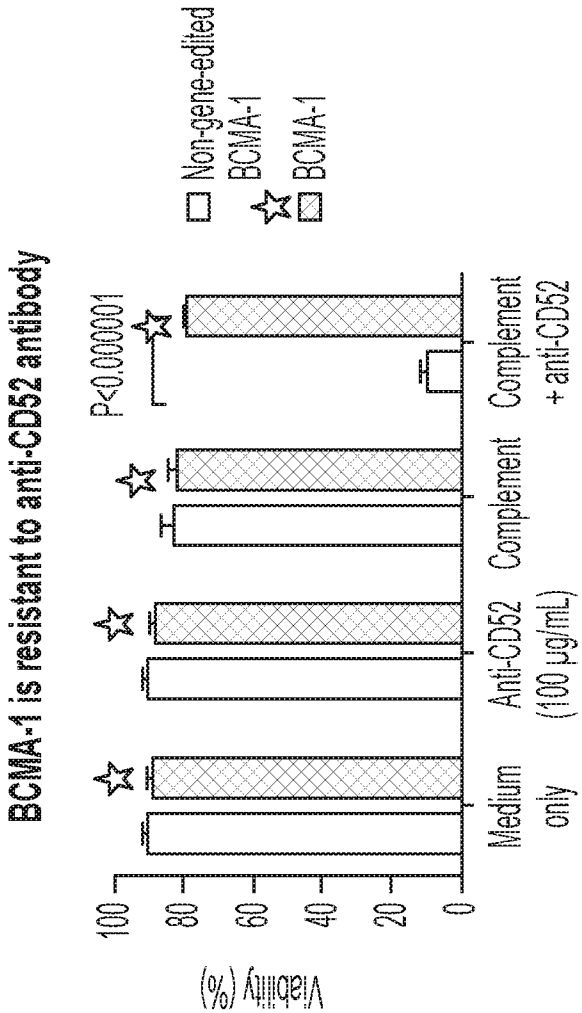

BCMA-1 is resistant to anti-CD52 antibody
Viability (%)
100
80
60
40
20
0
P<0.000001
Non-gene-edited
BCMA-1
BCMA-1
Medium only
Anti-CD52 (100 µg/mL)
Complement
Complement + anti-CD52

FIG. 3

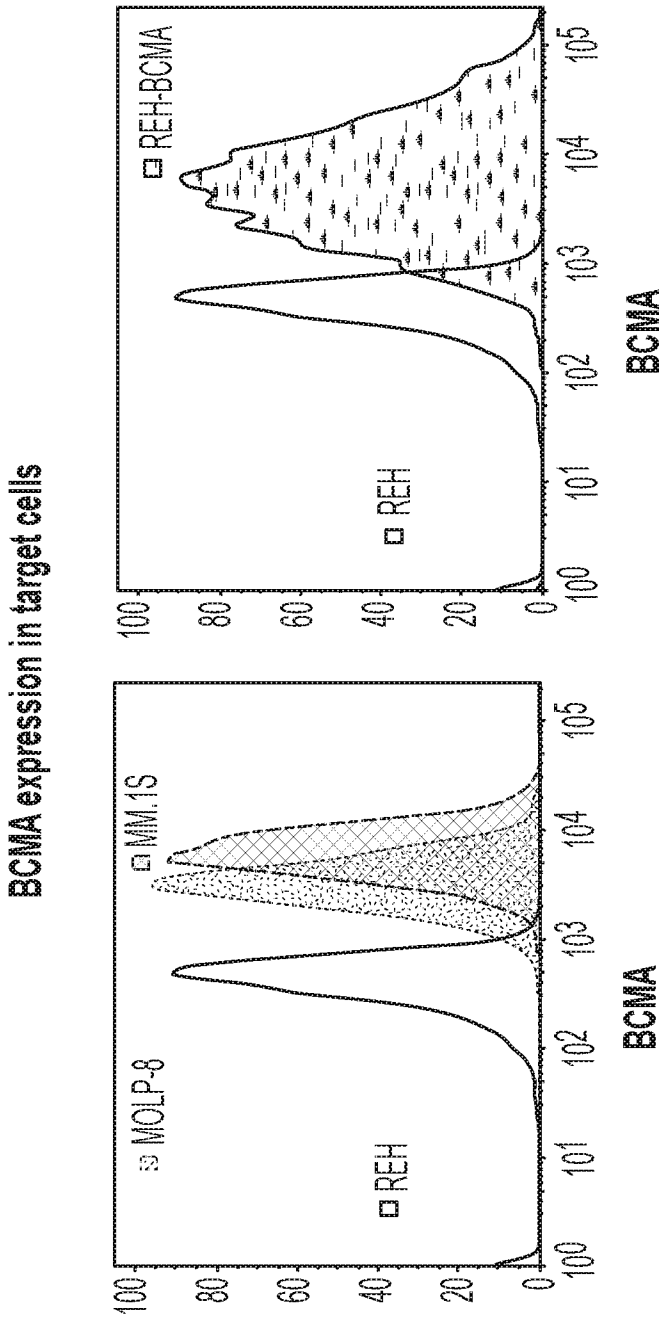

BCMA expression in target cells
MOLP-8
REH
MM.1S
REH
REH-BCMA
100
80
60
40
20
0
100
101
102
103
104
105
BCMA
BCMA

FIG. 4

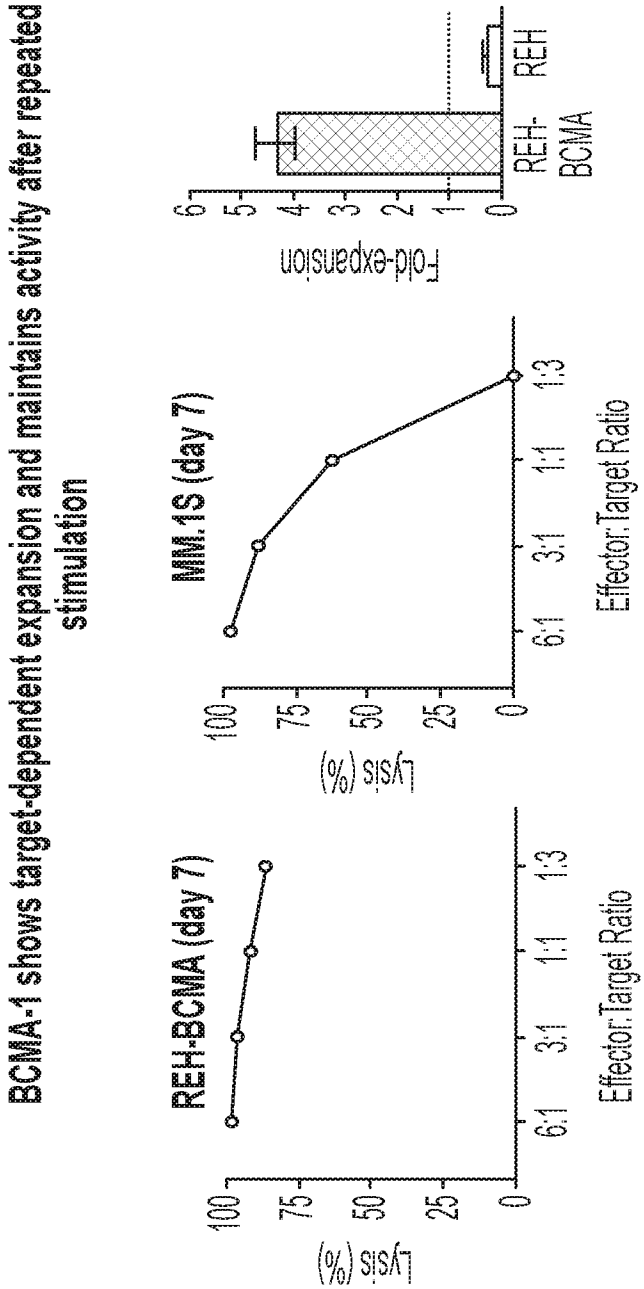

BCMA-1 shows target-dependent expansion and maintains activity after repeated stimulation
REH-BCMA (day 7)
Lysis (%)
100
75
50
25
0
6:1
3:1
1:1
1:3
Effector:Target Ratio
MM.1S (day 7)
Lysis (%)
100
75
50
25
0
6:1
3:1
1:1
1:3
Effector:Target Ratio
Fold-expansion
6
5
4
3
2
1
0
REH-BCMA
REH

FIG. 5

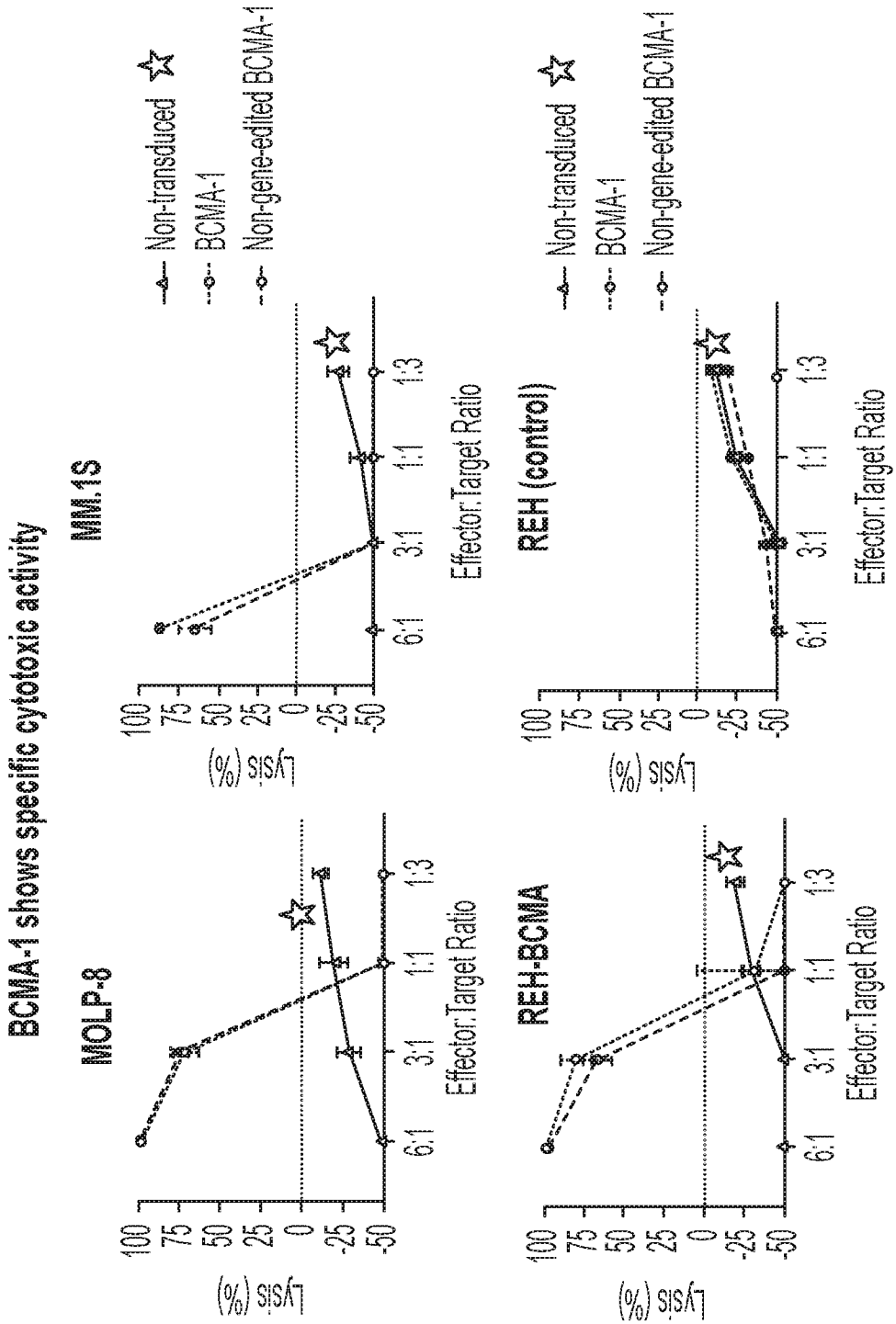

BCMA-1 shows specific cytotoxic activity
MOLP-8
MM.1S
REH-BCMA
REH (control)
Non-transduced
BCMA-1
Non-gene-edited BCMA-1
Lysis (%)
100
75
50
25
0
-25
-50
6:1
3:1
1:1
1:3
Effector:Target Ratio

FIG. 6

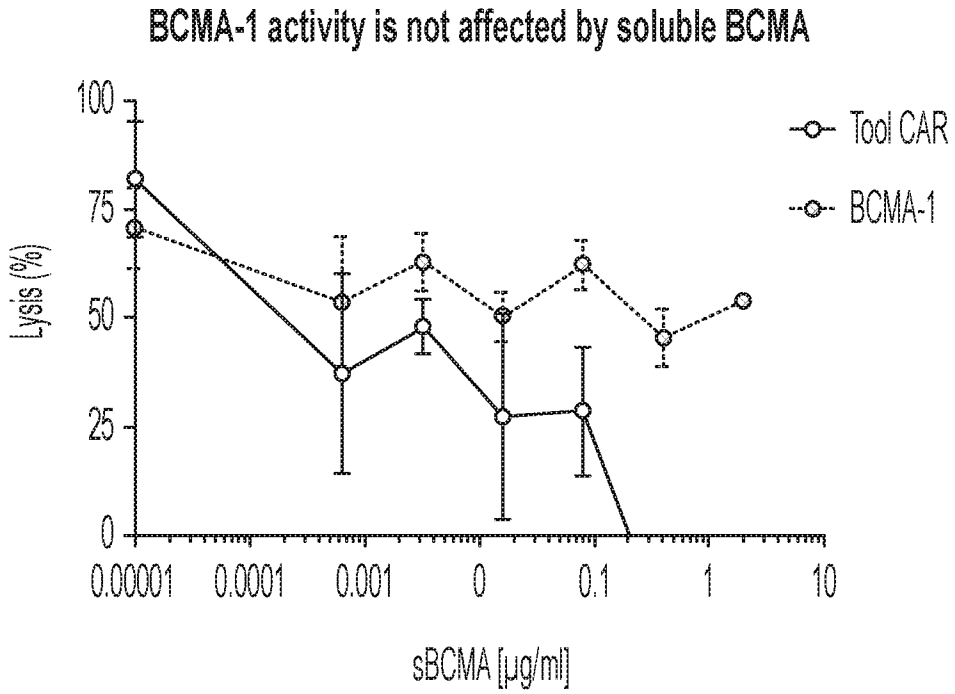

BCMA-1 activity is not affected by soluble BCMA
Tool CAR
BCMA-1
Lysis (%)
100
75
50
25
0
0.00001
0.0001
0.001
0
0.1
1
10
sBCMA [µg/ml]

FIG. 7

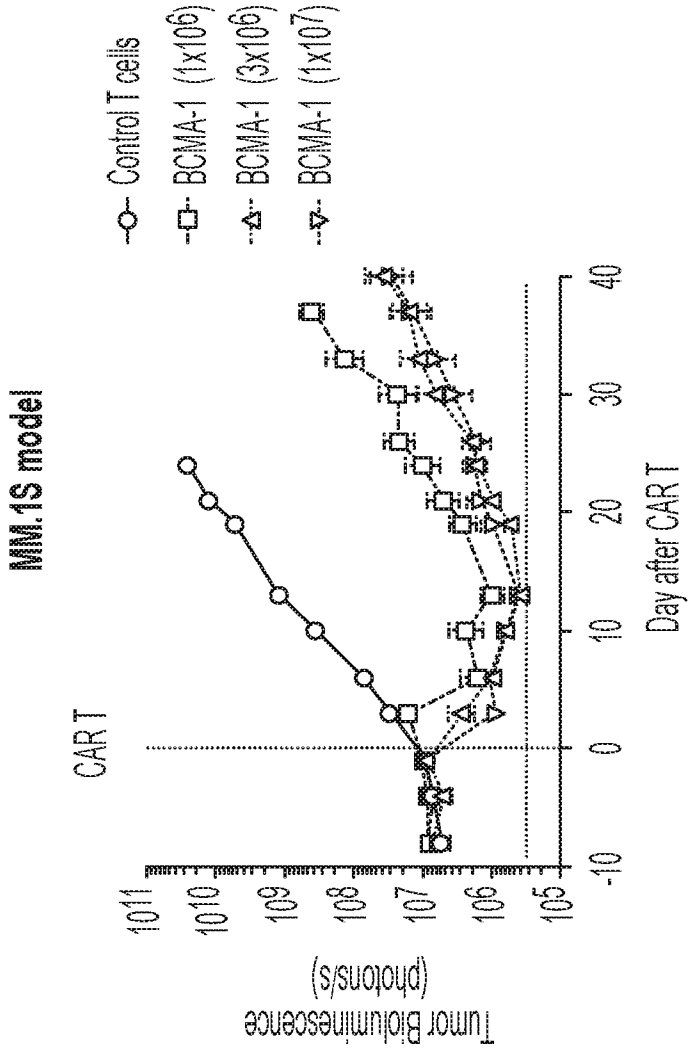

MM.1S model
CAR T
Control T cells
BCMA-1 (1x10^6)
BCMA-1 (3x10^6)
BCMA-1 (1x10^7)
Tumor Bioluminescence (photons/s)
10^11
10^10
10^9
10^8
10^7
10^6
10^5
-10
0
10
20
30
40
Day after CAR T

FIG. 8

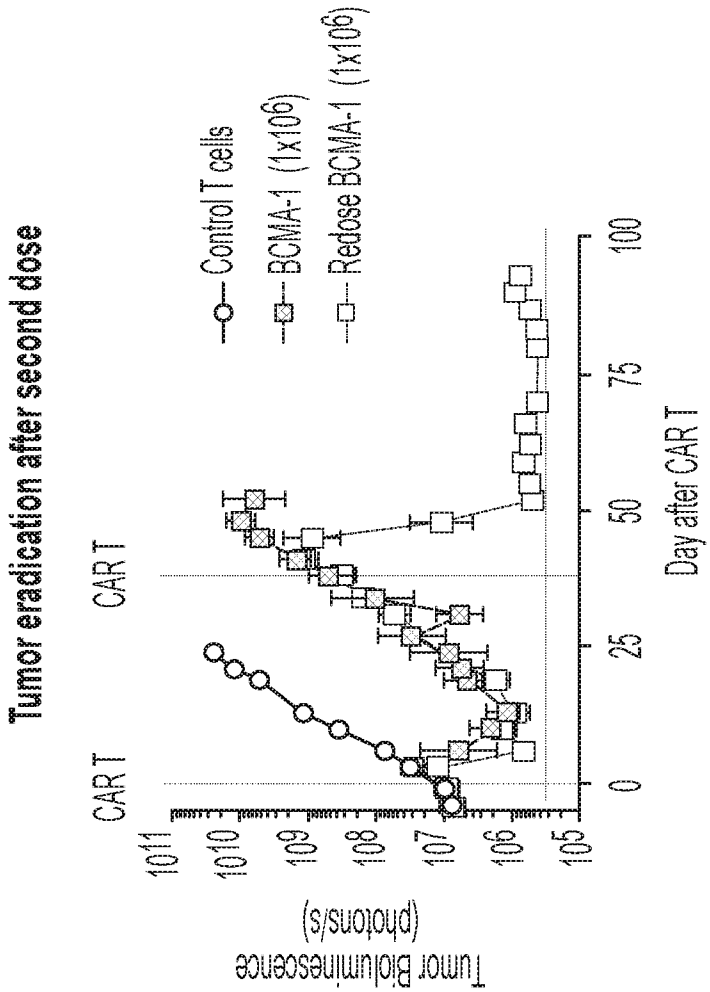

Tumor eradication after second dose
CAR T
CAR T
Control T cells
BCMA-1 (1x10^6)
Redose BCMA-1 (1x10^6)
Tumor Bioluminescence (photons/s)
10^11
10^10
10^9
10^8
10^7
10^6
10^5
0
25
50
75
100
Day after CAR T

FIG. 9

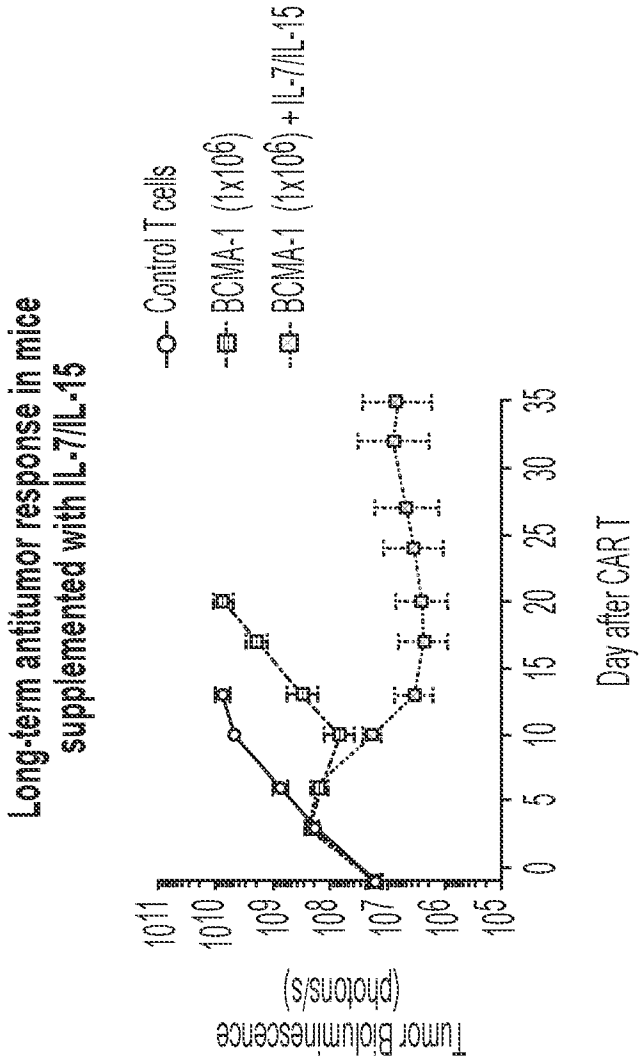

Long-term antitumor response in mice supplemented with IL-7/IL-15
Control T cells
BCMA-1 (1x10^6)
BCMA-1 (1x10^6) + IL-7/IL-15
Tumor Bioluminescence (photons/s)
10^11
10^10
10^9
10^8
10^7
10^6
10^5
0
5
10
15
20
25
30
35
Day after CAR T

FIG. 10

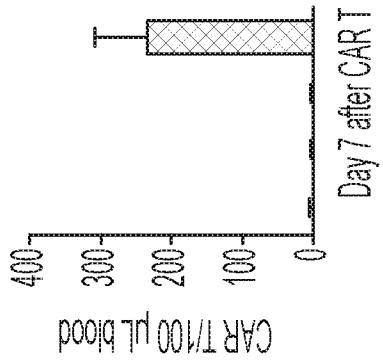


FIG. 11B

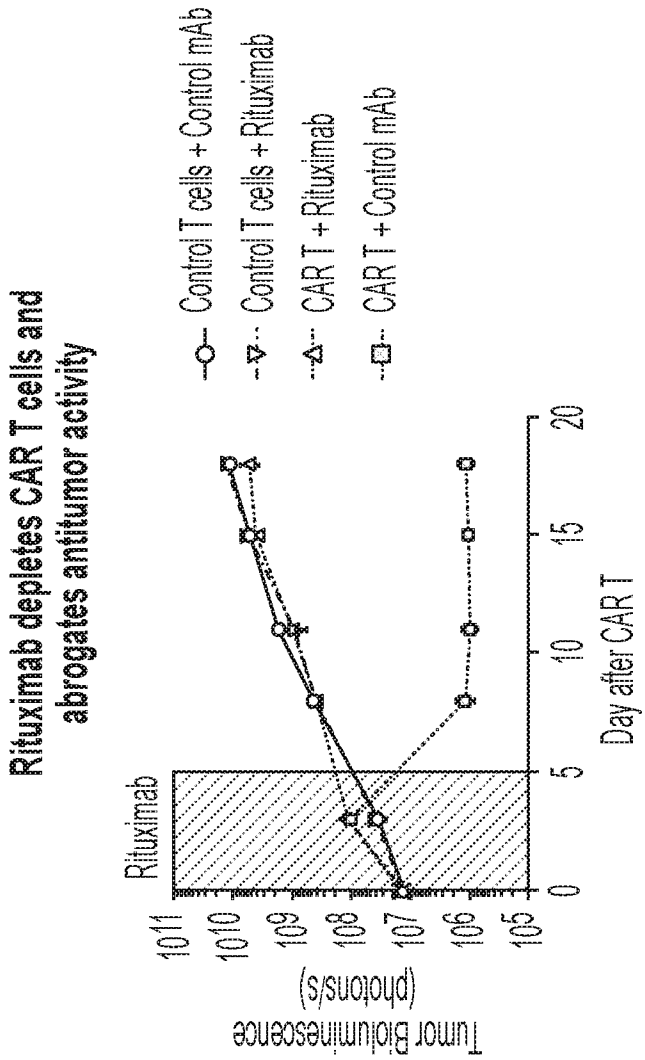


FIG. 11A

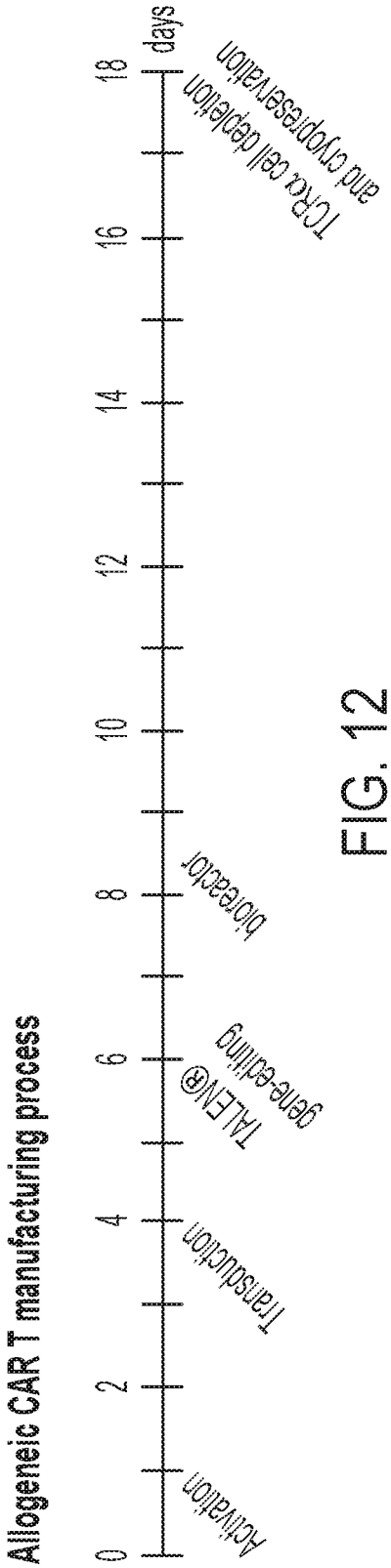

Allogeneic CAR T manufacturing process
0
2
4
6
8
10
12
14
16
18
days
Activation
Transduction
TALEN®
gene-editing
bioreactor
TCRα cell depletion
and cryopreservation

FIG. 12

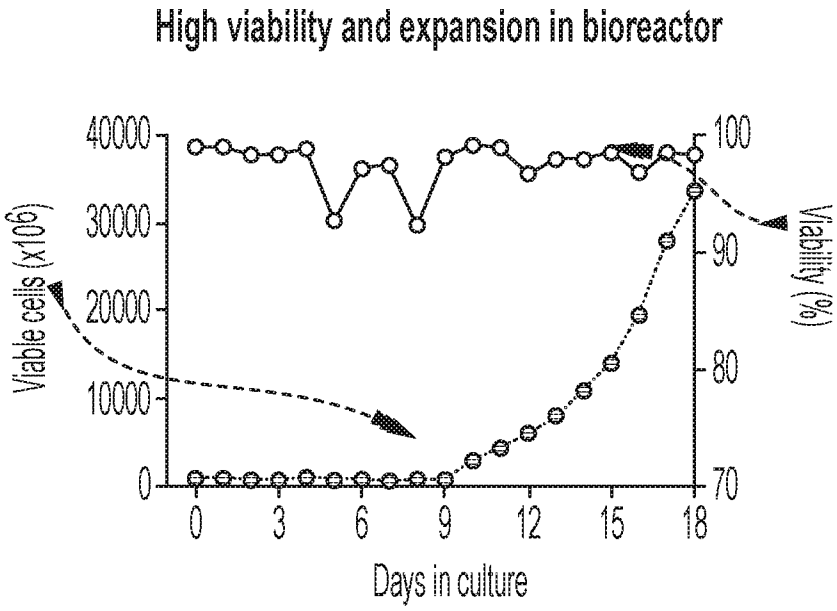

High viability and expansion in bioreactor
Viable cells (x10^6)
40000
30000
20000
10000
0
Viability (%)
100
90
80
70
0
3
6
9
12
15
18
Days in culture

FIG. 13

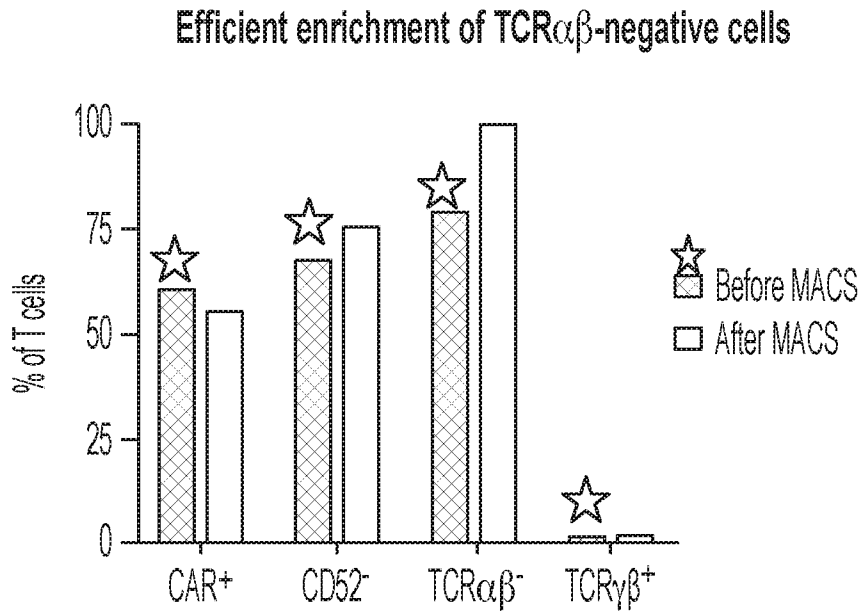

Efficient enrichment of TCRαβ-negative cells
100
75
50
25
0
% of T cells
CAR+
CD52-
TCRαβ-
TCRγβ+
Before MACS
After MACS

FIG. 14

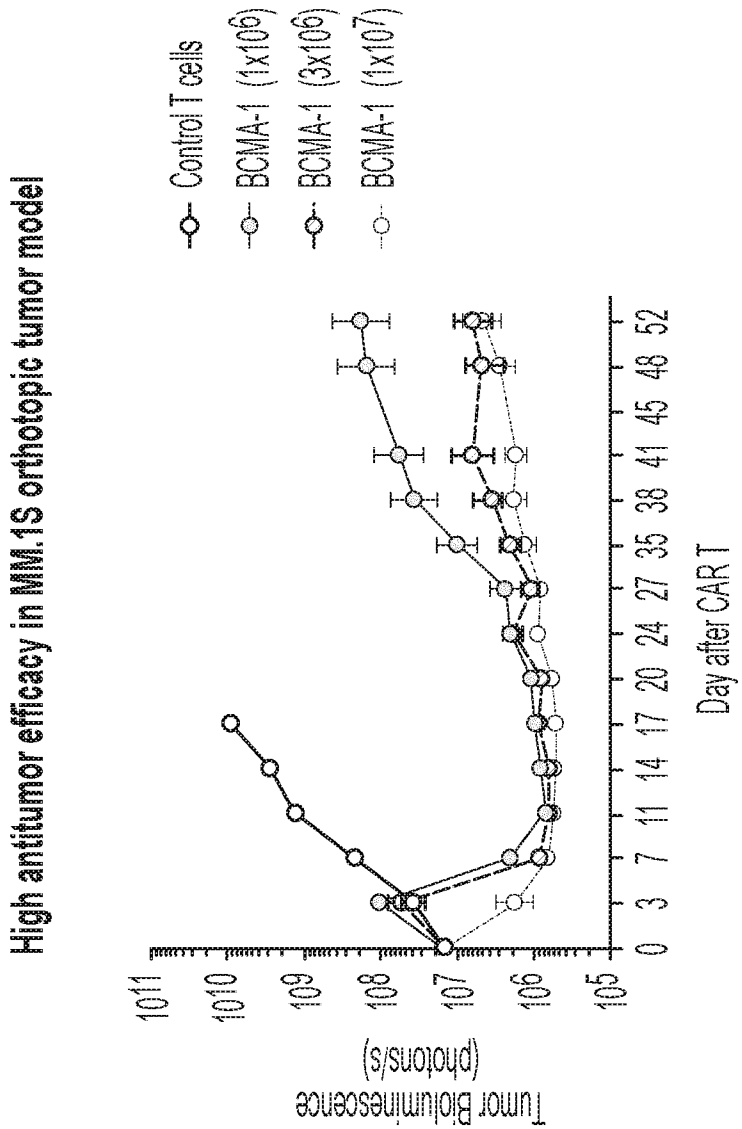

High antitumor efficacy in MM.1S orthotopic tumor model
Control T cells
BCMA-1 (1x10^6)
BCMA-1 (3x10^6)
BCMA-1 (1x10^7)
Tumor Bioluminescence (photons/s)
10^11
10^10
10^9
10^8
10^7
10^6
10^5
0 3 7 11 14 17 20 24 27 35 38 41 45 48 52
Day after CAR T

FIG. 15

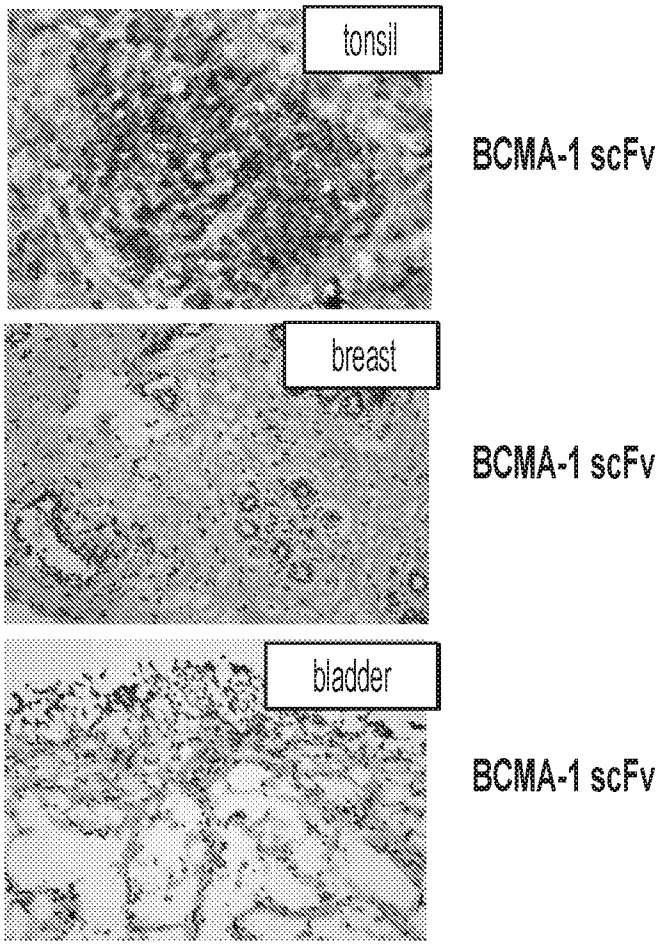


FIG. 16

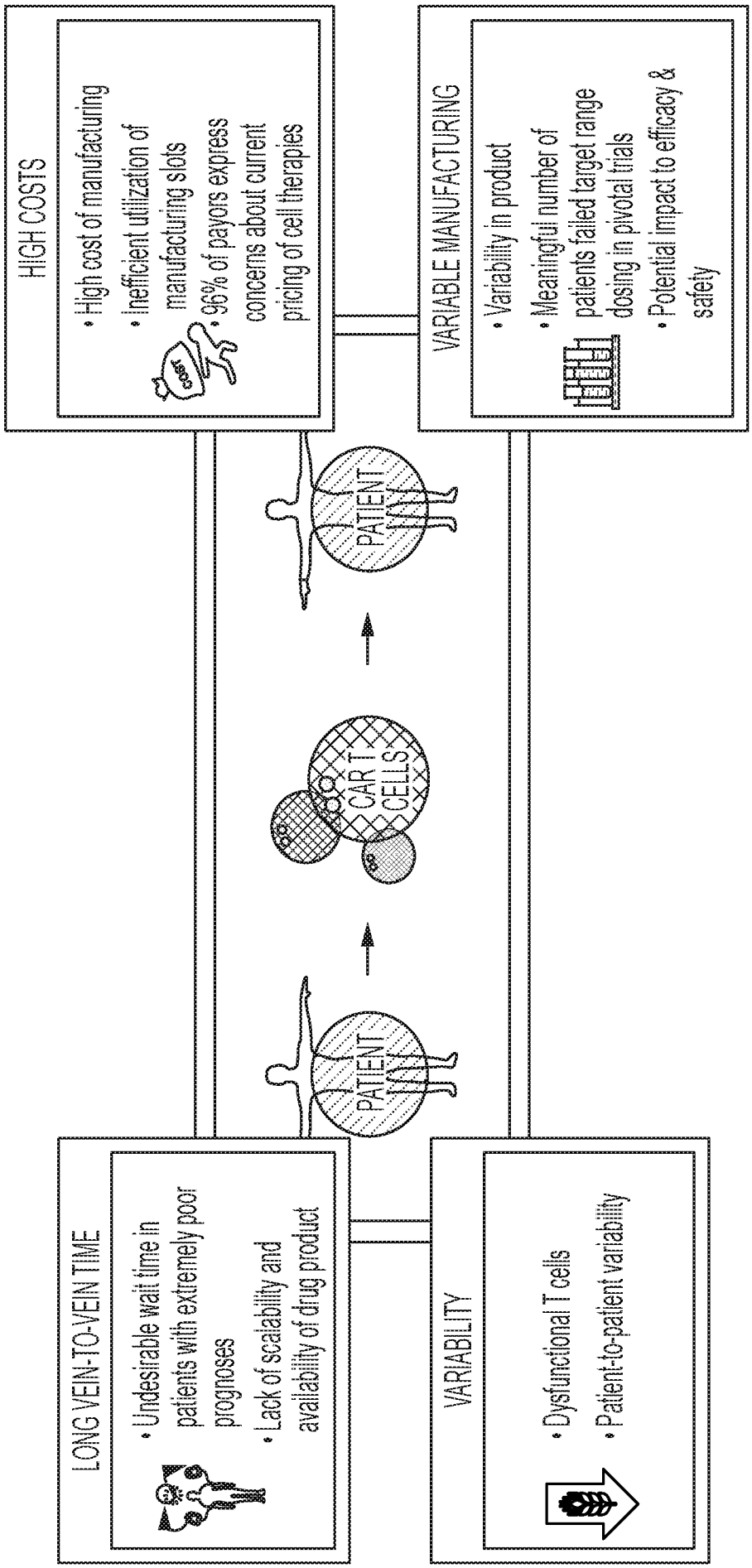

HIGH COSTS
• High cost of manufacturing
• Inefficient utilization of manufacturing slots
• 96% of payors express concerns about current pricing of cell therapies
VARIABLE MANUFACTURING
• Variability in product
• Meaningful number of patients failed target range dosing in pivotal trials
• Potential impact to efficacy & safety
PATIENT
CAR T CELLS
PATIENT
LONG VEIN-TO-VEIN TIME
• Undesirable wait time in patients with extremely poor prognoses
• Lack of scalability and availability of drug product
VARIABILITY
• Dysfunctional T cells
• Patient-to-patient variability

FIG. 17

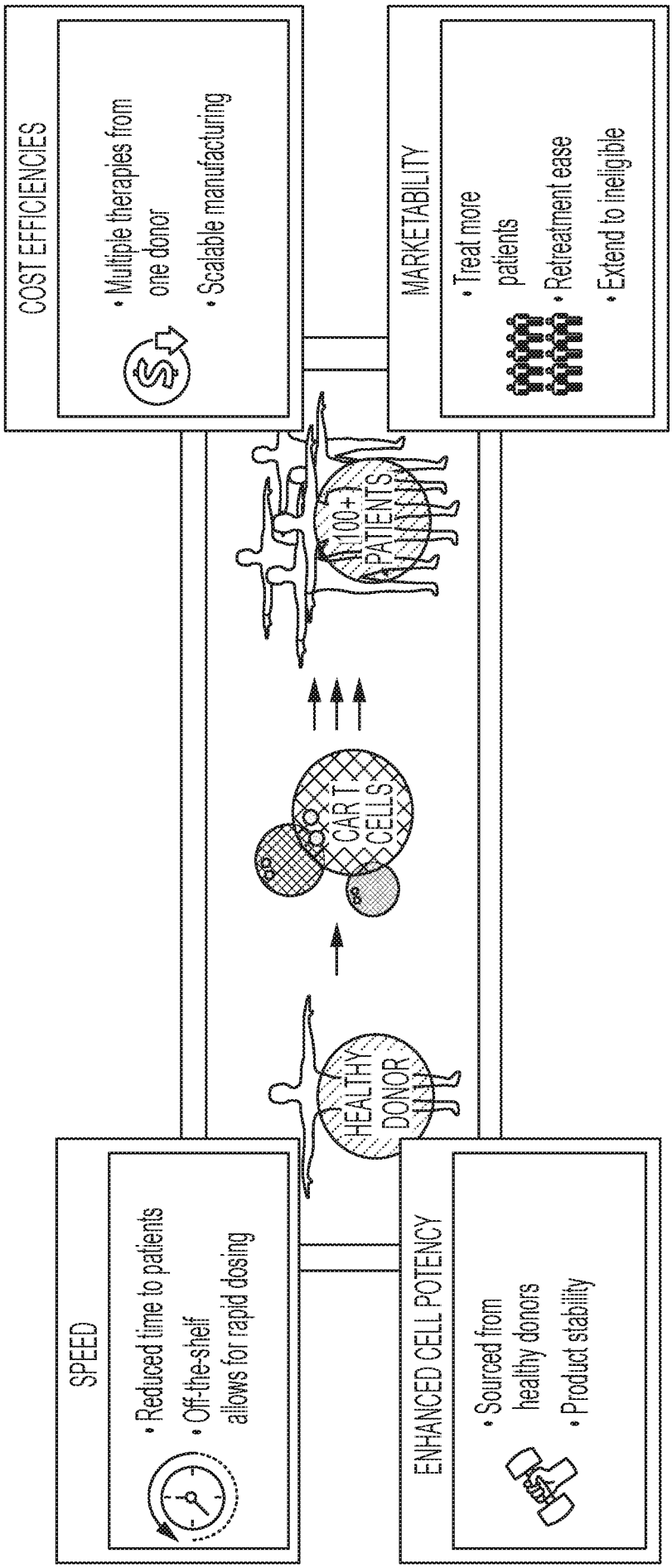

COST EFFICIENCIES
• Multiple therapies from one donor
• Scalable manufacturing
MARKETABILITY
• Treat more patients
• Retreatment ease
• Extend to ineligible
N100+ PATIENTS
CAR T CELLS
HEALTHY DONOR
SPEED
• Reduced time to patients
• Off-the-shelf allows for rapid dosing
ENHANCED CELL POTENCY
• Sourced from healthy donors
• Product stability

FIG. 18

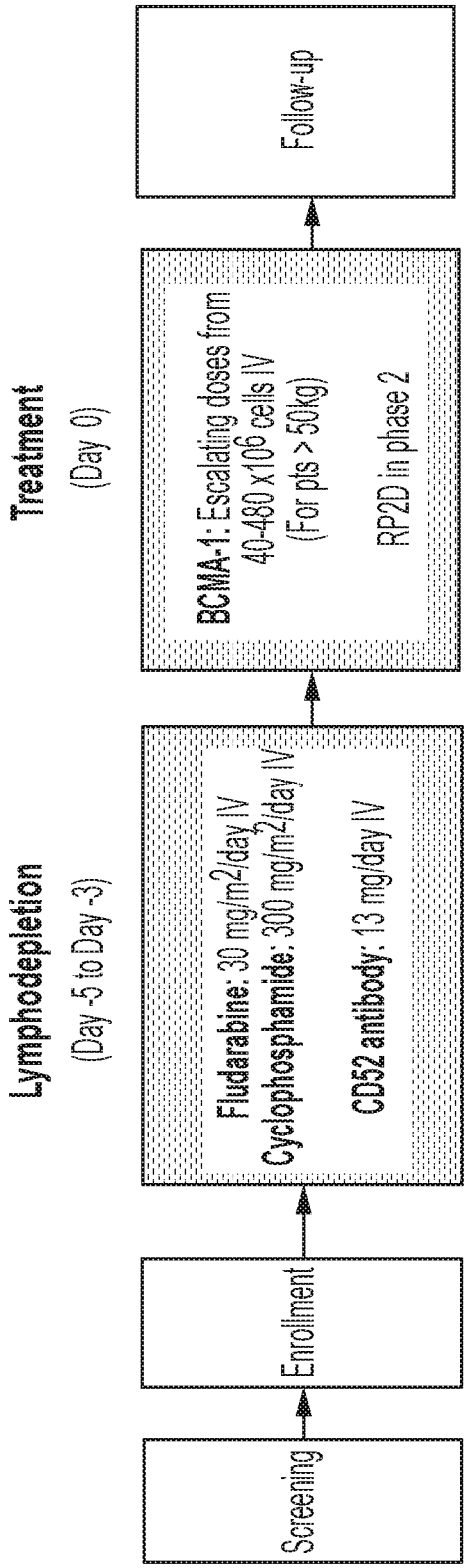
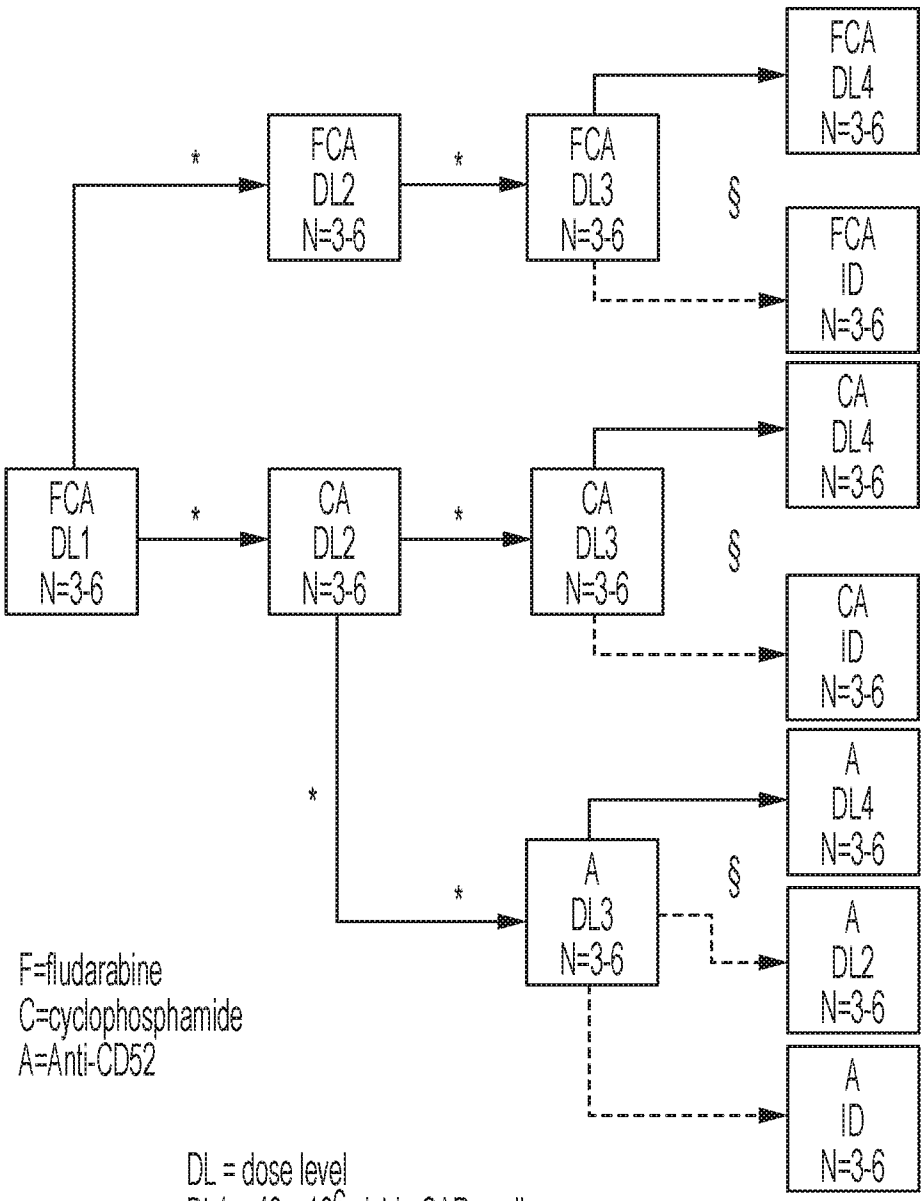

Screening
Enrollment
Lymphodepletion
(Day -5 to Day -3)
Fludarabine: 30 mg/m2/day IV
Cyclophosphamide: 300 mg/m2/day IV
CD52 antibody: 13 mg/day IV
Treatment
(Day 0)
BCMA-1: Escalating doses from
40-480 x10^6 cells IV
(For pts > 50kg)
RP2D in phase 2
Follow-up

FIG. 19



DL = dose level
DL1 = 40 x 10^6 viable CAR+ cells
DL2 = 160 x 10^6 viable CAR+ cells
DL3 = 320 x 10^6 viable CAR+ cells
ID = intermediate dose. A dose level between DL1 and DL3 if toxicity observed with DL3 or to determine a lower dose that is efficacious.
DL4 = 480 x 10^6 viable CAR+ cells. To be done if inadequate efficacy parameters are seen in DL3.

* If safety is maintained in the previous cohort then the dose escalation will move to the next cohort shown by the arrow.
If multiple cohorts are open at the same time, patients will be assigned to a specific cohort based on practical consideration.
§ DL4 or ID or neither.

FIG. 20

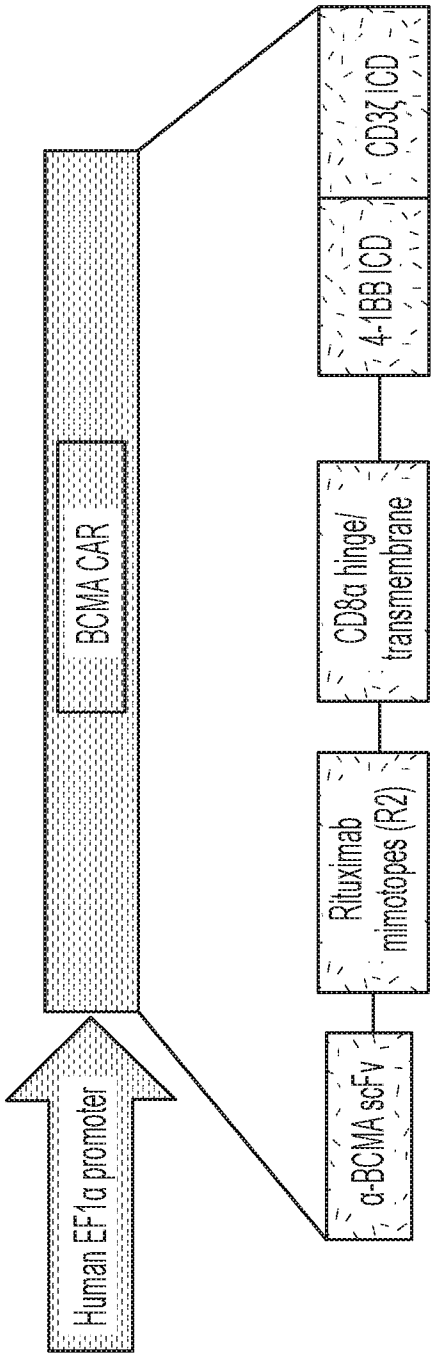

Human EF1α promoter
BCMA CAR
α-BCMA scFv
Rituximab mimotopes (R2)
CD8α hinge/ transmembrane
4-1BB ICD
CD3ζ ICD

FIG. 21

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/063282

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61P35/00 A61K35/17 C07K14/725 C07K16/28 C12N5/0783
ADD. A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61P C07K A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, Sequence Search, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/297884 A1 (KUO TRACY CHIA-CHIEN [US] ET AL) 13 October 2016 (2016-10-13) cited in the application	1-48
Y	table 4c paragraphs [0031], [0141], [0144] paragraphs [0188], [0189] paragraph [0033] - paragraph [0034] -----	50,51
Y	N.N.: "Yescarta - SPC", , 10 September 2018 (2018-09-10), pages 1-39, XP55671010, Retrieved from the Internet: URL:https://www.ema.europa.eu/en/documents/product-information/yescarta-epar-product-information_en.pdf [retrieved on 2020-02-21] page 35 -----	50,51
	-/--	

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 February 2020	06/03/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Wagner, René

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/063282

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2015/158671 A1 (CELLECTIS [FR]) 22 October 2015 (2015-10-22) the whole document -----	1-51
A	WASEEM QASIM ET AL: "Molecular remission of infant B-ALL after infusion of universal TALEN gene-edited CAR T cells", SCIENCE TRANSLATIONAL MEDICINE, vol. 9, no. 374, 25 January 2017 (2017-01-25), page eaaj2013, XP055498786, US ISSN: 1946-6234, DOI: 10.1126/scitranslmed.aaj2013 the whole document -----	1-51

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2019/063282

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		WO 2015158671 A1	22-10-2015