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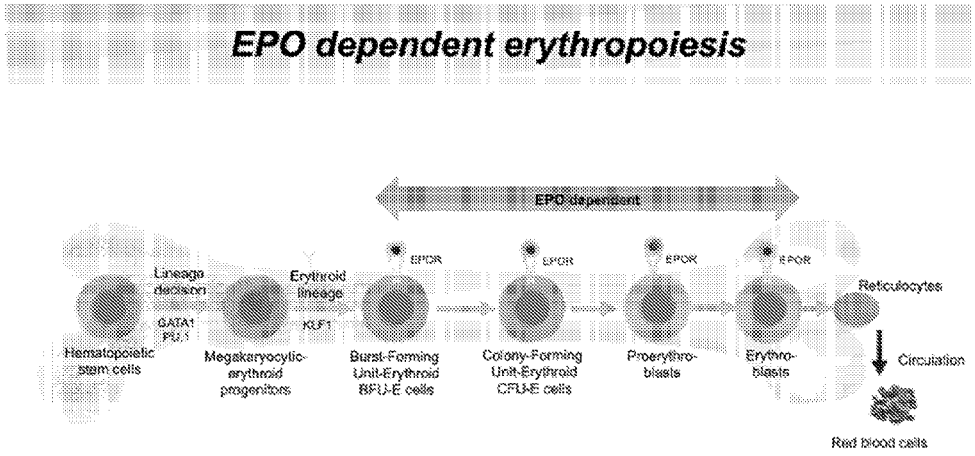


FIG. 1

(57) Abstract: The present disclosure provides EPO analogs, anti-EPOR antibodies, anti-EPO antibodies, and fragments thereof that specifically bind to the hetero-EPOR or homo-EPOR or EPO with high affinity. Also provided herein are engineered EPOs. The EPO analogs, anti-EPOR antibodies, anti-EPO antibodies, and/or engineered EPOs can be used to treat patients.

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EPO RECEPTOR AGONISTS AND ANTAGONISTS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/317,943, filed on March 8, 2022, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE DISCLOSURE

[0002] Erythropoietin (EPO) induces hematopoiesis by dimerizing EPO receptor (EPOR) molecules, which leads to the activation of the EPO receptor-associated Janus tyrosine kinase 2 (Jak2) and secondary signaling molecules such as Ssignal transducer and activator of transcription 5 (Stat5; Brines and Cerami, Nat Rev Neurosci, 2005; 6:484-94). EPO acts by binding to EPOR which is expressed on erythroid progenitor cells to inhibit apoptosis and promote cell survival, proliferation, and differentiation in production of mature red blood cells (**FIG. 1**). However, EPOR expression is not restricted to erythroid tissue. EPOR is also expressed in a number of non-hematopoietic tissues and elicits tissue protective effects in ischemic injury and promotes wound healing, cardiovascular protection, angiogenesis, neuroprotection, regulation of metabolic homeostasis, and bone remodeling.

SUMMARY OF THE DISCLOSURE

[0003] There are two major tyrosine kinase receptors for EPO: the homodimeric EPOR/EPOR ("homo-EPOR") and the heterodimeric EPOR/CD131 receptor ("hetero-EPOR"). The homo-EPOR signaling is critical for erythropoiesis, whereas the hetero-EPOR signaling is known to have tissue protection activities and can be involved in EPO-mediated immune-modulatory function on immune cells (e.g., myeloid cells, T-cells and B cells). Modulation of the EPO signaling through the hetero-EPOR can provide benefits in various pathological conditions, including but not limited to, inhibiting or stimulating immune response, inducing or breaking antigen-specific tolerance, stimulating erythropoiesis without immune tolerogenic or suppressive effects, providing neuroprotection and tissue protection without stimulating erythropoiesis, and inducing prophylactic or therapeutic immunity.

[0004] The present disclosure relates to new erythropoietin (EPO) analogs, and new EPO related antibodies. EPO analogs disclosed herein can include, for example, eight types. EPO analogs can bind the hetero-EPOR and not the homo-EPOR, and can be either agonists or antagonists of the hetero-EPOR. Other EPO analogs can bind the homo-EPOR and not the hetero-EPOR, and can be either agonists or antagonists of the homo-EPOR. EPO analogs can bind both the homo-EPOR and the hetero-EPOR and be agonists for both, antagonists for both,

or agonist for one and antagonist for the other. At least four types of anti-EPO receptor (anti-EPOR) antibodies can be obtained. Anti-EPOR antibodies can be agonists or antagonists of the hetero-EPOR, and anti-homo-EPOR antibodies can be agonists or antagonists of the homo-EPOR. At least two types of anti-CD131 antibodies can be obtained. Anti-CD131 antibodies can be agonists or antagonists of the hetero-EPOR. At least three types of anti-EPO antibodies can be obtained. Anti-EPO antibodies can inhibit binding to the homo-EPOR, inhibit binding to the hetero-EPOR, or inhibit EPO binding to both homo-EPOR and hetero-EPOR.

[0005] The antibodies disclosed herein, can include fragments thereof that specifically bind to the homo-EPOR, the hetero-EPOR, EPO, CD131, or a combination thereof with high binding affinity (collectively the hetero-EPOR and homo-EPOR are called "EPOR"). The antibodies can be monoclonal, and can be human, chimeric, or humanized antibodies. Chimeric anti-EPOR antibodies and/or anti-EPO antibodies, including fragments thereof, may have non-human (e.g., murine) complementarity-determining regions (CDRs) and/or non-human framework region(s), and optionally one or more human constant domains. Humanized anti-EPOR antibodies and/or humanized anti-EPO antibodies, including fragments thereof, may have non-human (e.g., murine) CDRs and/or human framework region(s), and optionally non-human framework amino acid residues adjacent to CDRs and optionally one or more human constant domains. In some embodiments, antibodies disclosed herein can be grafted antibodies.

[0006] The humanized antibodies disclosed herein can represent anti-EPOR and/or anti-EPO antibodies obtained from grafting the CDRs into a human framework for a heavy chain and/or a human framework for a light chain, along with a select number of framework residues from the mouse antibody. Anti-EPOR antibodies and/or anti-EPO antibodies disclosed herein also include those obtained from an affinity maturation library made from an anti-EPOR antibody or anti-EPO antibody. An anti-EPOR antibody and/or an anti-EPO antibody can also include a heavy chain variable region that has 99%, 95%, 90%, 80% or 70% sequence identity with one of the heavy chains, and a light chain variable region that has 99%, 95%, 90%, 80% or 70% sequence identity with one of the light chains. An anti-EPOR antibody can bind to a homo-EPOR or a hetero-EPOR with an affinity of from about 0.1 pM to about 300 nM, from about 1.0 nM to about 10.0 nM, from about 50 nM to about 100 nM, or from about 1.0 to about 100 nM. An anti-EPOR antibody can bind to a homo-EPOR or a hetero-EPOR with an affinity of at least about 100 nM, at least about 50 nM, at least about 10 nM, at least about 5 nm, or at least about 1.0 nM. An anti-EPO antibody can bind to EPO with an affinity of from about 1.0 nM to about10 nM, from about 50 nM to about 100 nM, or from about 1.0 to about 100 nM. An anti-EPO antibody can bind to EPO with an affinity of at least about 100 nM, at least about 50 nM, at least about 10 nM, at least about 5.0 nm, or at least about 1.0 nM.

[0007] The anti-EPOR antibodies and/or anti-EPO antibodies described herein may include modifications that provide a desired property to the antibody. For example, modifications can increase the serum half-life of the antibody or the modification can decrease serum half-life. The modification can also increase or decrease the effector function of the antibody. The modification can decrease immunogenicity, or reduce other unwanted side effects or adverse events caused by the antibodies.

[0008] EPO analogs that are antagonists for the hetero-EPOR, anti-hetero-EPOR antibodies that are antagonists for the hetero-EPOR, anti-CD131 antibodies that are antagonists for the hetero-EPOR, and/or anti-EPO antibodies that inhibit binding of EPO to the hetero-EPOR can be used to overcome immunosuppressive or tolerogenic states in a subject. For example, these EPO analogs, anti-hetero-EPOR antibodies, anti-CD131 antibodies and/or anti-EPO antibodies can be used to overcome a tumor immune suppressive microenvironment, boost immune response to vaccines, and/or enhance the immune response during an acute inflammatory response to disease (e.g., an infection from a microorganism or a virus).

[0009] EPO analogs that are agonists for the hetero-EPOR, anti-CD131 antibodies that are agonists for the hetero-EPOR, and/or anti-EPOR antibodies that are agonists for the hetero-EPOR can be used to induce a negative immune modulation in a subject (e.g., an immunosuppressive or tolerogenic state). For example, these EPO analogs, anti-CD131 antibodies that are agonists for the hetero-EPOR, and/or anti-hetero-EPOR antibodies can be used to suppress transplant rejection, induce antigen specific immune tolerance, reduce immune reaction in autoimmune diseases, reduce systemic chronic inflammation, and reduce damage to neural tissue and other tissue during injury or other stress. These EPO analogs, anti-CD131 antibodies that are agonists for the hetero-EPOR, and/or anti-hetero-EPOR antibodies can also be administered with an antigen to induce an immunotolerogenic state to the antigen.

[0010] EPO analogs that are agonists for the homo-EPOR and do not bind or are antagonists of the hetero-EPOR, and/or anti-EPO antibodies that inhibit binding of EPO to the hetero-EPOR, and/or anti-CD131 antibodies that inhibit binding of EPO to the hetero-EPOR, and/or anti-hetero-EPOR antibodies that are antagonists for the hetero-EPOR can be used with or without erythropoietin-stimulating agents (ESA) for cancer patients in need to an ESA treatment. Any cancer patient needing an ESA can be provided the ESA combined with these EPO analogs, and/or anti-EPOR antibodies, and/or anti-EPO antibodies.

[0011] Modulation of signaling from the homo-EPOR or hetero-EPOR can be done with RNA or small molecules. Stimulation of signaling from the homo-EPOR or hetero-EPOR may be achieved by delivery of mRNA of a positive regulator, siRNA of a negative regulator, small molecules that upregulate a positive regulator, or small molecules that downregulate a negative

regulator. Inhibition of signaling from the homo-EPOR or hetero-EPOR may be achieved by delivery of mRNA of a negative regulator, siRNA of a positive regulator, small molecules that upregulate a negative regulator, or small molecules that downregulate a positive regulator.

[0012] In some aspects, provided herein, is a composition comprising an antibody or a functional fragment thereof, wherein: (i) said antibody or said functional fragment thereof selectively binds to a target comprising an erythropoietin (EPO) protein, an EPO receptor subunit, a CD131 subunit, or a combination thereof; (ii) binding of said antibody or said functional fragment thereof to said target prevents (a) formation of an EPO protein-hetero-EPO receptor complex, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit, (b) formation of a hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or (c) activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit; and (iii) said antibody or said functional fragment thereof comprises an antigen binding domain.

[0013] In some aspects, provided herein is a method for treating cancer, wherein said method comprises administering a composition or a derivative thereof to a subject having cancer or at risk of having cancer, wherein said composition or said derivative thereof inhibits a hetero-erythropoietin (EPO) receptor activity in said subject.

[0014] In some aspects, provided herein, is a composition comprising an antibody or a functional fragment thereof, wherein: (i) said antibody or said functional fragment thereof selectively binds to a target comprising an erythropoietin (EPO) protein, an EPO receptor subunit, a CD131 subunit, or a combination thereof; (ii) binding of said antibody or said functional fragment thereof to said target promotes (a) formation of an EPO protein-hetero-EPO receptor complex, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit, (b) formation of a hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or (c) activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit; and (iii) said antibody or said functional fragment thereof comprises an antigen binding domain.

[0015] In some aspects, provided herein is a composition for administering to a subject having cancer or chronic infection condition, wherein said composition or derivative thereof inhibits erythropoietin (EPO) receptor activity in a myeloid cell in said subject.

[0016] In some aspects, provided herein is a composition comprising an engineered erythropoietin (EPO) protein, wherein said engineered EPO protein inhibits a hetero-erythropoietin (EPO) receptor activity in a myeloid cell. In some embodiments, said engineered EPO protein comprises at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E,

R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A, R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A.

[0017] In some aspects, provided herein, is a composition comprising an engineered erythropoietin (EPO) protein, wherein: said engineered EPO protein comprises at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A , R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A; and said engineered EPO protein inhibits a hetero-erythropoietin (EPO) receptor activity in a myeloid cell.

[0018] In some aspects, provided herein is a composition comprising an engineered erythropoietin (EPO) protein, wherein said engineered EPO protein promotes a hetero-erythropoietin (EPO) receptor activity to reduce immune response, wherein said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit. In some embodiments, said engineered EPO protein comprises at least one amino acid modification and/or at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A, R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A.

[0019] In some aspects, provided herein, is a composition comprising an engineered erythropoietin (EPO) protein, wherein: said engineered EPO protein comprises at least one amino acid modification and/or at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A , R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A; and said engineered EPO protein promotes a hetero-erythropoietin (EPO) receptor activity, wherein said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit.

[0020] In some aspects, provided herein is composition comprising an engineered erythropoietin (EPO) protein, said engineered EPO protein promotes a homo-erythropoietin (EPO) receptor activity and has reduced effect on a hetero-EPO receptor activity, wherein said homo-EPO receptor comprises at least two EPO receptor subunits and said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit. In some embodiments, said engineered EPO protein comprises at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A, R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A.

[0021] In some aspects, provided herein, is a composition comprising an engineered erythropoietin (EPO) protein, wherein: said engineered EPO protein comprises at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A , R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A; and said engineered EPO protein promotes a homo-erythropoietin (EPO) receptor activity and has no substantial effect on a hetero-EPO receptor activity, wherein said homo-EPO receptor comprises at least two EPO receptor subunits and said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit.

[0022] In some aspects, provided herein, is a composition comprising an engineered erythropoietin (EPO) protein, wherein: said engineered EPO protein comprises at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A , R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A; and said engineered EPO protein promotes a hetero-erythropoietin (EPO) receptor activity and has no substantial effect on a homo-EPO receptor activity, wherein said homo-EPO receptor comprises at least two EPO receptor subunits and said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit.

[0023] In some aspects, provided herein, is a composition for administering to a subject having cancer or chronic infection condition, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound inhibits an erythropoietin (EPO) receptor activity in a myeloid cell in said subject.

[0024] In some aspects, provided herein is a composition for administering to a subject having cancer or chronic infection condition, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound inhibits an erythropoietin (EPO) receptor activity so that an immune-checkpoint blockade resistance is reversed in said subject.

[0025] In some aspects, provided herein is a composition for administering to a subject, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound promotes a hetero-erythropoietin (EPO) receptor activity, wherein said hetero-EPO receptor comprises a EpoR subunit and CD131 subunit, so that immune tolerance to an antigen is increased in said subject; and wherein said compound has no substantial effect on a homo-EPO receptor activity wherein said homo-EPO receptor comprises at least two EPO receptor subunits.

[0026] In some aspects, provided herein is a composition for administering to a subject having cancer, comprising an RNA interference (RNAi) molecule, wherein said RNAi binds to an RNA

molecule that is selected from the group consisting of an mRNA molecule that encodes a erythropoietin (EPO) protein, an mRNA molecule that encodes a EPO receptor subunit, an mRNA molecule that encodes a CD131 subunit, and any combination thereof; wherein upon administering said RNAi to said subject, said subject's tumor mass is reduced.

[0027] In some aspects, provided herein is a composition for administering to a subject having cancer, comprising a RNA interference (RNAi) molecule, wherein said RNAi binds to an RNA molecule that is selected from the group consisting of an mRNA molecule that encodes a erythropoietin (EPO) protein, an mRNA molecule that encodes a EPO receptor subunit, an mRNA molecule that encodes a CD131 subunit, and any combination thereof; wherein upon administering said RNAi to said subject, said subject's immune response is increased by inducing more effector T (Teff) cells.

[0028] In some aspects, provided herein is a method for treating cancer in a subject, comprising administering a therapeutically effective amount of a pharmaceutical compositions comprising any one of single stranded siRNAs described herein to said subject in a dose and schedule sufficient to reduce an expression level of a erythropoietin (EPO) protein, a EPO receptor subunit, or a CD131 subunit.

INCORPORATION BY REFERENCE

[0029] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] A better understanding of features and advantages of the present disclosure will be obtained by reference to the following detailed description, which sets forth illustrative embodiments of the disclosure, and the accompanying drawings.

[0031] **FIG. 1** is an overview of erythropoiesis mediated by EPO and the homo-EPOR in erythroid progenitor cells.

[0032] **FIG. 2** is an overview of immune tolerance mediated by EPO and the hetero-EPOR in dendritic cells and macrophages.

[0033] **FIGs. 3A-3B** illustrate gene expression analysis of genes in $EpoR^+$ ($EpoR^+$) vs. $EpoR^-$ ($EpoR^-$). **FIG. 3A** shows a volcano plot of genes upregulated and downregulated in $EpoR^+$ $XCR1^+CD8\alpha^+$cDC1s vs. $EpoR^-$ $XCR1^+CD8\alpha^+$cDC1s. XCR1: XC-Chemokine Receptor 1. CD8α: Cluster of Differentiation 8α. cDC1: Conventional Type 1 Dendritic Cells. **FIG. 3B**

shows a heat map representing RNA-seq gene expression of the top upregulated and downregulated genes in $EpoR^+$ vs. $EpoR^-$.

[0034] **FIGs. 4A-4C** illustrate the effect of hetero-EPOR knockout in dendritic cells (DCs). **FIG. 4A** shows hetero-EPOR expression in DCs. **FIG. 4B** shows the number of donor $TCR\beta^+T$ cells in mice (C57BL/6J), Batf3 knockout mice ($Batf3^{-/-}$), mice with $CD11c^{Cre}$ ($CD11c^{Cre}$), mice with $EPOR^{flox/flox}$ ($EPOR^{flox/flox}$), and mice with knockout of hetero-EPOR in dendritic cells ($EPOR^{\Delta CD11c}$). TCRβ: T-Cell Receptor β. Batf3: Basic Leucine Zipper ATF-Like Transcription Factor 3. CD11c: Cluster of Differentiation 11c. *P* values by the 2-tailed *t* test of independent means. $*P < .05$; $**P < .01$; $***P < .001$; ns, not significant ($P > .05$). **FIG. 4C** shows percent of heart survival of C57BL/6J, $Batf3^{-/-}$, $EPOR^{flox/flox}$, and $EPOR^{\Delta CD11c}$ mice after heart transplant (TX). WT TX (C57BL/6J) vs $Batf3^{-/-}$ TX: $P < .001$; WT TX (C57BL/6J) vs $EpoR^{\Delta XCR1}$ TX: $P < .001$, log-rank; Mantel-Cox test.

[0035] **FIGs. 5A-5B** illustrate Antigen (Ag)-specific Regulatory T-cells (Treg) induction by EPOR in dendritic cells (cDC1s). **FIG. 5A** shows percent of $FoxP3^+$ Tregs in transgenic mice expressing mouse alpha-chain and beta-chain T-cell (OTII mice) with expression of (i) hetero-EPOR in cDC1s ($EpoR^+$cDCs) or with (ii) no expression of hetero-EPOR in cDC1s ($EpoR^-$cDCs) that are untreated (UNT) or treated with EPO (+EPO). FoxP3: Forkhead box P3. *P* values by the 2-tailed *t* test of independent means. $*P < .05$; $**P < .01$; $***P < .001$; ns, not significant ($P > .05$). **FIG. 5B** shows flow cytometry data measuring Ag-specific Treg of C57BL/6 mice or mice with knockout of EPOR in dendritic cells ($EPOR^{\Delta CD11c}$), treated with total lymphoid irradiation and anti-thymocyte serum (TLI/ATS) or untreated (UNT).

[0036] **FIGs. 6A-6B** illustrate tumor burden in mice with hetero-EPOR deleted from myeloid cells. **FIG. 6A** shows lung tumor size (Lewis lung carcinoma) of (i) wild-type (WT) mice, (ii) wild-type mice with PD-L1 treatment (WT+αPD-L1) and (iii) mice with knockout of hetero-EPOR in macrophages ($EpoR^{\Delta LysM}$). PD-L1: Programmed Death Ligand 1. **FIG. 6B** shows tumor size (breast adenocarcinoma) of (i) WT mice and (ii) mice with knockout of hetero-EPOR in dendritic cells ($EPOR^{\Delta CD11c}$).

[0037] **FIGs. 7A-7C** illustrate tumor burden in mice with hetero-EPOR deleted dendritic cells. **FIG. 7A** shows expression of EPOR-tdT in various immune cells of $Zbtb46^{gfp/+}EpoR^{tdTomato/+}$ mice. **FIG. 7B** shows tumor size (colon cancer) of (i) mice with hetero-EPOR deletion in dendritic cells ($EpoR^{\Delta XCR1}$) versus (ii) mice without hetero-EPOR deletion ($EPOR^{flox/flox}$). **FIG. 7B** shows tumor size of (i) mice with mTOR deletion in dendritic cells ($mTOR^{\Delta XCR1}$) versus (ii) mice without mTOR deletion ($mTOR^{flox/flox}$). mTOR: Mammalian target of Rapamycin. Data are mean ± Standard Error of the Mean (s.e.m.) $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ and $****P < 0.0001$, two-way ANOVA. **FIG. 7C** shows a picture of $EPOR^{\Delta XCR1}$ and $EPOR^{flox/flox}$ mice on

day 14 (left) and tumor size of mice with mTOR deletion in $EPOR^{\Delta XCR1}$ versus $EPOR^{flox/flox}$ on day 14 (right). Scale bar as indicated. Mean of the size of tumors. *P* values by the 2-tailed *t* test of independent means. ***$P < .001$.

[0038] **FIGs. 8A-8C** illustrate an alteration in resistance to immune checkpoint blockade in cold tumors of mice that have macrophages with EPOR deletion ($Epor^{\Delta LysM}$). **FIG. 8A** illustrates an experimental scheme for administering anti-Programmed Death-1 antibody (αPD-1) to mice bearing cold hepatocellular carcinoma (HCC). A spontaneous model of cold HCC was created by delivering plasmids pCMV-SB13, pT3-EF1a-C-Myc-IRES-Luciferase, and pX330-sgRNA targeting Trp53 to the liver of mice using hydrodynamic tail vein injection (HDTV) *in vivo*. After two weeks, mice of the C57BL/6 wild-type (WT) and $Epor^{\Delta LysM}$ strains were treated with either 2 mg/kg of αPD-1 or IgG isotype control via intraperitoneal injection every three days for a total of five doses. Trp53: cellular tumor antigen p53. C-myc: c-Myc oncoprotein. Luc: luciferase. **FIG. 8B** shows the tumor growth kinetics of wild type mice treated with IgG isotype (WT IgG Isotype), wild type mice treated with αPD-1 (WT αPD-1), mice with macrophage specific knockout of hetero-EPOR treated with IgG isotype ($Epor^{\Delta LysM}$ IgG Isotype), and mice with macrophage specific knockout of hetero-EPOR treated with αPD-1 ($Epor^{\Delta LysM}$ αPD-1), analyzed by measuring the luciferin-based bioluminescence. **FIG. 8C** shows survival curve of WT IgG Isotype, WT αPD-1, $Epor^{\Delta LysM}$ IgG Isotype, and $Epor^{\Delta LysM}$ αPD-1.

[0039] **FIGs. 9A-9C** illustrate change in immune checkpoint blockade resistant cold tumor of mice with EPO knockout in dendritic cells. **FIG. 9A** illustrates an experimental scheme of treating melanoma mice with αPD-1 (Programmed Death-1). **FIG. 9B** shows tumor size (melanoma) of (i) control mice, (ii) control mice treated with αPD-1 (Control+αPD-1), (iii) mice with hetero-EPOR deletion in dendritic cells ($EpoR^{\Delta XCR1}$) and (iv) mice with hetero-EPOR deletion in dendritic cells treated with αPD-1 ($EpoR^{\Delta XCR1}$+αPD-1). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ and ****$P < 0.0001$, two-way ANOVA. **FIG. 9C** shows flow cytometry data measuring perforin, granzymeB, interferon-gamma (IFNγ), and tumor necrosis factor alpha (TNFα) in mice without deletion of hetero-EPOR ($EPOR^{flox/flox}$) and in mice with hetero-EPOR deletion in dendritic cells ($EpoR^{\Delta XCR1}$).

[0040] **FIG. 10** shows percent survival data from The Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC) of patients with hepatocellular carcinoma with (i) low versus (ii) high levels of EPO.

[0041] **FIGs. 11A-11C** illustrate effect of EPO on advancement of tumors in mice with regressive hepatocellular carcinoma (HCC). **FIG. 11A** illustrates an experimental scheme of establishing regressive HCC model. Allogeneic 3×10^6 Hepa1-6 cells were orthotopically implanted in C57BL/6 mice. Two Hepa1-6 stable cell lines were generated using lentivirus

either with EPO overexpression (Hepa1-6_Epo^{OE}) or empty vehicle (Hepa1-6_EV). **FIG. 11B** shows tumors from hepatocellular carcinoma mice treated with Hepa1-6_EV or Hepa1-6_Epo^{OE} harvested on Day 14 and Day 21 following injection. **FIG. 11C** shows quantification of tumor volume and complete regression (CR) rate measurements of HCC mice treated with Hepa1-6_EV or Hepa1-6_Epo^{OE}.

[0042] **FIGs. 12A-12B** illustrate colon tumor growth in mice with or without liver metastasis. **FIG. 12A** shows change in colon tumor volume of wild type mice with or without liver metastasis. **FIG. 12B** shows change in colon tumor volume of mice with EPOR deletion in macrophages (EpoR $^{\Delta LysM}$), and with or without liver metastasis.

[0043] **FIGs. 13A-13C** illustrate effect of macrophage-targeted liposomes loaded with siRNA targeting EPOR (siEpor) in mice with hepatocellular carcinoma (Hepa1-6_Epo^{OE}). **FIG. 13A** illustrates an experimental scheme of liposome treatment in two HCC models. Hepa1-6_Epo^{OE}: 3 x 10^6 EPO-overexpressing Hepa1-6 cells were orthotopically implanted in C57BL/6 mice. After one week, mice were treated with liposomes containing 50 μg of either siEpor (siRNA targeting EPOR) or siNTC (non-target control) RNA via intravenous injection every four days for a total of three doses. HDTV: a spontaneous model of cold HCC was created by delivering plasmids pCMV-SB13, pT3-EF1a-C-Myc, and pX330-sgRNA targeting Trp53 to the liver of mice using hydrodynamic tail vein injection (HDTV) *in vivo*. After two weeks, mice were treated with liposomes containing 50 μg of either siEpor or siNTC RNA via intravenous injection every four days for a total of six doses. **FIG. 13B** shows tumor harvested from hepatocellular carcinoma mice treated with liposomes containing either siEpor or siNTC (left) and tumor volume (right). **FIG. 13C** shows liver harvested from mice with cold HCC treated with liposomes containing either siEpor or siNTC (left) and liver weight (right).

[0044] **FIGs. 14A-14C** illustrate effect of macrophage-targeted liposomes loaded with siRNA targeting hetero-EPOR. **FIG. 14A** shows physical properties of the macrophage-targeted liposomes. **FIG. 14B** shows flow cytometry analysis indicating macrophages as the major cell type that take up the liposomes. C57BL/6 mice implanted with Hepa1-6_Epo^{OE} were administrated with liposomes loaded with 50 μg of fluorescein isothiocyanate (FITC)-conjugated siRNA. After 24 hours, tumors were harvested and dissociated into single cell suspension. Flow cytometry analysis was performed to measure the percentage of FITC$^+$ cells in different myeloid cell types. **FIG. 14C** shows the knockdown efficiency of EPOR in tumor-infiltrating macrophages. 3 x 10^6 Epo-overexpressing Hepa1-6 cells were orthotopically implanted in C57BL/6 mice. After one week, mice were treated with liposomes containing 50 μg of either siRNA targeting EPOR (siEpor) or non-target control siRNA (siNTC) via intravenous injection every four days for a total of three doses. Tumors were harvested after 3 weeks post-injection

and dissociated into single cell suspension. Macrophages were isolated with magnetic-activated cell sorting and RNA was extracted for real-time PCR quantification.

[0045] **FIGs. 15A-15B** illustrate EPOR expression on myeloid cells from human fresh cancer specimens of breast cancer (**FIG. 15A**) and breast cancer left axillary lymph node metastasis metastatic site (**FIG. 15B**). **FIG. 15A** shows EPOR expression level analyzed by flow cytometry. $CD45^+$ cancer infiltrating lymphocytes were gated as live-dead aqua-$CD45^+$. Histogram showed EPOR expression on individual myeloid cell subsets. Left: breast cancer. Right: surrounding healthy tissue. Bottom: EPOR expression on dendritic cells gated as $CD11c^+HLA\text{-}DR^+CD14^-CD16^-$. **FIG. 15B** shows EPOR expression on tumor infiltrating lymphocytes of breast cancer left axillary lymph node (LN) metastatic site. Upper: EPOR expression on dendritic cells. Lower: EPOR expression on HLA-DR- cells.

[0046] **FIGs. 16A-16B** illustrate EPOR expression on myeloid cells in human fresh liver metastasis metastatic sites paired with peripheral blood samples. Samples were collected from three individual patients with different original tumor type. **FIG. 16A** shows EPOR expression level on liver metastatic site $CD45^+$ tumor-infiltrating lymphocytes analyzed by flow cytometry. $CD45^+$ cancer infiltrating lymphocytes were gated as live-dead aqua-$CD45^+$. Right: EPOR expression on liver metastasis patient peripheral blood samples compared with healthy donor blood. The percentage of $EPOR^+$ cells is shown in red rectangle. **FIG. 16B** shows percentage of $EPOR^+$ cells in liver metastasis patient blood, healthy donor blood and liver cancer or liver cirrhosis blood. Statistical analysis was done with unpaired two-tailed t test. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$ and $****P < 0.0001$.

[0047] **FIG. 17** shows an example of EPO blocking efficiency of hybridoma clones listed in **Table 11**.

[0048] **FIGs. 18A-18B** illustrate TLI/ATS-induced tolerance to allogeneic (allo) bone marrow (BM) and heart transplants. **FIG. 18A** illustrates an experimental scheme of performing heart transplantation on mice, treating mice with TLI/ATS, conducting bone marrow transplantation, checking allogeneic BM chimerism and heart survival. **FIG. 18B** shows heart graft survival in wild-type and $Baf3^{-/-}$ mice (left) and BM chimerism at day 34 post BM transplant (TX) in wild-type and $Baf3^{-/-}$ mice (right).

[0049] **FIGs. 19A-19E** show TLI/ATS-induced local apoptosis and extramedullary erythropoiesis, coupled with dendritic cell (DC) enrichment and systemic upregulation of EPO. **FIG. 19A** shows representative images of TUNEL staining on sections of untreated spleens (UNT) and spleens treated with TLI/ATS. **FIG. 19B** shows cell composition analysis of changes of different cell populations in the untreated spleen (UNT), spleen treated with ATS, spleen treated with TLI, and spleen treated with TLI/ATS. Pie chart shows the average frequencies of

indicated populations from one representative experiment (n=4). T cells ($TCR\beta^+CD19^-$), B cells ($TCR\beta^-CD19^+$), erythroid progenitors ($TER119^+CD71^+$), DCs ($CD11c^{high}MHCII^{high}$), $CD11b^+$ myeloid cells are subdivided into LyG^+, $Ly6C^+$ and $F4/80^+$ (RPMs, red pulp macrophages). **FIG. 19C** shows gating strategy of erythroid progenitors with treated and TLI treated spleen. **FIG. 19D** shows extramedullary erythropoiesis in spleen treated with TLI and bone marrow with TLI. **FIG. 19E** shows systemic increase of EPO in peripheral blood serum measured by enzyme-linked immunosorbent assay (ELISA).

[0050] **FIGs. 20A-20H** show RNA-seq analysis of $CD8\alpha^+$ cDC1s sorted from TLI/ATS-conditioned vs. untreated (UNT) mice. **FIG 20A.** shows a total splenic cell number in mice untreated or treated with TLI/ATS. **FIG. 20B** shows frequency of $CD11c^{high}MHCII^{high}$ DCs in live cells ($DAPI^-$) of mice untreated or treated with TLI/ATS. **FIG. 20C** shows gating-strategy for $CD8\alpha^+CD11b^-$ and $CD11b^+CD8\alpha^-$ cDCs (left) and frequency of $CD8a^+CD11b^-$ DCs in $CD11^{high}MHCII^{high}$ DCs, UNT vs. TLI/AT (right). Representative samples from TLI/AT-conditioned mice are shown. For **FIGs. 20A-20C**, numbers in plots indicate the percentage of positively stained cells within each gate. Data are mean ± s.e.m. , ***$p < 0.001$ and ****$p < 0.001$ determined by unpaired student t-test, number of mice per group as indicated. Results represent one of at least three similar experiments. **FIG. 20D** is a Principal Component Analysis (PCA) plot showing distinct clustering of $CD8\alpha^+$ DCs, UNT vs. TLI/AT. **FIG. 20E** shows a heat map representing RNA-seq gene expression of top 30 up-regulated ($P \leq 0.01$ and fold change≥log2) genes in TLI/AT-conditioned vs. UNT group. Biological replicates (n=2, each pooled from 3-5 mice) for each group are shown separately. The heat map was generated from differential expression analysis with DESeq2 based on R studio software. **FIG. 20F** shows Gene Set Enrichment Analysis (GSEA) analysis using hallmark gene sets in the Molecular Signatures Database (MSigDB) following TLI/AT. NES: normalized enrichment score. FDR: false discovery rate. Right half of the graph: up-regulated pathways. Left half of the graph: down-regulated pathways. **FIG. 20G** shows real-time PCR of indicated genes in splenic $CD8\alpha^+$ cDC1s and $CD11b^+$ cDC2s. $CD8\alpha^+$ cDC1s (top panel) and $CD11b^+$ cDC2s (bottom panel) were sorted by flow cytometry from (i) UNT, (ii) ATS, (iii) TLI, (iv) TLI/ATS-conditioned mice on the next day of last dose of TLI. Gating strategy is shown in **FIG. 20C**. Data are mean ± S.E.M., *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.001$, ns (no significant differences) determined by unpaired student T-test. **FIG. 20H** shows EPOR expression in $CD8\alpha^+$ cDC1s in UNT, TLI, and TLI/ATS-treated EPOR-tdT mice. In TLI and TLI/ATS group, spleen was harvested on the next day of last dose of TLI.

[0051] **FIG. 21** shows TLI-ATS-induced chimerism in wild type (WT), EPOR flox/flox mice, mice with dendritic cell (DC)-specific hetero-EPOR gene deletion ($EPOR^{\Delta CD11c}$),and Baft3 knock

out (KO) mice in B cells, T cells, granulocytes, and macrophages (MΦ). Percentages of donor type cells among T cells ($TCR\beta^+$), B cells ($B220^+$), and granulocytes ($Ly6G^+$) in the blood of hosts 14 days after BM transplant. Bars show the mean percentages of donor cells. P values by the 2-tailed t-test of independent means. *P <05; **P <01; ***P <001; ns, no significant differences.

[0052] **FIGs. 22A-22B** show abrogation of both bone marrow chimerism establishment and maintenance by administration of diphtheria toxin (DT) administration to FoxP3-DTR (forkhead box P3-diphtheria toxin receptor) recipient mice. **FIG. 22A** illustrates an experimental scheme of two groups ofFoxP3-DTR mice with different treatment of DT. FoxP3-DTR mice were conditioned with TLI/ATS, and DT was administered either on day 3 after allogeneic BM by intravenous *(i.v.)* injection (Group A; top) or on day 15 after BM chimerism establishment (Group B; bottom). DT was given every 2 days. Bone marrow chimerism was examined on days 14 and 29 in both groups. **FIG. 22B** shows percentages of donor (MHCI-H2kb)-derived T cells ($TCR\beta^+$), B cells ($B220^+$), macrophages (MΦ; $CD64^+$), and granulocytes ($Ly6G^+$) in Group A (left 3 bars in all 4 graphs) and Group B (right 3 bars in all 4 graphs).

[0053] **FIGs. 23A-23D** show requirement of $CD8\alpha^+$ cDC1 for Antigen-specific $CD4^+$ $FoxP3^+$ Treg induction and expansion. C57BL/6 (Wildtype) or $Batf3^{-/-}$ mice, or $EPOR^{\Delta CD11c}$ recipient mice were either untreated (UNT) or TLI-conditioned. Macrophages negatively selected OTII cells (cells expressing ovalbumin (Ova) specific αβTCRs) were injected intravenously (i.v.) 1 day after the last dose of TLI, and Ova-expressing bone marrow cells were injected i.v. after another day. After 5 days, FoxP3 expression was examined by flow cytometry on adoptively transferred OTII cells defined as TCR-$v\alpha2^+$ $CD4^+$. **FIGs. 23A** and **23C** show plots for gating strategy of $FoxP3^+$ Tregs in TCR-$v\alpha2^+$ $CD4^+$ OTII cells. Graphs show the percentages of $FoxP3^+$ Tregs among $TCRv\alpha2^+$ CD4+ live OTII cells from spleen of C57BL/6 (FIG. 23A), mice with Batf knockout (KO) (FIG. 23A), mice with hetero-EPOR deleted in dendritic cells ($EPOR^{\Delta CD11c}$) (FIG. 23C) either untreated (UNT) or treated with TLI. **FIGs. 23B** and **23D** show histograms of the expression of FoxP3 in adoptively transferred OTII cells. Graphs show FoxP3 mean fluorescence intensity (MFIs) or UNT vs. TLI treated C57BL/6 mice or mice with Batf3 KO(FIG. 23B) or $EPOR^{\Delta CD11c}$ mice (FIG. 23D). Data are mean ± S.E.M., *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.001$, ns (no significant differences) determined by unpaired student T-test, number of mice per group as indicated.

[0054] **FIGs. 24A-24D** show induction of $CD4^+$ $FoxP3^-$ $CD73^+$ folate receptor 4+ ($FR4^+$)anergic T cells upon allo-bone marrow loading and induction is dependent on the presence of Tregs. **FIG. 24A** shows BM chimerism without (w/o) and with diphtheria toxin (DT) in B cells, T cells, granulocytes, and macrophages (MΦ). DT was injected on day -1 to day 1. **FIG.**

24B shows analysis of Tregs and anergic T cells for intercellular IFNγ expression on day 5 after allo-BM loading with or without DT. **FIG. 24C** shows statistical analysis of **FIG. 24B**. **FIG. 24D** shows correlation between FoxP3$^+$Treg frequency (X axis) and CD4$^+$ FoxP3$^-$ CD73$^+$ FR4$^+$ anergic T cell frequency (Y axis). Linear regression was determined by Prism. Data are mean ± S.E.M., *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ and ****$p < 0.001$, ns (no significant differences) determined by unpaired student T-test, number of mice per group as indicated.

[0055] **FIGs. 25A-25C** show 5-chloromethylfuorescein diacetate+ (CMFDA$^+$) allogeneic bone marrow uptake by CD8α$^+$ cDC1s following TLI. **FIG. 25A** is plots showing engulfment of live allogeneic BM cells in recipient CD11^{high}MHCII^{high}DCs (left) and comparison of the frequencies of CMFDA$^+$ CD8α$^+$ and CD8α$^-$ cDCs among CD11^{high}MHCII^{high}recipient DCs, 12 hour after BM injection, respectively (right). **FIG. 25B** shows percentages of CMFDA$^+$ cells in gated CD11^{high}MHCII^{high}CD8α$^+$ cDC1s that were untreated (UNT) or treated with TLI. **FIG. 27C** shows CD103 and DEC-205 expression in CD8α$^+$ CMFDA$^+$ cDC1s. UNT (black) with superimposed distribution by TLI (pink).

[0056] **FIGs. 26A-26B** illustrates expression of Epo-EPOR downstream signaling molecules in CD8α$^+$ cDC1s and CD11b$^+$ cDC2s and percent of donor cells from various mouse strains. **FIG. 26A.** shows expression of EPO-EPOR downstream signaling molecules in CD8α$^+$ cDC1s and CD11b$^+$ cDC2s from untreated (UNT) mice, mice treated with TLI, and mice treated with TLI and ATS, as measured by MFI. Intracellular phospho-flow was performed one day after the last dose of TLI. **FIG. 26B** shows percent of donor cells of B cells, T cells, granulocytes, and macrophageswith C57/6J, Baftf3-/-, CD11c^{Cre}, EPOR$^{flox/flox}$, mTOR$^{flox/flox}$, EPOR$^{\Delta XCR1}$, and mTOR$^{\Delta XCR1}$.

[0057] **FIGs. 27A-27C** illustrate the effect of XCR1-specific deletion of EpoR or mTOR on tumor Ag-specific CD8+ T-cells in tumor-draining lymph nodes (tdLN). **FIG. 27A** illustrates an experimental scheme of analyzing OT-I (CD8+ T-cells expressing T cell antigen receptor) in control mice, mice with EpoR knockout in dendritic cells (EpoR$^{\Delta XCR1}$), and mice with mTOR knockout in dendritic cells (mTOR$^{\Delta XCR1}$). **FIG. 27B** shows measurement of CD44, SLAMF6, PD-1, and Tim3-expressing cells, and measurement of proliferative cells (cell trace violet (CTV)) via flow cytometry. **FIG. 27C** shows percentage of proliferated OT-1 in control, EpoR$^{\Delta XCR1}$ mice, and mTOR$^{\Delta XCR1}$ mice. ***$P < 0.001$; ns= not significant.

[0058] **FIGs. 28A-28B** illustrate analyses of antibodies in the supernatants of the hybridoma clones. **FIG. 28A** shows the percentage of cell staining for 293T cells expressing EPOR, CD131, or both, binding kinetics data (EPOR-CD131-Fc, EPOR-Fc, and CD131-Fc), and the data for blocking EPO/EPOR interaction in percentage for 17 clones with unique antibody sequences. **FIG. 28B** shows expression of human EPOR (hEPOR) and human CD131 (hCD131)

measured by flow cytometry with Phycoerthyrin (PE)-labeled anti-EPOR and Alexa Fluor® 647 (AF647)-labeled anti-CD131, respectively.

[0059] **FIGs. 29A-29D** illustrate mean or median fluorescence intensity (MFI) of human leukemia UT-7 cells, 293T cells expressing EPOR (293T/EPOR), 293T cells expressing CD131 (293T/CD131), and 293T cells expressing both EPOR and CD131 (293T/EPOR/CD131), stained with purified antibodies. **FIG. 29A** shows MFI of 293T/EPOR cells labeled with purified hybridoma clones M2 and M41 across different antibody concentrations. **FIG. 29B** shows MFI of 293T/EPOR/CD131 cells labeled with purified hybridoma clones M2 and M41 across different antibody concentrations. **FIG. 29C** shows MFI of 293T/CD131 cells labeled with purified hybridoma clones M2 and M41 across different antibody concentrations. **FIG. 29D** shows MFI of UT-7 cells labeled with purified hybridoma clones M2 and M41 across different antibody concentrations.

[0060] **FIG. 30** shows phosphorylated STAT5 analyzed with flow-based assay. UT-7 cells, 293T cells expressing EPOR (293T/EPOR), and 293T cells expressing both EPOR and CD131 (293T/EPOR/CD131) were incubated with anti-EPOR antibody (hybridoma clone M2; top panels or hybridoma clone M41; bottom panels) after stimulation with (EPO + M2 or EPO + M41) or without recombinant human EPO (No EPO control). The same cells without anti-EPOR antibody incubation after EPO stimulation were used as control (EPO, no Ab control).

[0061] **FIGs. 31A-31B** illustrate SDS-PAGE analyses of IME001, IME003, IME004, carbamylated EPO (CEPO), and recombinant human EPO (rhEPO). **FIG. 31A** shows SDS-PAGE of expression vectors IME001 and IME003, which have EPO fused at the N-terminus of human IgG4 or human serum albumin, and of expression vector IME004, which has EPO fused at the C-terminus of human albumin. **FIG. 31B** shows SDS-PAGE of BSA control, rhEPO with or without Lyc-C digestion, and of CEPO with or without Lyc-C digestion.

[0062] **FIGs. 32A-32D** illustrate cell staining assay, measuring receptor binding activities of IME001, IME003, and IME004. **FIG. 32A** shows flow cytometry analysis of 293T cells (left) or 293T/EPOR cells (right) stained with anti-EPOR PE conjugate. **FIG. 32B** shows flow cytometry analysis of 293T/EPOR cells incubated with 1 μg/ml (left), 0.1 μg/ml (middle), or 0.01 μg/ml (right) of IME001, and stained with anti-human Fc PE conjugate. **FIG. 32C** shows flow cytometry analysis of 293T/EPOR cells incubated with 10 μg/ml (left), 1 μg/ml (middle), or 0.1 μg/ml (right) of IME003 (top panel) or IME004 (bottom panel), biotinylated anti-HSA (human serum albumin), and streptavidin PE conjugate. **FIG. 32D** shows binding of IME003 EPOR-Fc, IME003 IME 020, IME004 EPOR-Fc, IME004 IME020 at various concentrations of IME003/IME004.

[0063] **FIGs. 33A-33B** illustrate analysis of STAT5 phosphorylation in 293T/EPOR cells stimulated with various EPO proteins. **FIG. 33A** shows a western blot analysis with human phosphor-STAT5a/b (Y694/Y699) of 293T/EPOR cells untreated (control) or stimulated with CEPO, IME001, IME003, or IME004. **FIG. 33B** shows result of Phospho-STAT5 enzyme-linked immunosorbent assay (ELISA) with lysate of 293T/EPOR cells untreated (untreated control) or stimulated with IME001, IME003, IME004, IME005, IME008, or IME013.

[0064] **FIG. 34** illustrates the amino acid sequence and nucleic acid sequence of human EPO, including the signal peptide sequence.

[0065] **FIGs. 35A-35E** illustrate EpoR expression on peripheral lymph node (pLN) migratory cDC1s. **FIG. 35A** shows flow cytometry analysis of EpoR expression in pLN migratory and resident cDC1s from $EpoR^{tdt/+}$, $Zbtb46^{gfp/+}EpoR^{tdT/+}$, $CCR7^{-/-}EpoR^{tdT/+}$, and $Batf3^{-/-}EpoR^{tdT/+}$ mice. **FIG. 35B** shows histograms of EpoR expression in migratory and resident cDC1s of individual mouse stain. **FIG. 35C** shows flow analysis of EPOR expression in individual inguinal, axillary, branchial, or superficial cervical lymph nodes. **FIG. 35D** shows flow cytometry analysis of EPOR and CD103 expression in pLN migratory cDCs. **FIG. 35E** shows experimental scheme of EpoR-tdT-cre mice cross bred with Rosa26-lox-Stop-lox-EYFP mice, and flow cytometry analysis of pLN migratory cDC1s ($MHCII^{high}CD11^{inter}XCR1^{+}$) for EYFP expression.

[0066] **FIG. 36** shows flow cytometry analysis of Peripheral LN migratory $EpoR^{+}XCR1^{+}$ cDC1s expressing $DEC205^{+}$ and $CCR7^{+}$. **FIG. 36** also shows histograms comparing of PD-L1, Tim3, Axl and CD131 expression on $EpoR^{high}$ migratory cDC1s with $EpoR^{low}$ migratory cDCs.

[0067] **FIGs. 37A-37C** illustrate the effect of peripheral LN (pLN) migratory $EpoR^{+}XCR1^{+}$ cDC1s on inducing Ag-specific Tregs towards DEC205-Ova and Ova-expressing cells. **FIG 37A** shows flow cytometry analysis of pLN migratory and resident $EpoR^{+}$ cDC1s and $EpoR^{-}$ cDC1s. **FIG. 37B** shows flow cytometry and quantification of FoxP3 expression of CellTrace™ Violet (CTV) labeled naïve $CD45.1^{+}$ OT-II cells cultured with $CD45.2^{+}$ cDC1s, purified macrophages, and DEC-205-Ova, with or without TGFβ treatment. **FIG. 37C** shows flow cytometry and quantification of FoxP3 expression of CellTrace™ Violet (CTV) labeled naïve $CD45.1^{+}$ OT-II cells cultured with $CD45.2^{+}$ cDC1s, purified macrophages, and Gray irradiated Act-mOVA thymocytes ($CD45.2^{+}$), with or without TGFβ treatment, or with or without EPO treatment.

[0068] **FIGs. 38A-38C** illustrate *in vitro* Antigen (Ag)-specific Regulatory T-cells (Treg) induction with carbomylated EPO (CEPO) treatment. **FIG. 38A** shows flow cytometry analysis of FoxP3 expression and proliferation (CellTrace™ Violet (CTV)) of $CD11c^{Int}MHCII^{High}XCR1^{+}$cDC1s with EPO or with CEPO treatment. **FIG. 38A** also shows quantification of percent FoxP3+Tregs in live OTII untreated (UNT) or with EPO or with CEPO

treatment. **FIG. 38B** shows experimental scheme of studying the effect of EPO or CEPO on antigen-specific tolerance with mice with mTOR knockout in dendritic cells ($mTOR^{\Delta XCR1}$), mice with EPOR knockout in dendritic cells ($EPOR^{\Delta XCR1}$), and littermate control.

[0069] **FIGs. 39A-39C** illustrate expression of EPOR in migratory cDCs carrying apoptotic cells. **FIG. 39A** shows experimental scheme of mice injected at the 3rd mammary fat pad with cDC1s. **FIG. 39B** shows flow cytometry analysis of EPOR expression in 3rd mammary fat pad cDC1s. **FIG. 39C** shows flow cytometry analysis of EPOR expression in draining lymph node (inguinal LN), injected with PKH67 labeled $CD45.1^+$ dexamethasone (DEX)-induced apoptotic thymocytes.

[0070] **FIGs. 40A-40B** illustrate the effect of EPO on peripheral Ag-specific tolerance in the draining lymph nodes towards cell associated Ags (Ova). **FIG. 40A** shows experimental scheme of injecting i.v. $5x10^5$ purified macrophages and CellTrace™ Violet (CTV) labeled naïve $CD45.1^+$ OT-II cells at day -1. At day 0, Dexamethasone (DEX)-induced apoptotic Act-mOVA thymocytes were s.c. injected into the 3rd mammary fat pad. 50 IU EPO was given i.p. for over the course of 4 consecutive days. **FIG. 40B** shows flow cytometry analysis and quantification of FoxP3 expression in $CD45.1^+$OT-II in the draining lymph node (inguinal LN) with or without EPO.

[0071] **FIGs. 41A-41C** illustrate binding activity of IME003 and IME004. **FIG. 41A** shows binding of IME003 and IME004 to IME083 or IME020 at various concentration of IME003 and IME004. **FIG. 41B** shows binding of IME061/IME062, IME061/IME063, IME061/IME064, IME063/IME084 to IME003 at varying concentration of IME003. **FIG. 41C** shows binding of IME061/IME062, IME061/IME063, IME061/IME064, IME063/IME084 to IME004 at varying concentration of IME004.

[0072] **FIGs. 42A-42D** illustrate the amino acid sequence and nucleic acid sequence of human EPOR extracellular domain (ECD) or human CD131 ECD, human CD131 D3D4 domains, and human EPOR (F93A) domains, including the signal peptide sequences in red. **FIG. 42A** shows the amino acid sequence and nucleic acid sequence of human EPOR ECD in IME020 and IME061. **FIG. 42B** shows the amino acid sequence and nucleic acid sequence of human CD131 ECD in IME062. **FIG. 42C** shows the amino acid sequence and nucleic acid sequence of human CD131 D3D4 domain in IME063. **FIG. 42D** shows the amino acid sequence and nucleic acid sequence of human EPOR (F93A) domains in IME083 and IME034.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0073] While various embodiments of the present disclosure are described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only.

Numerous modifications and changes to, and variations and substitutions of, the embodiments described herein will be apparent to those skilled in the art without departing from the disclosure. It is understood that various alternatives to the embodiments described herein can be employed in practicing the disclosure. It is also understood that every embodiment of the disclosure can optionally be combined with any one or more of the other embodiments described herein which are consistent with that embodiment.

[0074] Where elements are presented in list format (e.g., in a Markush group), it is understood that each possible subgroup of the elements is also disclosed, and any one or more elements can be removed from the list or group.

[0075] It is also understood that, unless clearly indicated to the contrary, in any method described or claimed herein that includes more than one act or step, the order of the acts or steps of the method is not necessarily limited to the order in which the acts or steps of the method are recited, but the disclosure encompasses embodiments in which the order is so limited.

[0076] It is further understood that, in general, where an embodiment in the description or the claims is referred to as comprising one or more features, the disclosure also encompasses embodiments that consist of, or consist essentially of, such feature(s).

[0077] It is also understood that any embodiment of the disclosure, e.g., any embodiment found within the prior art, can be explicitly excluded from the claims, regardless of whether or not the specific exclusion is recited in the specification.

[0078] It is further understood that reference to a peptide, a polypeptide or a protein herein, such as an antibody or a fragment thereof, includes pharmaceutically acceptable salts thereof unless specifically stated otherwise or the context clearly indicates otherwise. Such salts can have a positive net charge, a negative net charge or no net charge.

[0079] Headings are included herein for reference and to aid in locating certain sections. Headings are not intended to limit the scope of the embodiments and concepts described in the sections under those headings, and those embodiments and concepts may have applicability in other sections throughout the entire disclosure.

[0080] All patent literature and all non-patent literature cited herein are incorporated herein by reference in their entirety to the same extent as if each patent literature or non-patent literature were specifically and individually indicated to be incorporated herein by reference in its entirety.

[0081] Beyond erythroid progenitors, a growing body of evidence suggests broad EPOR expression in non-erythroid cells, such as hematopoietic stem cells (HSCs), megakaryocytes, B cells, T cells, macrophages (MΦs), endothelial cells, and neurons (Broxmeyer, J Exp Med 2013:210:205-208). Notably, the immune-modulatory role of EPO is increasingly recognized (Cantarelli et al., Am J Transplant 2019:19:2407-2414; Peng et al., Cell Death Dis 2020:11:79).

The engagement of EPO signaling suppresses inflammatory responses by inhibiting the NFκB inducible immune pathway (Nairz et al., Immunity 2011:34:61-74). Moreover, EPO primes MΦs for effective efferocytosis thereby preventing autoimmunity (Luo et al., Immunity 2016:44:287-302).

[0082] EPO is cardioprotective in ischemia reperfusion injury and myocardial infarction. EPO improves cardiac function linked to neovascularization mediated by stimulating coronary endothelial cells to activate endothelial nitric oxide (NO) synthase (eNOS) and NO production (Teng et al., Basic Res. Cardiol. 2011:106:343–354).

[0083] EPO stimulates neovascularization and angiogenesis by activating endothelial cells (ECs) and endothelial progenitor cells (EPCs) in physiological conditions and pathological conditions, e.g., ischemia cardio-vascular diseases and tumors. Activation of EPOR leads to mobilization, proliferation, migration, and differentiation of ECs and EPCs (Annese et al., Experimental Cell Research, 2019: 374(2):266-273).

[0084] In the central nervous system, EPO and EPOR are expressed by neurons, glial cells and cerebrovasculature endothelium. EPO was shown to be neurotrophic and neuroprotective *in vitro* and in animal models of neuronal injury associated with trauma, stroke, ischemia, inflammation and epileptic seizures. The beneficial effects of EPO were also demonstrated in clinical studies of stroke, schizophrenia and progressive multiple sclerosis. EPO protects neurons both directly, by preventing apoptosis, and indirectly, by modulating inflammatory processes and stimulating neurogenesis and angiogenesis (Wang et al., Stroke 2004:35:1732-7).

[0085] EPO regulation of metabolism extends beyond oxygen delivery and contributes to maintenance of white adipose tissue and metabolic homeostasis. EPO is protective in diet-induced obesity, improves glucose tolerance, reduces insulin resistance and regulates fat mass accumulation, particularly in male mice (Alnaeeli and Noguchi, Adipocyte 2015:4:153–157). EPO modulates the proinflammatory response of macrophage infiltration in white adipose tissue and promotes an anti-inflammatory phenotype by inhibiting expression of proinflammatory cytokines and reducing macrophage infiltration (Alnaeeli et al., Diabetes Metab. Res. Rev. 2014:63:2415–2431).

[0086] It has been shown that some of the cytoprotective effects of EPO are mediated through its binding to heterodimers containing the canonical EPOR and the common beta receptor (βcR or CD131; Brines et al., Proc Natl Acad Sci USA 2004; 101: 14 907-14 912). Interestingly, carbamylated EPO binds to these heteroreceptors and exerts tissue-protective effects, whereas it does not bind to the classical EPOR and does not stimulate erythropoiesis. βcR is not required for erythropoiesis. It is assumed that βcR in combination with the EPOR expressed by

nonhematopoietic cells constitutes a tissue-protective receptor, thus creating a tissue-protective heteroreceptor.

[0087] The expression levels of EPO and EPOR are regulated. EPO production is induced under hypoxic conditions mediated by HIF (Semenza, Blood 2009:114(10):2015-9). Expression of EPOR is regulated by transcription factors Sp1, GATA1, and TAL1. Binding of EPO to EPOR on erythroid progenitor cells increases expression of transcription factors GATA1 and TAL1, that in turn transactivate EPOR expression (Suresh et al., Front Physiol. 2020:10:1534). EPOR is also regulated at the protein level. P85 promotes EPOR endocytosis and degradation. Prolyl hydroxylase D3 (PHD3) mediates proline hydroxylation of EPOR leading to proteasomal degradation. TFR2 and Scribble facilitate recycling of EPOR recycling (Bhoopalan et al., F1000Res. 2020; 9: F1000 Faculty Rev-1153).

[0088] Inventors have recently found that EPOR plays a critical role in the induction of tumor immune tolerance by myeloid cells, including dendritic cells (DCs) and macrophages (MΦs in a wide range of primary and metastatic tumors, including liver metastasis-induced systemic antigen-specific immune tolerance (**FIG. 2**). Moreover, EPOR is indispensable in myeloid cell-mediated tolerance in transplantation of allogeneic organs such as kidney, liver, lung, heart, etc (**FIG. 2**).

Definitions

[0089] Unless defined otherwise or clearly indicated otherwise by their use herein, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this application belongs.

[0090] As used in the specification and the appended claims, the indefinite articles "a" and "an" and the definite article "the" can include plural referents as well as singular referents unless specifically stated otherwise or the context clearly indicates otherwise.

[0091] The term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within one standard deviation. In some embodiments, when no particular margin of error (e.g., a standard deviation to a mean value given in a chart or table of data) is recited, the term "about" or "approximately" means that range which would encompass the recited value and the range which would be included by rounding up or down to the recited value as well, taking into account significant figures. In certain embodiments, the term "about" or "approximately" means within ± 10%, 5%, 4%, 3%, 2% or 1% of the specified value. Whenever the term "about" or "approximately" precedes the first numerical value in a series of two or more numerical values or

in a series of two or more ranges of numerical values, the term "about" or "approximately" applies to each one of the numerical values in that series of numerical values or in that series of ranges of numerical values.

[0092] The term "antibody" can refer to a protein functionally defined as a binding protein and structurally defined as comprising an amino acid sequence that is recognized as being derived from the framework region of an immunoglobulin (Ig) encoding gene. An antibody can comprise one or more polypeptides substantially encoded by immunoglobulin genes or fragments of immunoglobulin genes. The recognized immunoglobulin genes can include the kappa, lambda, alpha, gamma, delta, epsilon and mu constant region genes, as well as myriad immunoglobulin variable region genes. Light chains can be classified as either kappa or lambda. Heavy chains can be classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively. In some embodiments, these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2.

[0093] A typical gamma immunoglobulin (antibody) structural unit is known to comprise a tetramer. Each tetramer can be composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminus of each chain can define a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (V_L) and variable heavy chain (V_H) can refer to these light and heavy chains respectively.

[0094] Antibodies can exist as intact immunoglobulins or as a number of well-characterized fragments. Thus, for example, pepsin can digest an antibody below the disulfide linkages in the hinge region to produce F(ab)'$_2$, a dimer of Fab' which itself is naturally a light chain joined to VH-CH1-Hinge by a disulfide bond. The F(ab)'$_2$ may be reduced under mild conditions to break the disulfide linkage/s in the hinge region thereby converting the (Fab')$_2$ dimer into an Fab' monomer. The Fab' monomer is essentially a Fab with part of the hinge region (see, Fundamental Immunology, W. E. Paul, ed., Raven Press, N.Y. (1993), for a more detailed description of other antibody fragments). While various antibody fragments are defined in terms of the digestion of an intact antibody, one of skill in the art will appreciate that fragments can be synthesized de novo either chemically or by utilizing recombinant DNA methods. Thus, the term antibody, as used herein can also include antibody fragments either produced by the modification of whole antibodies or synthesized using recombinant DNA methodologies. Preferred antibodies can include V_H-V_L dimers, including single chain antibodies (antibodies that exist as a single polypeptide chain), such as single chain Fv antibodies (sFv or scFv) in which a variable heavy and a variable light region are joined together (directly or through a peptide linker) to form a continuous polypeptide. The single chain Fv antibody is a covalently linked V_H-V_L heterodimer

which may be expressed from a nucleic acid including V_H- and V_L-encoding sequences either joined directly or joined by a peptide-encoding linker (e.g., Huston, et al. Proc. Nat. Acad. Sci. USA, 85:5879-5883, 1988, which is hereby incorporated by reference in its entirety). While the V_H and V_L are connected to each as a single polypeptide chain, the V_H and V_L domains associate non-covalently. Alternatively, the antibody can be another fragment. Other fragments can also be generated, including using recombinant techniques. For example Fab molecules can be displayed on phage if one of the chains (heavy or light) is fused to g3 capsid protein and the complementary chain exported to the periplasm as a soluble molecule. The two chains can be encoded on the same or on different replicons; the two antibody chains in each Fab molecule assemble post-translationally and the dimer is incorporated into the phage particle via linkage to one of the chains of g3p (see, e.g., U.S. Pat. No: 5,733,743, which is hereby incorporated by reference in its entirety). The scFv antibodies and a number of other structures converting the naturally aggregated, but chemically separated light and heavy polypeptide chains from an antibody V region into a molecule that folds into a three dimensional structure substantially similar to the structure of an antigen-binding site are known to those of skill in the art (see e.g., U.S. Pat. Nos. 5,091,513, 5,132,405, and 4,956,778, all of which are hereby incorporated by reference in their entirety). Particularly preferred antibodies can include all those that have been displayed on phage or generated by recombinant technology using vectors where the chains are secreted as soluble proteins, e.g., scFv, Fv, Fab, $(Fab')_2$. Antibodies can also include diabodies and minibodies.

[0095] Antibodies can also include heavy chain dimers, such as antibodies from camelids. Since the V_H region of a heavy chain dimer IgG in a camelid does not have to make hydrophobic interactions with a light chain, the region in the heavy chain that normally contacts a light chain is changed to hydrophilic amino acid residues in a camelid. V_H domains of heavy-chain dimer IgGs are called V_{HH} domains.

[0096] In camelids, the diversity of antibody repertoire can be determined by the complementary determining regions (CDR) 1, 2, and 3 in the V_H or V_{HH} regions. The CDR3 in the camel V_{HH} region can be characterized by its relatively long length averaging 16 amino acids (Muyldermans et al., 1994, Protein Engineering 7(9): 1129, which is hereby incorporated by reference in its entirety). This is in contrast to CDR3 regions of antibodies of many other species. For example, the CDR3 of mouse V_H can have an average of 9 amino acids.

[0097] Libraries of camelid-derived antibody variable regions, which maintain the *in vivo* diversity of the variable regions of a camelid, can be made by, for example, the methods disclosed in U.S. Patent Application publication No. US20050037421, published Feb. 17, 2005, which is hereby incorporated by reference in its entirety.

[0098] The terms "functional fragments," "antigen-binding portions," "antigen-binding fragments," "antigen-binding domains," or "antibody fragments" can be used interchangeably herein to refer to one or more fragments of an antibody that retain the ability to specifically bind to an antigen. Representative antigen-binding fragments can include, but are not limited to, a Fab, a Fab', a $(Fab')_2$, a Fv, a scFv, a dsFv, a variable heavy domain, a variable light domain, a variable NAR domain, bi-specific scFv, a bi-specific Fab_2, a tri-specific Fab_3, an AVIMER®, a minibody, a diabody, a maxibody, a camelid, a VHH, an intrabody, fusion proteins comprising an antibody portion (e.g., a domain antibody), a single chain binding polypeptide, a scFv-Fc, or a Fab-Fc.

[0099] In some instances, an antibody or functional fragment thereof can comprise an isolated antibody or functional fragment thereof, a purified antibody or functional fragment thereof, a recombinant antibody or functional fragment thereof, a modified antibody or functional fragment thereof, or a synthetic antibody or functional fragment thereof. It would be understood that the antibodies described herein can be modified as described herein or as known in the art. In some instances, antibodies and functional fragments thereof described herein can be partly or wholly synthetically produced. An antibody or functional fragment thereof can be a polypeptide or protein having a binding domain which can be or can be homologous to an antigen binding domain. In some instances, an antibody or functional fragment thereof can be produced in an appropriate *in vivo* animal model and then isolated and/or purified.

[00100] The term "Fc region" can be used to define a C-terminal region of an immunoglobulin heavy chain. The "Fc region" can be a native sequence Fc region or a variant Fc region. The Fc region of an immunoglobulin generally can comprise two constant domains, CH2 and CH3.

[00101] "Antibodies" can include, but are not limited to, monoclonal antibodies, polyclonal antibodies, chimeric antibodies, bispecific antibodies, multispecific antibodies, heteroconjugate antibodies, humanized antibodies, human antibodies, deimmunized antibodies, mutants thereof, fusions thereof, immunoconjugates thereof, antigen-binding fragments thereof, functional fragments thereof, and/or any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity, including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and/or covalently modified antibodies.

[00102] An antibody can be a human antibody. A human antibody can be an antibody having an amino acid sequence corresponding to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies known in the art or disclosed herein. This definition of a human antibody includes antibodies comprising at least one human heavy chain polypeptide or at least one human light chain polypeptide. One such example is an antibody comprising murine light chain and human heavy chain polypeptides. Human antibodies

can be produced using various techniques known in the art. In one embodiment, the human antibody is selected from a phage library, where that phage library expresses human antibodies (Vaughan et al., 1996, Nature Biotechnology, 14:309-314; Sheets et al., 1998, PNAS USA, 95:6157-6162; Hoogenboom and Winter, 1991, J. Mol. Biol., 227:381; Marks et al., 1991, J. Mol. Biol., 222:581). Human antibodies can also be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. This approach is described in U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016. Alternatively, the human antibody may be prepared by immortalizing human B lymphocytes that produce an antibody directed against a target antigen (such B lymphocytes may be recovered from an subject or may have been immunized *in vitro*). See, e.g., Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985); Boerner et al., 1991, J. Immunol., 147 (1):86-95; and U.S. Pat. No. 5,750,373.

[00103] As used herein, the term "binding specificity" of an antibody or "antibody specificity" can refer to the identity of the antigen to which the antibody binds, preferably to the identity of the epitope to which the antibody binds.

[00104] As used herein, the term "chimeric polynucleotide" can mean that the polynucleotide comprises regions which are wild-type and regions which are mutated. It may also mean that the polynucleotide comprises wild-type regions from one polynucleotide and wild-type regions from another related polynucleotide.

[00105] As used herein, the term "complementarity-determining region" or "CDR" can refer to the art-recognized term as exemplified by Kabat and Chothia. CDRs are also generally known as hypervariable regions or hypervariable loops (Chothia and Lesk (1987) J Mol. Biol. 196: 901; Chothia et al. (1989) Nature 342: 877; E. A. Kabat et al., Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md.) (1987); and Tramontano et al. (1990) J Mol. Biol. 215: 175, all of which are hereby incorporated by reference in their entirety). "Framework region" or "FR" can refer to the region of the V domain that flank the CDRs. The positions of the CDRs and framework regions can be determined using various well known definitions in the art, e.g., Kabat, Chothia, international ImMunoGeneTics database (IMGT), and AbM (see, e.g., Johnson et al., supra; Chothia & Lesk, 1987, Canonical structures for the hypervariable regions of immunoglobulins. J. Mol. Biol. 196, 901-917; Chothia C. et al., 1989, Conformations of immunoglobulin hypervariable regions. Nature 342, 877-883; Chothia C. et al., 1992, structural repertoire of the human VH segments J. Mol. Biol. 227, 799-817; Al-Lazikani et al., J. Mol. Biol 1997, 273(4)). Definitions of antigen combining sites are also described in the following: Ruiz et al., IMGT, the international ImMunoGeneTics database.

Nucleic Acids Res., 28, 219-221 (2000); and Lefranc, M.-P. IMGT, the international ImMunoGeneTics database. Nucleic Acids Res. Jan 1;29(1):207-9 (2001); MacCallum et al, Antibody-antigen interactions: Contact analysis and binding site topography, J. Mol. Biol., 262 (5), 732-745 (1996); and Martin et al, Proc. Natl Acad. Sci. USA, 86, 9268-9272 (1989); Martin, et al, Methods Enzymol., 203, 121-153, (1991); Pedersen et al, Immunomethods, 1, 126, (1992); and Rees et al, In Sternberg M. J. E. (ed.), Protein Structure Prediction. Oxford University Press, Oxford, 141-172 1996, all of which are hereby incorporated by reference in their entirety).

[00106] As used herein, the term "affinity" can refer to the equilibrium constant for the reversible binding of two agents and is expressed as binding affinity (K_D). In some cases, K_D can be represented as a ratio of k_{off}, which can refer to the rate constant for dissociation of an antibody from the antibody or antigen-binding fragment/antigen complex, to k_{on}, which can refer to the rate constant for association of an antibody, an antigen binding domain, or an antigen binding fragment to an antigen. Binding affinity may be determined using methods known in the art including, for example, surface plasmon resonance (SPR; Biacore), Kinexa Biocensor, scintillation proximity assays, enzyme linked immunosorbent assay (ELISA), ORIGEN immunoassay (IGEN), fluorescence quenching, fluorescence transfer, yeast display, or any combination thereof. Binding affinity may also be screened using a suitable bioassay. The binding affinity (K_D) of an antibody, antigen-binding domain, or antigen-binding fragment herein can be less than 600 nM, 590 nM, 580 nM, 570 nM, 560 nM, 550 nM, 540 nM, 530 nM, 520 nM, 510 nM, 500 nM, 490 nM, 480 nM, 470 nM, 460 nM, 450 nM, 440 nM, 430 nM, 420 nM, 410 nM, 400 nM, 390 nM, 380 nM, 370 nM, 360 nM, 350 nM, 340 nM, 330 nM, 320 nM, 310 nM, 300 nM, 290 nM, 280 nM, 270 nM, 260 nM, 250 nM, 240 nM, 230 nM, 220 nM, 210 nM, 200 nM, 190 nM, 180 nM, 170 nM, 160 nM, 150 nM, 140 nM, 130 nM, 120 nM, 110 nM, 100 nM, 90 nM, 80 nM, 70 nM, 50 nM, 50 nM, 49 nM, 48 nM, 47 nM, 46 nM, 45 nM, 44 nM, 43 nM, 42 nM, 41 nM, 40 nM, 39 nM, 38 nM, 37 nM, 36 nM, 35 nM, 34 nM, 33 nM, 32 nM, 31 nM, 30 nM, 29 nM, 28 nM, 27 nM, 26 nM, 25 nM, 24 nM, 23 nM, 22 nM, 21 nM, 20 nM, 19 nM, 18 nM, 17 nM, 16 nM, 15 nM, 14 nM, 13 nM, 12 nM, 11 nM, 10 nM, 9 nM, 8 nM, 7 nM, 6 nM, 5 nM, 4 nM, 3 nM, 2 nM, 1 nM, 990 pM, 980 pM, 970 pM, 960 pM, 950 pM, 940 pM, 930 pM, 920 pM, 910 pM, 900 pM, 890 pM, 880 pM, 870 pM, 860 pM, 850 pM, 840 pM, 830 pM, 820 pM, 810 pM, 800 pM, 790 pM, 780 pM, 770 pM, 760 pM, 750 pM, 740 pM, 730 pM, 720 pM, 710 pM, 700 pM, 690 pM, 680 pM, 670 pM, 660 pM, 650 pM, 640 pM, 630 pM, 620 pM, 610 pM, 600 pM, 590 pM, 580 pM, 570 pM, 560 pM, 550 pM, 540 pM, 530 pM, 520 pM, 510 pM, 500 pM, 490 pM, 480 pM, 470 pM, 460 pM, 450 pM, 440 pM, 430 pM, 420 pM, 410 pM, 400 pM, 390 pM, 380 pM, 370 pM, 360 pM, 350 pM, 340 pM, 330 pM, 320 pM, 310 pM, 300 pM,

290 pM, 280 pM, 270 pM, 260 pM, 250 pM, 240 pM, 230 pM, 220 pM, 210 pM, 200 pM, 190 pM, 180 pM, 170 pM, or any integer therebetween.

[00107] An antibody can selectively bind to a target if it can bind to a target with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, an anti-EPO antibody or functional fragment thereof that selectively binds to an EPO protein is an antibody or functional fragment that can bind this target with greater affinity, avidity, more readily, and/or with greater duration than it binds to a protein that is not an EPO protein.

[00108] As used herein, the term "EPO analog" can refer to a polypeptide having modifications of its polypeptide structure, or polypeptides having shorter, longer, and/or different amino acid sequence compared to wild-type human erythropoietin, and all of which bind with high affinity to the hetero-EPOR or the homo-EPOR. EPO analogs may be antagonists or agonists of the hetero-EPOR or homo-EPOR. EPO analogs may block the activity of the hetero-EPOR or the activity of the homo-EPOR. EPO analogs may activate the hetero-EPOR without activating the homo-EPOR. EPO analogs may activate the homo-EPOR without activating the hetero-EPOR. EPO analogs may inhibit the hetero-EPOR without inhibiting the homo-EPOR. EPO analogs may inhibit the homo-EPOR without inhibiting the hetero-EPOR.

[00109] Whenever the term "at least" or "greater than" precedes the first numerical value in a series of two or more numerical values, the term "at least" or "greater than" applies to each one of the numerical values in that series of numerical values.

[00110] The term "heterologous" can refer to an amino acid or nucleotide sequence that is not naturally found in association with the amino acid or nucleotide sequence with which it is associated.

[00111] As used herein, the term "immunotherapy" can refer to particular therapies aimed at modulating immune system components, such as antibodies or immunocytes, or by drugs or other agents that stimulate, inhibit or otherwise modulate the immune system. For example, "immunotherapy" can refer to checkpoint inhibitor therapy, adoptive cell therapy and/or autologous or allogeneic CAR T-cell therapy.

[00112] Whenever the term "no more than" or "less than" precedes the first numerical value in a series of two or more numerical values, the term "no more than" or "less than" applies to each one of the numerical values in that series of numerical values.

[00113] The term "polynucleotide" can refer to a polymer composed of nucleotide units. Polynucleotides can include naturally occurring nucleic acids, such as deoxyribonucleic acid ("DNA") and ribonucleic acid ("RNA"), as well as nucleic acid analogs. Nucleic acid analogs can include those which contain non-naturally occurring bases, nucleotides that engage in

linkages with other nucleotides other than the naturally occurring phosphodiester bond, or/and bases attached through linkages other than phosphodiester bonds. Non-limiting examples of nucleotide analogs can include phosphorothioates, phosphorodithioates, phosphorotriesters, phosphoramidates, boranophosphates, methylphosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs), and the like. Such polynucleotides can be synthesized, e.g., using an automated DNA synthesizer. The term "nucleic acid molecule" can refer to larger polynucleotides. The term "oligonucleotide" can refer to shorter polynucleotides. In certain embodiments, an oligonucleotide can comprise no more than about 50 nucleotides. It is understood that when a nucleotide sequence is represented by a DNA sequence (i.e., A, T, G, C), this also includes an RNA sequence (i.e., A, U, G, C) in which "U" replaces "T".

[00114] The term "polypeptide" can refer to a polymer composed of natural or/and unnatural amino acid residues, naturally occurring structural variants thereof, or/and synthetic non-naturally occurring analogs thereof, linked via peptide bonds. Synthetic polypeptides can be synthesized, e.g., using an automated polypeptide synthesizer. Polypeptides can also be produced recombinantly in cells expressing nucleic acid sequences that encode the polypeptides. The term "protein" can refer to larger polypeptides. The term "peptide" can refer to shorter polypeptides. In certain embodiments, a peptide can comprise no more than about 50, about 40, or about 30 amino acid residues. Polypeptides can include antibodies and fragments thereof. Conventional notation is used herein to portray polypeptide sequences: the left-hand end of a polypeptide sequence is the amino (N)-terminus; the right-hand end of a polypeptide sequence is the carboxyl (C)-terminus.

[00115] Polypeptides can include one or more modifications that may be made during the course of synthetic or cellular production of the polypeptide, such as one or more post-translational modifications, whether or not the one or more modifications are deliberate. Modifications can include, without limitation, glycosylation (e.g., N-linked glycosylation and O-linked glycosylation), lipidation, phosphorylation, sulfation, acetylation (e.g., acetylation of the N-terminus), amidation (e.g., amidation of the C-terminus), hydroxylation, methylation, formation of an intramolecular or intermolecular disulfide bond, formation of a lactam between two side chains, formation of pyroglutamate, carbamylation, and ubiquitination. As another example, a polypeptide can be attached to a natural polymer (e.g., a polysaccharide) or a synthetic polymer (e.g., polyethylene glycol [PEG]), lipidated (e.g., acylated with a C_8-C_{20} acyl group), or labeled with a detectable agent (e.g., a radionuclide, a fluorescent dye or an enzyme). PEGylation can increase the protease resistance, stability and half-life, increase the solubility and reduce the aggregation of the polypeptide.

[00116] The term "conservative substitution" can refer to substitution of an amino acid in a polypeptide with a functionally, structurally or chemically similar natural or unnatural amino acid. In certain embodiments, the following groups each contain natural amino acids that are conservative substitutions for one another:

1) Glycine (Gly/G), Alanine (Ala/A);

2) Isoleucine (Ile/I), Leucine (Leu/L), Methionine (Met/M), Valine (Val/V);

3) Phenylalanine (Phe/F), Tyrosine (Tyr/Y), Tryptophan (Trp/W);

4) Serine (Ser/S), Threonine (Thr/T), Cysteine (Cys/C);

5) Asparagine (Asn/N), Glutamine (Gln/Q);

6) Aspartic acid (Asp/D), Glutamic acid (Glu/E); and

7) Arginine (Arg/R), Lysine (Lys/K), Histidine (His/H).

[00117] In further embodiments, the following groups each contain natural amino acids that are conservative substitutions for one another:

1) non-polar: Ala, Val, Leu, Ile, Met, Pro (proline/P), Phe, Trp;

2) hydrophobic: Val, Leu, Ile, Phe, Tyr, Trp;

3) aliphatic: Ala, Val, Leu, Ile;

4) aromatic: Phe, Tyr, Trp, His;

5) uncharged polar or hydrophilic: Gly, Ala, Pro, Ser, Thr, Cys, Asn, Gln, Tyr (tyrosine may be regarded as a hydrophobic amino acid with a polar side group);

6) aliphatic hydroxyl- or sulfhydryl-containing: Ser, Thr, Cys;

7) amide-containing: Asn, Gln;

8) acidic: Asp, Glu;

9) basic: Lys, Arg, His; and

10) small: Gly, Ala, Ser, Cys.

[00118] In other embodiments, amino acids may be grouped as set out below:

1) hydrophobic: Val, Leu, Ile, Met, Phe, Trp, Tyr;

2) aromatic: Phe, Tyr, Trp, His;

3) neutral hydrophilic: Gly, Ala, Pro, Ser, Thr, Cys, Asn, Gln;

4) acidic: Asp, Glu;

5) basic: Lys, Arg, His; and

6) residues that influence backbone orientation: Pro, Gly.

[00119] A polypeptide having one or more modifications relative to a parent polypeptide may be called an "analog", "derivative" or "variant" of the parent polypeptide as appropriate.

[00120] The disclosure encompasses pharmaceutically acceptable salts of polypeptides, including those with a positive net charge, those with a negative net charge, and those with no net charge.

[00121] The term "pharmaceutically acceptable" can refer to a substance (e.g., an active ingredient or an excipient) that is suitable for use in contact with the tissues and organs of a subject without excessive irritation, allergic response, immunogenicity and toxicity, is commensurate with a reasonable benefit/risk ratio, and is effective for its intended use. A "pharmaceutically acceptable" excipient or carrier of a pharmaceutical composition is also compatible with the other ingredients of the composition. The term "Pharmaceutically acceptable" can refer to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material may be administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained. A pharmaceutically acceptable excipient can denote any pharmaceutically acceptable ingredient in a pharmaceutical composition having no therapeutic activity and being non-toxic to the subject administered, such as disintegrators, binders, fillers, solvents, buffers, tonicity agents, stabilizers, antioxidants, surfactants, carriers, diluents, excipients, preservatives or lubricants used in formulating pharmaceutical products. Pharmaceutical compositions can facilitate administration of the compound to an organism and can be formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that can be used pharmaceutically. A proper formulation is dependent upon the route of administration chosen and a summary of pharmaceutical compositions can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference. In some embodiments, pharmaceutical compositions can be formulated by dissolving active substances (e.g., EPOR agonists or antagonists described herein) in aqueous solution for injection into disease tissues or disease cells. In some embodiments, pharmaceutical compositions can be formulated by dissolving active substances (e.g., EPOR agonists or antagonists described herein) in aqueous solution for direct injection into disease tissues or disease cells.

[00122] The term "stringent hybridization conditions" can refer to hybridizing in 50% formamide at 5XSSC at a temperature of 42 °C and washing the filters in 0.2XSSC at 60 °C.

(1XSSC is 0.15M NaCl, 0.015M sodium citrate.) Stringent hybridization conditions also encompasses low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50 °C; hybridization with a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42 °C; or 50% formamide, 5XSSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5X Denhardt's solution, sonicated salmon sperm DNA (50 μg/ml), 0.1% SDS, and 10% dextran sulfate at 42 °C, with washes at 42 °C in 0.2XSSC (sodium chloride/sodium citrate) and 50% formamide at 55 °C, followed by a high-stringency wash consisting of 0.1XSSC containing EDTA at 55 °C.

[00123] The term "subject" can refer to an animal, including, but not limited to, a mammal, such as a primate (e.g., a human, a chimpanzee or a monkey), a rodent (e.g., a rat, a mouse, a guinea pig, a gerbil or a hamster), a lagomorph (e.g., a rabbit), a swine (e.g., a pig), an equine (e.g., a horse), a canine (e.g., a dog) or a feline (e.g., a cat). Additional examples of mammals can include, but are not limited to, any member of the mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In some cases, the mammal is a human. In some instances, the subject is an adult, a child, or an infant. In some cases, the subject may be an animal. In some cases, an animal may comprise human beings and non-human animals. In one embodiment, a non-human animal may be a non-human mammal described herein. In some instances, the subject is a companion animal. In some instances, the subject is a feline, a canine, or a rodent.

[00124] The term "substantially homologous" or "substantially identical" in the context of two polypeptides or polynucleotides can refer to two or more sequences or subsequences that have at least about 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid or nucleic acid residue sequence identity, when compared and aligned for maximum correspondence, as measured using a sequence comparison algorithm or by visual inspection. The terms "substantially homologous" or "substantially identical" can mean at least about 70% amino acid or nucleic acid residue identity. The term "substantially homologous" or "substantially identical" can mean at least about 85% amino acid or nucleic acid residue sequence identity. The substantial homology or identity can exist over a region of the sequences that is at least about 20, 30, 40, 50, 100, 150, or 200 residues in length. The sequences

can be substantially homologous or identical over the entire length of either or both comparison biopolymers.

[00125] Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman, *Adv. Appl. Math.*, **2**:482 (1981); by the homology alignment algorithm of Needleman and Wunsch, *J. Mol. Biol.*, **48**:443 (1970); by the search for similarity method of Pearson and Lipman, *Proc. Natl. Acad. Sci. USA*, **85**:2444 (1988); by computerized implementations of these algorithms (e.g., GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, Madison, Wisconsin); or by visual inspection.

[00126] One example of a useful algorithm is PILEUP. PILEUP creates a multiple sequence alignment from a group of related sequences using progressive, pairwise alignments to show relationship and percent sequence identity. It also plots a tree or dendogram showing the clustering relationships used to create the alignment. PILEUP uses a simplification of the progressive alignment method of Feng and Doolittle, *J. Mol. Evol.*, **35**:351-360 (1987). The method used is similar to the method described by Higgins and Sharp, *CABIOS*, **5**:151-153 (1989). The program can align up to about 300 sequences, each having a maximum length of about 5,000 nucleotides or amino acids. The multiple alignment procedure begins with the pairwise alignment of the two most similar sequences, producing a cluster of two aligned sequences. This cluster is then aligned to the next most related sequence or cluster of aligned sequences. Two clusters of sequences are aligned by a simple extension of the pairwise alignment of two individual sequences. The final alignment is achieved by a series of progressive, pairwise alignments. The program is run by designating specific sequences and their amino acid or nucleotide coordinates for regions of sequence comparison and by designating the program parameters. For example, a reference sequence can be compared to other test sequences to determine the percent sequence identity relationship using the following parameters: default gap weight (3.00), default gap length weight (0.10), and weighted end gaps. Another algorithm that is useful for generating multiple alignments of sequences is Clustal W (see, e.g., Thompson *et al.*, *Nucleic Acids Research*, **22**:4673-4680 [1994]).

[00127] Another example of an algorithm that is suitable for determining percent sequence identity and sequence similarity is the BLAST algorithm, which is described in Altschul *et al.*, *J. Mol. Biol.*, **215**:403-410 (1990). Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the

neighborhood word score threshold (Altschul 1990). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are then extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always > 0) and N (penalty score for mismatching residues; always < 0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction is halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults, e.g., a wordlength (W) of 11, an expectation (E) of 10, M = 5, N = –4, and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults, e.g., a wordlength (W) of 3, an expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff, *Proc. Natl. Acad. Sci. USA*, **89**:10915 [1989]).

[00128] In addition to calculating percent sequence identity, the BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g., Karlin and Altschul, *Proc. Natl. Acad. Sci. USA*, **90**:5873-5787 [1993]). One measure of similarity provided by the BLAST algorithm is the smallest sum probability [P(N)], which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. In certain embodiments, a polynucleotide is considered similar to a reference sequence if the smallest sum probability in a comparison of the test polynucleotide to the reference polynucleotide is less than about 0.1, 0.01 or 0.001.

[00129] A polypeptide can be substantially homologous or identical to a second polypeptide if the two polypeptides differ only by conservative amino acid substitutions. Two nucleic acid sequences can be substantially homologous or identical if the two polynucleotides hybridize to each other under stringent conditions, or under highly stringent conditions, as described herein.

[00130] The term “therapeutically effective amount” can refer to an amount of a compound that, when administered to a subject, is sufficient to prevent, reduce the risk of developing, delay the onset of, slow the progression or cause regression of the medical condition being treated, or to alleviate to some extent the medical condition or one or more symptoms or complications of that condition. The term “therapeutically effective amount” can also refer to an amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, organ, system, animal or human which is sought by a researcher, veterinarian, medical doctor or clinician.

[00131] The terms "treat", "treating" and "treatment" can include alleviating, ameliorating or abrogating a medical condition or one or more symptoms or complications associated with the condition, alleviating, ameliorating or eradicating one or more causes of the condition, preventing additional symptoms, inhibiting the disease or the condition, e.g., arresting the development of the disease or the condition, relieving the disease or the condition, causing regression of the disease or the condition, relieving a condition caused by the disease or the condition, or stopping the symptoms of the disease or the condition either prophylactically and/or therapeutically. In some embodiments, treating a disease or condition cam comprise reducing the size of disease tissues or disease cells. In some embodiments, treating a disease or a condition in a subject can comprise increasing the survival of a subject. In some embodiments, treating a disease or condition can comprise reducing or ameliorating the severity of a disease, delaying onset of a disease, inhibiting the progression of a disease, reducing hospitalization of or hospitalization length for a subject, improving the quality of life of a subject, reducing the number of symptoms associated with a disease, reducing or ameliorating the severity of a symptom associated with a disease, reducing the duration of a symptom associated with a disease, preventing the recurrence of a symptom associated with a disease, inhibiting the development or onset of a symptom of a disease, or inhibiting of the progression of a symptom associated with a disease. In some embodiments, treating a cancer can comprise reducing the size of tumor or increasing survival of a patient with a cancer. Reference to "treatment" of a medical condition can include prevention of the condition. The terms "prevent", "preventing" and "prevention" can include precluding, reducing the risk of developing and delaying the onset of a medical condition or one or more symptoms or complications associated with the condition.

Erythropoietin (EPO) Analogs or Engineered EPOs

[00132] In some aspects, provided herein are at least eight types of EPO analogs that can be generated or engineered. In some embodiments, EPO analogs can be referred to as engineered EPOs. EPO analogs or engineered EPOs can bind the hetero-EPOR and not the homo-EPOR, and can be either agonists or antagonists of the hetero-EPOR. Other EPO analogs or engineered EPOs can bind the homo-EPOR and not the hetero-EPOR, and can be either agonists or antagonists of the homo-EPOR. EPO analogs or engineered EPOs can bind both the homo-EPOR and the hetero-EPOR and be agonists for both, antagonists for both, or agonist for one and antagonist for the other. The term EPO analogs or engineered EPOs can include EPO as set out in SEQ ID NO:1.

[00133] Erythropoietin (EPO) is a pleiotropic cytokine glycoprotein that was initially identified as a regulator of red blood cell production in response to hypoxia. The mature human 165 amino acid-long EPO protein sequence is presented by SEQ ID NO: 1

APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVPDTKVNFYAWKRMEVGQQ AVEVWQGLALLSEAVLRGQALLVNSSQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKE AISPPDAASAAPLRTITADTFRKLFRVYSNFLR GKLKLYTGEACRTGDR (SEQ ID NO: 1). The amino acid sequence and nucleic acid sequence of human EPO including the signal peptide sequence are shown in **FIG. 34**. The amino acid residue position numbers in engineered EPO variants and analogs described herein may not include the amino acid residue position numbers of the signal peptide. In some embodiments, the amino acid residue position of engineered EPO variants and analogs described herein can be determined by alignment with SEQ ID NO: 1.

[00134] EPO comprises four alpha-helices (A, B, C, and D), forming a compact globular structure. Human recombinant erythropoietin (expressed in mammalian cells) contains three N-linked and one O-linked oligosaccharide chains which together comprise about 40% of the total molecular weight of the glycoprotein. N-linked glycosylation occurs at asparagine residues (Asn) located at positions 24, 38 and 83 whereas O-linked glycosylation occurs at a serine residue (Ser) located at position 126.

[00135] Three of the helices (A, C and D) participate in the two binding sites with the homo-EPOR. The helix B is involved in the interaction with the hetero-EPOR. The interaction interface of EPO and homo-EPOR has been mapped in a crystal structure (Syed et al, Nature. 1998:395(6701):511-6) which contains a high affinity site (site 1) and a low affinity site (site 2). The site 1 is characterized by a central hydrophobic binding pocket flanked at opposite ends by hydrophilic interactions including the amino acid residues S9, R10, E13, L16, L17, K20, T44, K45, V46, N47, F48, Y49, K52, R131, I133, K140, R143, N147, R150, G151, K154, and L155. Mutations of K20E, T44I, K45I, V46A, F48G, R143A, R150A, R150Q, L155A, and L155N have been shown to lose the *in vitro* bioactivity >5 times, whereas mutations of K45I, N147K, R150E, and G151A have been shown to lose the activity >50 times. The site 1 mutations lead to much reduced affinity to homo-EPOR. The site 2 include the amino acid residues L5, D8, R10, V11, R14, Y15, Q78, D96, K97, V99, S100, R103, S104, T107, L108, and R110. The mutations of V11S, R14A, R14E, Y15I, K97A, K97E, S104A, L108A, and R110E have been shown to lose the *in vitro* bioactivity >5 times, whereas mutations of R14Q, S100E, S100T, R103A, R103E, R103H, R103N, R103Q, S104I, and L108K have been shown to lose the activity >50 times. The EPO analogs or engineered EPOs with the site 2 mutations may retain high affinity binding to homo-EPOR but lose the signaling activity. These EPO variants with mutations in site 1 or 2 but not in the helix B should have activity with the hetero-EPOR.

[00136] Helix B is not involved in binding to the homo-EPOR. The hetero-EPOR has an EPOR chain and CD131 chain. The CD131 can be a homodimer resulting in a heterohexameric

receptor and a higher order dodecamer complex with EPO receptor chains. The helix B of EPO is likely critical for the binding of EPOR/CD131 (hetero-EPOR).

[00137] Carbamylated EPO (CEPO) is a chemically modified EPO analog in which the Lys residues present in the helices A, C, and D are modified by carbamylation. Helix B does not have Lys residues and so is not modified. CEPO has been shown to be equally active for the hetero-EPOR as EPO, but not active to the homo-EPOR. Other modifications of the Lys residues in helices A, C and D can be used to make EPO analogs or engineered EPOs that interact with the hetero-EPOR and not the homo-EPOR. For example, using well known PEGylating reagents, PEG can be attached to the Lys residues in EPO to make a chemical modified EPO analog that will have improved serum half-life and preference for activating the hetero-EPOR and not the homo-EPOR. The PEG can be a low molecular weight PEG (e.g., 5000 daltons) and the Lys reactive groups on the PEG can be used to modify all or most or all of the Lys residues in helices A, C and D. Similarly, other chemical modifications can be made attaching other moieties to the Lys residues in EPO resulting on other chemical derivatives that can bind to the hetero-EPOR and not the homo-EPOR. In some embodiments, one or more Lys residues on EPO analogs or engineered EPOs described herein can be carbamylated. In some embodiments, all Lys residues on EPO analogs or engineered EPOs described herein can be carbamylated. In some embodiments, no Lys residues on EPO analogs or engineered EPOs described herein may be carbamylated.

[00138] Peptide analogs of helix B have also exhibited similar activities to CEPO. Activation of the hetero-EPOR leads to phosphorylation of the intracellular domain of CD131 rather than EPOR. Activation of both homo-EPOR and hetero-EPOR results in JAK2 and STAT5 activation. For example, an eleven-amino acid linear peptide, QEQLERALNSS (SEQ ID NO: 2), mimicking the three-dimensional structure of the external aqueous face of the helix B peptide is such a peptide analog that activates the hetero-EPOR. This peptide can be cyclized to make a circular peptide because the N-terminal residue is glutamine. The circular peptide also activates hetero-EPOR.

[00139] EPO has been previously expressed as functional Fc fusion proteins to enhance its *in vivo* half-life (Schriebl et al, Protein Expr Purif. 2006, 49(2):265-75; Shi et al, PLoS One, 2013 8(8):e72673). Other methods including albumin fusion, PEGylation, or engineering more glycosylation sites can improve the *in vivo* PK properties (Joung et al, Protein Expr Purif. 2009:68(2):137-45; Elliott et al, Nat Biotechnol. 2003:21(4):414-21). The EPO variants described herein can be expressed as Fc fusion proteins and tested for receptor specificity. They can also be expressed as albumin fusions or in other modalities (e.g., PEGylated).

[00140] In some aspects, human EPO analogs that bind the hetero-EPOR (as an antagonist) and do not bind the homo-EPOR can be generated or engineered. In some embodiments, these EPO analogs or engineered EPOs can be expressed as Fc fusion proteins. The surface residues (Q58, E62, Q65, L69, E72, R76, A79, L80, N83, S84, and S85) in the helix B can play important roles in interaction with the hetero-EPOR, and can be mutated/substituted. For example, the nucleic acid encoding helix B can be mutagenized using alanine scanning and/or saturation mutagenesis. The mutations in EPO that allow binding to the hetero-EPOR and cause reduced activation of the hetero-EPOR (but still bind the hetero-EPOR) can be combined with mutations described above that reduce EPO analog binding to the homo-EPOR. The resulting EPO analog or engineered EPOs can antagonize the hetero-EPOR and may have reduced binding or may not bind to the homo-EPOR.

[00141] In some aspects, human EPO analogs or engineered EPOs described herein can comprise at least one amino acid substitution or mutation. In some embodiments, human EPO analogs or engineered EPOs described herein can comprise at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten amino acid substitutions. For example, human EPO analogs or engineered EPOs described herein can comprise at least one amino acid substitution or mutation on amino acid residue K20, N24, N38, K45, K52, Q58, E62, Q65, L69, E72, R76, L80, N83, S84, S85, K97, R103, K116, K140, N147, R150, G151, K152, or K154, or a combination thereof. In some embodiments, human EPO analogs or engineered EPOs described herein can comprise at least one amino acid substitution or mutation on amino acid residue K20, N24, N38, K45, K52, Q58, E62, Q65, L69, E72, R76, L80, N83, S84, S85, K97, R103, K116, K140, N147, R150, G151, K152, or K154, or a combination thereof. In this embodiment, the at least one amino acid comprising K20, N24, N38, K45, K52, Q58, E62, Q65, L69, E72, R76, L80, N83, S84, S85, K97, R103, K116, K140, N147, R150, G151, K152, or K154, or a combination thereof can be substituted with or mutated to any other amino acid (e.g., A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, S, T, W, Y, or V). In some embodiments, the amino acid residue position can be determined by alignment with SEQ ID NO: 1. For example, human EPO analogs or engineered EPOs described herein can comprise at least one amino acid substitution comprising K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A , R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A, or a combination thereof. In some embodiments, human EPO analogs or engineered EPOs comprising at least one amino acid substitution or mutation described herein can be an agonist or an antagonist of a hetero-EPOR. In some embodiments,

human EPO analogs or engineered EPOs comprising at least one amino acid substitution or mutation described herein can be an agonist or an antagonist of a homo-EPOR.

[00142] In some embodiments, In some embodiments, human EPO analogs or engineered EPOs can comprise R103A. In some embodiments, human EPO analogs or engineered EPOs can comprise K45D. In some embodiments, human EPO analogs or engineered EPOs can comprise N147K. In some embodiments, human EPO analogs or engineered EPOs can comprise R150E. In some embodiments, human EPO analogs or engineered EPOs can comprise Q58A. In some embodiments, human EPO analogs or engineered EPOs can comprise E62R. In some embodiments, human EPO analogs or engineered EPOs can comprise E62A. In some embodiments, human EPO analogs or engineered EPOs can comprise Q65A. In some embodiments, human EPO analogs or engineered EPOs can comprise L69A. In some embodiments, human EPO analogs or engineered EPOs can comprise E72R. In some embodiments, human EPO analogs or engineered EPOs can comprise E72A. In some embodiments, human EPO analogs or engineered EPOs can comprise R76E. In some embodiments, human EPO analogs or engineered EPOs can comprise R76A. In some embodiments, human EPO analogs or engineered EPOs can comprise L80A. In some embodiments, human EPO analogs or engineered EPOs can comprise N83A. In some embodiments, human EPO analogs or engineered EPOs can comprise S84A. In some embodiments, human EPO analogs or engineered EPOs can comprise S85A. In some embodiments, human EPO analogs or engineered EPOs can comprise K97A. In some embodiments, human EPO analogs or engineered EPOs can comprise K116A. In some embodiments, human EPO analogs or engineered EPOs can comprise K140A. In some embodiments, human EPO analogs or engineered EPOs can comprise G151A. In some embodiments, human EPO analogs or engineered EPOs can comprise K152A. In some embodiments, human EPO analogs or engineered EPOs can comprise K154A. In some embodiments, human EPO analogs or engineered EPOs can comprise K45D. In some embodiments, human EPO analogs or engineered EPOs can comprise N147K. In some embodiments, human EPO analogs or engineered EPOs can comprise R150E. In some embodiments, human EPO analogs or engineered EPOs can comprise K45D and R103A. In some embodiments, human EPO analogs or engineered EPOs can comprise N147K and R103A. In some embodiments, human EPO analogs or engineered EPOs can comprise R150E and R103A. In some embodiments, human EPO analogs or engineered EPOs can comprise Q65A and E72R. In some embodiments, human EPO analogs or engineered EPOs can comprise Q65A, E72R, and N83A. In some embodiments, human EPO analogs or engineered EPOs can comprise K140A and K152A. In some embodiments, human EPO analogs or engineered EPOs can

comprise K140A, K152A, and K154A. In some embodiments, human EPO analogs or engineered EPOs can comprise N24Q, N38Q, and N83Q. In some embodiments, human EPO analogs or engineered EPOs can comprise E62A, Q65A, E72A, and R76A. In some embodiments, human EPO analogs or engineered EPOs can comprise N24A, N38A, and N83A. In some embodiments, human EPO analogs or engineered EPOs can comprise N24S, N38S, and N83S. In some embodiments, human EPO analogs or engineered EPOs can comprise R103A and G151A. In some embodiments, human EPO analogs or engineered EPOs can comprise K20A, K45A, and K52A. In some embodiments, human EPO analogs or engineered EPOs can comprise K20A, K45A, K52A, K140A, K152A, and K154A. In some embodiments, human EPO analogs or engineered EPOs can comprise K97A and K116A. In some embodiments, human EPO analogs or engineered EPOs can comprise K20A, K45A, K52A, K97A, K116A, K140A, K152A, and K154A. In some embodiments, human EPO analogs or engineered EPOs can comprise Q58A, Q65A, and E72R. In some embodiments, human EPO analogs or engineered EPOs can comprise L80A, N83A, S84A, and S85A. In some embodiments, human EPO analogs or engineered EPOs can comprise Q58A, Q65A, E72R, L80A, N83A, S84A, and S85A. In some embodiments, human EPO analogs or engineered EPOs can comprise Q58A and L69A. In some embodiments, human EPO analogs or engineered EPOs can comprise Q58A and L80A. In some embodiments, human EPO analogs or engineered EPOs can comprise L69A and L80A. In some embodiments, human EPO analogs or engineered EPOs can comprise Q58A, L69A, and L80A.

[00143] In some embodiments, human EPO analogs or engineered EPOs can comprise an amino acid sequence with at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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%, at least 99%, at least 99.1%, at least 99.2%, at least 99.3%, at least 99.4%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, or 100% sequence identity to any one of SEQ ID NOs: 1973-2019. In some embodiments, human EPO analogs or engineered EPOs can comprise an amino acid sequence of any one of SEQ ID NOs: 1973-2019.

[00144] In some embodiments, human EPO analogs or engineered EPOs can have a nucleotide sequence comprising a sequence with at least 70%, at least 71%, at least 72%, at least 73%, at least 74%, at least 75%, at least 76%, at least 77%, at least 78%, at least 79%, at least 80%, at least 81%, at least 82%, at least 83%, at least 84%, at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, 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%, at least 99%, at least 99.1%, at least 99.2%, at least 99.3%, at least 99.4%, at least 99.5%, at least 99.6%, at least 99.7%, at least 99.8%, at least 99.9%, or 100% sequence identity to any one of SEQ ID NOs: 2020-2064. In some embodiments, human EPO analogs or engineered EPOs can have a nucleotide sequence of any one of SEQ ID NOs: 2020-2064.

[00145] In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can bind to a homo-EPOR with a binding affinity of less than about 600 nM, about 590 nM, about 580 nM, about 570 nM, about 560 nM, about 550 nM, about 540 nM, about 530 nM, about 520 nM, about 510 nM, about 500 nM, about 490 nM, about 480 nM, about 470 nM, about 460 nM, about 450 nM, about 440 nM, about 430 nM, about 420 nM, about 410 nM, about 400 nM, about 390 nM, about 380 nM, about 370 nM, about 360 nM, about 350 nM, about 340 nM, about 330 nM, about 320 nM, about 310 nM, about 300 nM, about 290 nM, about 280 nM, about 270 nM, about 260 nM, about 250 nM, about 240 nM, about 230 nM, about 220 nM, about 210 nM, about 200 nM, about 190 nM, about 180 nM, about 170 nM, about 160 nM, about 150 nM, about 140 nM, about 130 nM, about 120 nM, about 110 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 50 nM, about 50 nM, about 49 nM, about 48 nM, about 47 nM, about 46 nM, about 45 nM, about 44 nM, about 43 nM, about 42 nM, about 41 nM, about 40 nM, about 39 nM, about 38 nM, about 37 nM, about 36 nM, about 35 nM, about 34 nM, about 33 nM, about 32 nM, about 31 nM, about 30 nM, about 29 nM, about 28 nM, about 27 nM, about 26 nM, about 25 nM, about 24 nM, about 23 nM, about 22 nM, about 21 nM, about 20 nM, about 19 nM, about 18 nM, about 17 nM, about 16 nM, about 15 nM, about 14 nM, about 13 nM, about 12 nM, about 11 nM, about 10 nM, about 9 nM, about 8 nM, about 7 nM, about 6 nM, about 5 nM, about 4 nM, about 3 nM, about 2 nM, about 1 nM, about 990 pM, about 980 pM, about 970 pM, about 960 pM, about 950 pM, about 940 pM, about 930 pM, about 920 pM, about 910 pM, about 900 pM, about 890 pM, about 880 pM, about 870 pM, about 860 pM, about 850 pM, about 840 pM, about 830 pM, about 820 pM, about 810 pM, about 800 pM, about 790 pM, about 780 pM, about 770 pM, about 760 pM, about 750 pM, about 740 pM, about 730 pM, about 720 pM, about 710 pM, about 700 pM, about 690 pM, about 680 pM, about 670 pM, about 660 pM, about 650 pM, about 640 pM, about 630 pM, about 620 pM, about 610 pM, about 600 pM, about 590 pM, about 580 pM, about 570 pM, about 560 pM, about 550 pM, about 540 pM, about 530 pM, about 520 pM, about 510 pM, about 500 pM, about 490 pM, about 480 pM, about 470 pM, about 460 pM, about 450 pM, about 440 pM, about 430 pM, about 420 pM, about 410 pM, about 400 pM, about 390 pM, about 380 pM, about 370 pM, about 360 pM, about 350 pM, about 340 pM, about 330 pM, about 320 pM, about 310 pM, about 300 pM, about 290 pM, about 280 pM, about 270 pM, about 260 pM, about 250 pM, about 240 pM, about 230 pM, about 220 pM,

about 210 pM, about 200 pM, about 190 pM, about 180 pM, about 170 pM, about or any integer therebetween.

[00146] In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can bind to a hetero-EPOR with a binding affinity of less than about 600 nM, about 590 nM, about 580 nM, about 570 nM, about 560 nM, about 550 nM, about 540 nM, about 530 nM, about 520 nM, about 510 nM, about 500 nM, about 490 nM, about 480 nM, about 470 nM, about 460 nM, about 450 nM, about 440 nM, about 430 nM, about 420 nM, about 410 nM, about 400 nM, about 390 nM, about 380 nM, about 370 nM, about 360 nM, about 350 nM, about 340 nM, about 330 nM, about 320 nM, about 310 nM, about 300 nM, about 290 nM, about 280 nM, about 270 nM, about 260 nM, about 250 nM, about 240 nM, about 230 nM, about 220 nM, about 210 nM, about 200 nM, about 190 nM, about 180 nM, about 170 nM, about 160 nM, about 150 nM, about 140 nM, about 130 nM, about 120 nM, about 110 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 50 nM, about 50 nM, about 49 nM, about 48 nM, about 47 nM, about 46 nM, about 45 nM, about 44 nM, about 43 nM, about 42 nM, about 41 nM, about 40 nM, about 39 nM, about 38 nM, about 37 nM, about 36 nM, about 35 nM, about 34 nM, about 33 nM, about 32 nM, about 31 nM, about 30 nM, about 29 nM, about 28 nM, about 27 nM, about 26 nM, about 25 nM, about 24 nM, about 23 nM, about 22 nM, about 21 nM, about 20 nM, about 19 nM, about 18 nM, about 17 nM, about 16 nM, about 15 nM, about 14 nM, about 13 nM, about 12 nM, about 11 nM, about 10 nM, about 9 nM, about 8 nM, about 7 nM, about 6 nM, about 5 nM, about 4 nM, about 3 nM, about 2 nM, about 1 nM, about 990 pM, about 980 pM, about 970 pM, about 960 pM, about 950 pM, about 940 pM, about 930 pM, about 920 pM, about 910 pM, about 900 pM, about 890 pM, about 880 pM, about 870 pM, about 860 pM, about 850 pM, about 840 pM, about 830 pM, about 820 pM, about 810 pM, about 800 pM, about 790 pM, about 780 pM, about 770 pM, about 760 pM, about 750 pM, about 740 pM, about 730 pM, about 720 pM, about 710 pM, about 700 pM, about 690 pM, about 680 pM, about 670 pM, about 660 pM, about 650 pM, about 640 pM, about 630 pM, about 620 pM, about 610 pM, about 600 pM, about 590 pM, about 580 pM, about 570 pM, about 560 pM, about 550 pM, about 540 pM, about 530 pM, about 520 pM, about 510 pM, about 500 pM, about 490 pM, about 480 pM, about 470 pM, about 460 pM, about 450 pM, about 440 pM, about 430 pM, about 420 pM, about 410 pM, about 400 pM, about 390 pM, about 380 pM, about 370 pM, about 360 pM, about 350 pM, about 340 pM, about 330 pM, about 320 pM, about 310 pM, about 300 pM, about 290 pM, about 280 pM, about 270 pM, about 260 pM, about 250 pM, about 240 pM, about 230 pM, about 220 pM, about 210 pM, about 200 pM, about 190 pM, about 180 pM, about 170 pM, about or any integer therebetween.

[00147] In some embodiments, EPO analogs or engineered EPOs described herein can have a lower binding affinity to a hetero-EPOR compared to a wild-type or native EPO protein. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can have a hetero-EPOR binding affinity that is lower than that of a wild-type or a native EPO protein that does not comprise one or more amino acid substitutions described herein. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can have a hetero-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% lower than a hetero-EPOR binding affinity of a wild-type or native EPO protein that does not comprise one or more amino acid substitutions described herein.

[00148] In some embodiments, EPO analogs or engineered EPOs described herein can have a higher binding affinity to a hetero-EPOR compared to a wild-type or native EPO protein. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can have a hetero-EPOR binding affinity that is higher than that of a wild-type or a native EPO protein that does not comprise one or more amino acid substitutions described herein. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can have a hetero-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at

least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a hetero-EPOR binding affinity of a wild-type or native EPO protein that does not comprise one or more amino acid substitutions described herein.

[00149] In some embodiments, EPO analogs or engineered EPOs described herein can have the same level of binding affinity to a hetero-EPOR compared to a wild-type or native EPO protein. For example, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can have a hetero-EPOR binding affinity that is the same as or similar to that of a wild-type or native EPO protein that does not comprise one or more amino acid substitutions described herein. In some embodiments, EPO analogs or engineered EPOs described herein can have the same level of binding affinity to a homo-EPOR compared to a wild-type or native EPO protein. For example, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can have a homo-EPOR binding affinity that is the same as or similar to that of a wild-type or native EPO protein that does not comprise one or more amino acid substitutions described herein.

[00150] In some embodiments, EPO analogs or engineered EPOs described herein can have a lower binding affinity to a homo-EPOR compared to a wild-type or native EPO protein. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can have a homo-EPOR binding affinity that is lower than that of a wild-type or a native EPO protein that does not comprise one or more amino acid substitutions described herein. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can have a homo-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at

least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% lower than a homo-EPOR binding affinity of a wild-type or native EPO protein that does not comprise one or more amino acid substitutions described herein.

[00151] In some embodiments, EPO analogs or engineered EPOs described herein can have a higher binding affinity to a homo-EPOR compared to a wild-type or native EPO protein. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can have a homo-EPOR binding affinity that is higher than that of a wild-type or a native EPO protein that does not comprise one or more amino acid substitutions described herein. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can have a homo-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a homo-EPOR binding affinity of a wild-type or native EPO protein that does not comprise one or more amino acid substitutions described herein.

[00152] In some embodiments, EPO analogs or engineered EPOs described herein can bind to a homo-EPO receptor with a binding affinity that is higher than a binding affinity to a hetero-EPO receptor. In some embodiments, EPO analogs or engineered EPOs described herein can bind to a homo-EPO receptor with a binding affinity that is lower than a binding affinity to a hetero-EPO receptor. In some embodiments, EPO analogs or engineered EPOs described herein can bind to a hetero-EPO receptor with a binding affinity that is higher than a binding affinity to a homo-EPO receptor. In some embodiments, EPO analogs or engineered EPOs described herein can bind to a hetero-EPO receptor with a binding affinity that is lower than a binding affinity to a homo-EPO receptor.

[00153] In some embodiments, EPO analogs or engineered EPOs described herein can promote an activity or increase the level of an activity of a homo-EPOR. In some embodiments, EPO analogs or engineered EPOs described herein can have no effect on the level of an activity of a homo-EPOR. In some embodiments, EPO analogs or engineered EPOs described herein can inhibit an activity or decrease the level of an activity of a homo-EPOR. In some embodiments, a homo-EPOR activity can include, but are not limited to, phosphorylation of an intracellular domain of a homo-EPOR, Janus tyrosine kinase 2 (Jak2), or Signal transducer and activator of transcription 5 (Stat5). In some embodiments, a homo-EPOR activity can include, but are not limited to, activation of Jak2, Jak2 pathway, Stat5 pathway, mitogen-activated protein kinase (MAPK), MAPK pathway, extracellular signal-regulated kinase (ERK), ERK pathway, phosphatidylinositol 3-kinase (PI3K), PI3K pathway, v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), Akt/PKB pathway, Mammalian Target of rapamycin (mTOR), or mTOR pathway.

[00154] In some embodiments, EPO analogs or engineered EPOs described herein can promote an activity or increase the level of an activity of a hetero-EPOR. In some embodiments, EPO analogs or engineered EPOs described herein can have no effect on the level of an activity of a hetero-EPOR. In some embodiments, EPO analogs or engineered EPOs described herein can inhibit an activity or decrease the level of an activity of a hetero-EPOR. In some embodiments, a hetero-EPOR activity can include, but are not limited to, phosphorylation of an intracellular domain of a hetero-EPOR, Janus tyrosine kinase 2 (Jak2), or Signal transducer and activator of transcription 5 (Stat5). In some embodiments, a hetero-EPOR activity can include, but are not limited to, activation of Jak2, Jak2 pathway, Stat5 pathway, mitogen-activated protein kinase (MAPK), MAPK pathway, extracellular signal-regulated kinase (ERK), ERK pathway, phosphatidylinositol 3-kinase (PI3K), PI3K pathway, v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), Akt/PKB pathway, Mammalian Target of rapamycin (mTOR), or mTOR pathway.

[00155] In some embodiments, EPO analogs or engineered EPOs described herein may not affect the level of Jak2, Stat5, mTOR, MAPK, ERK, PI3K, Akt/PKB activation or phosphorylation of an intracellular domain of a homo-EPOR or a hetero EPOR compared to a wild-type or native EPO protein. For example, when EPO analogs or engineered EPOs comprising one or more amino acid substitution described herein are introduced to a cell or a population of cells, the cell or the population of cells can have a Jak2 Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation level that is the same as or a similar to that of a cell or a population of cells to which a wild-type or native EPO protein that does not comprise one or more amino acid substitutions described herein is introduced. Activation or phosphorylation of

homo-EPOR, hetero-EPOR, Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR can be measured using any methods known in the art. Examples of methods to measure Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation level include, but are not limited to, western blotting, a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or enzyme-linked immunosorbant assay (ELISA).

[00156] In some embodiments, EPO analogs or engineered EPOs described herein can increase or promote Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation. For example, a cell or a population of cells to which EPO analogs or engineered EPOs comprising one or more amino acid substitution described herein are introduced can have a Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation level that is higher than that of a cell or a population of cells to which a wild-type or native EPO protein that does not comprise one or more amino acid substitutions described herein is introduced. In some embodiments, a cell or a population of cells to which EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein are introduced can have a Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation level that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation level of a cell or a population of cells to which a wild-type or native EPO protein that does not comprise one or more amino acid substitutions described herein is introduced.

[00157] In some embodiments, EPO analogs or engineered EPOs described herein can decrease or inhibit Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation. For example, a cell or a population of cells to which EPO analogs or engineered EPOs comprising one or more amino acid substitution described herein are introduced can have a Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation level that is lower than that of a cell or a population of cells to which a wild-type or native EPO protein that does not comprise one or more amino acid

substitutions described herein is introduced. In some embodiments, a cell or a population of cells to which EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein are introduced can have a Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation level that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% lower than a Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation level of a cell or a population of cells to which a wild-type or native EPO protein that does not comprise one or more amino acid substitutions described herein is introduced.

[00158] In some embodiments, EPO analogs or engineered EPOs described herein can act as an agonist for homo-EPOR and selectively bind to a homo-EPOR. In some embodiments, EPO analogs or engineered EPOs that are agonists for homo-EPOR can have a higher binding affinity to a homo-EPOR than to a hetero-EPOR. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can be agonists for homo-EPOR and have a homo-EPOR binding affinity that is higher than a hetero-EPOR binding affinity. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can be agonists for homo-EPOR and have a homo-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about

45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a hetero-EPOR binding affinity.

[00159] In some embodiments, EPO analogs or engineered EPOs described herein can act as an agonist for homo-EPOR and have binding specificity or selectivity for a homo-EPOR. In some embodiments, EPO analogs or engineered EPOs that are agonists for homo-EPOR can have a higher binding specificity or selectivity to a homo-EPOR than to a hetero-EPOR. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can be agonists for homo-EPOR and have a homo-EPOR binding specificity or selectivity that is higher than a hetero-EPOR binding specificity or selectivity. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can be agonists for homo-EPOR and have a homo-EPOR binding specificity or selectivity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a hetero-EPOR binding specificity or selectivity.

[00160] In some embodiments, EPO analogs or engineered EPOs described herein can act as an antagonist for homo-EPOR and selectively bind to a homo-EPOR. In some embodiments, EPO analogs or engineered EPOs that are antagonists for homo-EPOR can have a higher binding affinity to a homo-EPOR than to a hetero-EPOR. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can be antagonists for homo-EPOR and have a homo-EPOR binding affinity that is higher than a hetero-EPOR binding affinity. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can be antagonists for homo-EPOR and have a homo-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%,

at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a hetero-EPOR binding affinity.

[00161] In some embodiments, EPO analogs or engineered EPOs described herein can act as an antagonist for homo-EPOR and have binding specificity or selectivity for a homo-EPOR. In some embodiments, EPO analogs or engineered EPOs that are antagonists for homo-EPOR can have a higher binding specificity or selectivity to a homo-EPOR than to a hetero-EPOR. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can be antagonists for homo-EPOR and have a homo-EPOR binding specificity or selectivity that is higher than a hetero-EPOR binding specificity or selectivity. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can be antagonists for homo-EPOR and have a homo-EPOR binding specificity or selectivity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a hetero-EPOR binding specificity or selectivity.

[00162] In some embodiments, EPO analogs or engineered EPOs described herein can act as an agonist for hetero-EPOR and selectively bind to a hetero-EPOR. In some embodiments, EPO analogs or engineered EPOs that are agonists for hetero-EPOR can have a higher binding affinity to a hetero-EPOR than to a homo-EPOR. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can be agonists for hetero-EPOR and have a hetero-EPOR binding affinity that is higher than a homo-EPOR binding affinity. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can be agonists for hetero-EPOR and have a hetero-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a homo-EPOR binding affinity.

[00163] In some embodiments, EPO analogs or engineered EPOs described herein can act as an agonist for hetero-EPOR and have binding specificity or selectivity for a hetero-EPOR. In some embodiments, EPO analogs or engineered EPOs that are agonists for hetero-EPOR can have a higher binding specificity or selectivity to a hetero-EPOR than to a homo-EPOR. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can be agonists for hetero-EPOR and have a hetero-EPOR binding specificity or selectivity that is higher than a homo-EPOR binding specificity or selectivity. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can be agonists for hetero-EPOR and have a hetero-EPOR binding specificity or selectivity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at

least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a homo-EPOR binding specificity or selectivity.

[00164] In some embodiments, EPO analogs or engineered EPOs described herein can act as an antagonist for hetero-EPOR and selectively bind to a hetero-EPOR. In some embodiments, EPO analogs or engineered EPOs that are antagonists for hetero-EPOR can have a higher binding affinity to a hetero-EPOR than to a homo-EPOR. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can be antagonists for hetero-EPOR and have a hetero-EPOR binding affinity that is higher than a homo-EPOR binding affinity. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can be antagonists for hetero-EPOR and have a hetero-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a homo-EPOR binding affinity.

[00165] In some embodiments, EPO analogs or engineered EPOs described herein can act as an antagonist for hetero-EPOR and have binding specificity or selectivity for a hetero-EPOR. In some embodiments, EPO analogs or engineered EPOs that are antagonists for hetero-EPOR can have a higher binding specificity or selectivity to a hetero-EPOR than to a homo-EPOR. For example, EPO analogs or engineered EPOs comprising one or amino acid substitutions described herein can be antagonists for hetero-EPOR and have a hetero-EPOR binding specificity or

selectivity that is higher than a homo-EPOR binding specificity or selectivity. In some embodiments, EPO analogs or engineered EPOs comprising one or more amino acid substitutions described herein can be antagonists for hetero-EPOR and have a hetero-EPOR binding specificity or selectivity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a homo-EPOR binding specificity or selectivity.

[00166] In some embodiments, EPO analogs or engineered EPOs described herein can have a half-life of from 1 hour to 5 days in human plasma. In some embodiments, EPO analogs or engineered EPOs described herein can have a half-life about 1 hour to about 120 hours. In some embodiments, EPO analogs or engineered EPOs described herein can have a half-life about 1 hour to about 5 hours, about 1 hour to about 10 hours, about 1 hour to about 12 hours, about 1 hour to about 24 hours, about 1 hour to about 36 hours, about 1 hour to about 48 hours, about 1 hour to about 60 hours, about 1 hour to about 72 hours, about 1 hour to about 84 hours, about 1 hour to about 96 hours, about 1 hour to about 120 hours, about 5 hours to about 10 hours, about 5 hours to about 12 hours, about 5 hours to about 24 hours, about 5 hours to about 36 hours, about 5 hours to about 48 hours, about 5 hours to about 60 hours, about 5 hours to about 72 hours, about 5 hours to about 84 hours, about 5 hours to about 96 hours, about 5 hours to about 120 hours, about 10 hours to about 12 hours, about 10 hours to about 24 hours, about 10 hours to about 36 hours, about 10 hours to about 48 hours, about 10 hours to about 60 hours, about 10 hours to about 72 hours, about 10 hours to about 84 hours, about 10 hours to about 96 hours, about 10 hours to about 120 hours, about 12 hours to about 24 hours, about 12 hours to about 36 hours, about 12 hours to about 48 hours, about 12 hours to about 60 hours, about 12 hours to about 72 hours, about 12 hours to about 84 hours, about 12 hours to about 96 hours, about 12 hours to about 120 hours, about 24 hours to about 36 hours, about 24 hours to about 48 hours, about 24 hours to about 60 hours, about 24 hours to about 72 hours, about 24 hours to about 84

hours, about 24 hours to about 96 hours, about 24 hours to about 120 hours, about 36 hours to about 48 hours, about 36 hours to about 60 hours, about 36 hours to about 72 hours, about 36 hours to about 84 hours, about 36 hours to about 96 hours, about 36 hours to about 120 hours, about 48 hours to about 60 hours, about 48 hours to about 72 hours, about 48 hours to about 84 hours, about 48 hours to about 96 hours, about 48 hours to about 120 hours, about 60 hours to about 72 hours, about 60 hours to about 84 hours, about 60 hours to about 96 hours, about 60 hours to about 120 hours, about 72 hours to about 84 hours, about 72 hours to about 96 hours, about 72 hours to about 120 hours, about 84 hours to about 96 hours, about 84 hours to about 120 hours, or about 96 hours to about 120 hours. In some embodiments, EPO analogs or engineered EPOs described herein can have a half-life about 1 hour, about 5 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours, about 72 hours, about 84 hours, about 96 hours, or about 120 hours. In some embodiments, EPO analogs or engineered EPOs described herein can have a half-life at least about 1 hour, about 5 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours, about 72 hours, about 84 hours, or about 96 hours. In some embodiments, EPO analogs or engineered EPOs described herein can have a half-life at most about 5 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours, about 72 hours, about 84 hours, about 96 hours, or about 120 hours.

[00167] The disclosure also encompasses engineered EPORs comprising extracellular domain (ECD) of EPOR. The ECD of EPOR comprises 2 domains, D1 and D2, and these two domains are required for EPO binding. In some embodiments, Fc fusion protein of ECD EPOR-Fc can bind to EPO. In some embodiments, Fc fusion protein of ECD EPOR-Fc can block EPOR activation. In some embodiments, Fc fusion protein of ECD EPOR-Fc can comprise a mutation. For example, Fc fusion protein of ECD EPOR-Fc can comprise a mutation at amino acid residue F93. In some embodiments, Fc fusion protein of ECD EPOR-Fc can comprise F93A mutation. In some embodiments, Fc fusion protein of ECD EPOR-Fc comprising F93A mutation may not bind EPO. For example, a monomeric EPOR ECD comprising F93A mutation or a dimeric EPOR-Fc comprising F93A mutation may not bind EPO.

[00168] The disclosure also encompasses engineered hetero-EPORs comprising extra cellular domain (ECD) of CD131. The ECD of CD131 comprises 4 domains, D1, D2, D3, and D4. D1 and D2 domains are responsible for dimerization distal to the cell membrane. Without wishing to be bound by theory, D3 and D4 domains can be the regions interacting with EPOR to form a hetero-EPOR. In some embodiments, knobs-in-holes technology can be used to generate heterodimeric Fc fusion proteins with EPOR ECD and CD131 ECD. Non-limiting examples of designs of heterodimeric Fc fusion proteins with EPOR ECD and CD131 ECD are shown in

Table 3-3 and the sequences are shown in **FIGs. 42A-42D**. In some embodiments, EPO binding may require D3 and D4 domains of CD131. For example, the monomeric or dimeric EPOR with the F93A substitution may not bind EPO, however, a hetero-EPOR of a monomeric EPOR with the F93A mutation and a CD131 monomer binds EPO. It seems that EPO binding to the hetero-EPOR is specific to CDC131 subunit. In some embodiments, heterodimeric EPOR(F93A)/CD131-Fc may be used to specifically block hetero-EPORs but not homo-EPORs.

Anti-EPOR, anti-CD131, and anti-EPO Antibodies

[00169] In some aspects, provided herein, are antibodies, antigen-binding fragments thereof, or functional fragments thereof that can selectively binds to a target. In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can bind to an antigen of a target protein or an epitope on an antigen of a target protein.

[00170] In some embodiments, an antibody can be a monospecific antibody and binds a single epitope. For example, a monospecific antibody can have a plurality of immunoglobulin variable domain sequences, each of which binds the same epitope. In some embodiments, an antibody can be a bispecific antibody. A bispecific antibody can have specificity for no more than two antigens. A bispecific antibody can be characterized by a first immunoglobulin variable domain sequence which has binding specificity for a first epitope and a second immunoglobulin variable domain sequence that has binding specificity for a second epitope. In some embodiments, the first and second epitopes can be on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In some embodiments, the first and second epitopes can overlap. In some embodiments, the first and second epitopes do not overlap. In some embodiments, the first and second epitopes can be on different antigens, e.g., different proteins (or different subunits of a multimeric protein). In some embodiments, a bispecific antibody can comprise a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a first epitope and a heavy chain variable domain sequence and a light chain variable domain sequence which have binding specificity for a second epitope. In some embodiments, a bispecific antibody can comprise a half antibody having binding specificity for a first epitope and a half antibody having binding specificity for a second epitope. In some embodiments, a bispecific antibody can comprise a half antibody, or a fragment thereof, having binding specificity for a first epitope and a half antibody, or a fragment thereof, having binding specificity for a second epitope. In some embodiments, a bispecific antibody can comprise a scFv or a Fab, or fragment thereof, have binding specificity for a first epitope and a scFv or a Fab, or fragment thereof, have binding specificity for a second epitope.

[00171] In some embodiments, an antibody can be a multispecific or multifunctional antibody. For example, a multispecific or multifunctional antibody can comprise a plurality of

immunoglobulin variable domains sequences, wherein a first immunoglobulin variable domain sequence of the plurality has binding specificity for a first epitope and a second immunoglobulin variable domain sequence of the plurality has binding specificity for a second epitope. In some embodiments, the first and second epitopes are on the same antigen, e.g., the same protein (or subunit of a multimeric protein). In some embodiments, the first and second epitopes can overlap. In some embodiments, the first and second epitopes may not overlap. In some embodiments, the first and second epitopes can be on different antigens, e.g., different proteins (or different subunits of a multimeric protein). In some embodiments a multispecific antibody can comprise a third, a fourth or a fifth immunoglobulin variable domain. In some embodiments, a multispecific antibody can be a bispecific antibody, a trispecific antibody, or a tetraspecific antibody. In some embodiments, multispecific antibodies can optionally further comprise one or more additional binding domain(s) that selectively bind(s) to an IgE, a FcεRIα, a FcεRII, a tumor associated antigen (FAA), or a combination thereof. Any bispecific or multispecific antibodies described herein can be isolated, purified, recombinant, synthetic, or any combination thereof. A bispecific or mutispecific antibodies described herein can be made via any suitable method and may be recombinant, synthetic, or a combination thereof. In one aspect, provided herein can be a liquid composition or a lyophilized composition comprising one or more of bispecific or multispecific antibodies described herein. In one embodiment, a composition can comprise a population of a bispecific or multispecific antibodies. In another embodiments, a composition can comprise a population of two, three, four, five, six, seven, eight, nine, ten, or more bispecific or multispecific antibodies described above. A bispecific or multispecific antibodies described herein can be utilized in an *in vitro* assay to, for example, identify and/or purify one or more tumor cell(s) from a mixed culture (e.g., a biological sample such as a biopsy or a blood sample). A bispecific or multispecific antibodies described herein can be utilized in an *in vivo* animal model to test the therapeutic efficacy of the bispecific or multispecific antibodies against a tumor.

[00172] In some embodiments, an antibody can comprise a diabody, and a single-chain molecule, as well as an antigen-binding fragment of an antibody (e.g., Fab, F(ab')2, and Fv). For example, an antibody molecule can include a heavy (H) chain variable domain sequence (abbreviated herein as VH), and a light (L) chain variable domain sequence (abbreviated herein as VL). In some embodiments, an antibody can comprise a heavy chain and a light chain (referred to herein as a half antibody. In another example, an antibody can comprise two heavy (H) chain variable domain sequences and two light (L) chain variable domain sequence, thereby forming two antigen binding sites, such as Fab, Fab', F(ab')2, Fc, Fd, Fd', Fv, single chain antibodies (scFv for example), single variable domain antibodies, diabodies (Dab) (bivalent and bispecific), and chimeric (e.g., humanized) antibodies, which may be produced by the

modification of whole antibodies or those synthesized *de novo* using recombinant DNA technologies. These functional antibody fragments can retain the ability to selectively bind with their respective antigen. Antibodies and antibody fragments can be from any class of antibodies including, but not limited to, IgG, IgA, IgM, IgD, and IgE, and from any subclass (e.g., IgG1, IgG2, IgG3, and IgG4) of antibodies. A preparation of antibodies can be monoclonal or polyclonal. An antibody can also be a human, humanized, CDR-grafted, or *in vitro* generated antibody. An antibody can have a heavy chain constant region chosen from, e.g., IgG1, IgG2, IgG3, or IgG4. An antibody can also have a light chain chosen from, e.g., kappa or lambda. The term "immunoglobulin" (Ig) is used interchangeably with the term "antibody" herein.

[00173] Non-limiting examples of antigen-binding fragments of an antibody can include: a Fab fragment (a monovalent fragment consisting of the VL, VH, CL and CH1 domains); a F(ab')2 fragment (a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region); a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a diabody (dAb) fragment consisting of a VH domain; a camelid or camelized variable domain; a single chain Fv (scFv) (see e.g., Bird et al. (1988) Science 242:423-426; and Huston et al. (1988) Proc. Natl. Acad. Sci. USA 85:5879-5883); and a single domain antibody. These antibody fragments can be obtained using conventional techniques known to those with skill in the art, and the fragments can be screened for utility in the same manner as are intact antibodies. For example, a single-chain antibody (scFV) can be engineered (see, for example, Colcher, D. et al. (1999) Ann N Y Acad Sci 880:263-80; and Reiter, Y. (1996) Clin Cancer Res 2:245-52). In some embodiments, a single chain antibody can be dimerized or multimerized to generate multivalent antibodies having specificities for different epitopes of the same target protein. In some embodiments, antibodies can include intact molecules as well as functional fragments thereof. Constant regions of antibodies can be altered or mutated to modify one or more properties of antibodies (*e.g.*, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function). Methods for altering antibody constant regions are known in the art. In some embodiments, antibodies with altered function, e.g., altered affinity for an effector ligand, such as FcR on a cell, or the C1 component of complement can be produced by replacing at least one amino acid residue in the constant portion of the antibody with a different residue (see e.g., EP 388,151 A1, U.S. Pat. No. 5,624,821 and U.S. Pat. No. 5,648,260, the contents of all of which are hereby incorporated by reference).

[00174] In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can include a non-antibody scaffold. Non-limiting examples of non-antibody scaffolds include Affibodies, Affilins, Anticalins, Atrimers, Avimers, Bicyclic

peptides, Cys-knots, DARPins, FN3 scaffolds (e.g., adnectins, centyrins, pronectins, Tn3), Fynomers, Kunitz domains, or OBodies.

[00175] In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can be derivatized or linked to another functional molecule (e.g., another peptide or protein). As used herein, a "derivatized" antibody is an antibody that has been modified. Methods of derivatization can include, but are not limited to, the addition of a fluorescent moiety, a radionucleotide, a toxin, an enzyme or an affinity ligand such as biotin. For example, an antibody can be functionally linked to one or more other molecular entities, such as another antibody (e.g., a bispecific antibody or a diabody), a detectable agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate association of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag) by e.g., chemical coupling, genetic fusion, noncovalent association, or using other methods. One type of derivatized antibody can be produced by crosslinking two or more antibodies (of the same type or of different types, e.g., to create bispecific antibodies). Suitable crosslinkers can include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (e.g., m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (e.g., disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

[00176] In some embodiments, antibodies can also be single domain antibodies. Single domain antibodies can include antibodies whose complementary determining regions are part of a single domain polypeptide. Non-limiting examples can include heavy chain antibodies, antibodies naturally devoid of light chains, single domain antibodies derived from conventional 4-chain antibodies, engineered antibodies and single domain scaffolds other than those derived from antibodies. Single domain antibodies can be any of the art, or any future single domain antibodies. Single domain antibodies can be derived from any species including, but not limited to mouse, human, camel, llama, fish, shark, goat, rabbit, and bovine. In some embodiments, a single domain antibody can be a naturally occurring single domain antibody known as heavy chain antibody devoid of light chains. Such single domain antibodies are disclosed in WO 94/04678, for example. In some embodiments, this variable domain derived from a heavy chain antibody naturally devoid of light chain is known herein as a VHH or nanobody. Such a VHH molecule can be derived from antibodies raised in Camelidae species, for example in camel, llama, dromedary, alpaca and guanaco. Other species besides Camelidae may produce heavy chain antibodies naturally devoid of light chain.

[00177] The VH and VL regions can be subdivided into regions of hypervariability, termed "complementarity determining regions" (CDR), interspersed with regions that are more

conserved, termed "framework regions" (FR or FW). The extent of the framework region and CDRs has been precisely defined by a number of methods (*see*, Kabat, E. A., *et al.* (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Chothia, C. *et al.* (1987) *J. Mol. Biol.* 196:901-917; and the AbM definition used by Oxford Molecular's AbM antibody modeling software. *See*, generally, *e.g.*, *Protein Sequence and Structure Analysis of Antibody Variable Domains.* In: Antibody Engineering Lab Manual (Ed.: Duebel, S. and Kontermann, R., Springer-Verlag, Heidelberg). In some embodiments, CDRs can comprise amino acid sequences within antibody variable regions that confer antigen specificity and binding affinity. In some embodiments, antibodies can have three CDRs in each heavy chain variable region (VH-CDR1, VH-CDR2, and VH-CDR3) and three CDRs in each light chain variable region (VL-CDR1, VL-CDR2, and VL-CDR3). In some embodiments, boundaries of amino acid sequences of a given CDR can be determined using any of a number of known schemes, including those described by Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme), Al-Lazikani et al., (1997) JMB 273,927-948 ("Chothia" numbering scheme).

[00178] Antibodies described herein can be produced recombinantly, for example, using phase display or by using combinatorial methods. Phage display and combinatorial methods for generating antibodies are known in the art (as described in, e.g., Ladner et al. U.S. Patent No. 5,223,409; Kang et al. International Publication No. WO 92/18619; Dower et al. International Publication No. WO 91/17271; Winter et al. International Publication WO 92/20791; Markland et al. International Publication No. WO 92/15679; Breitling et al. International Publication WO 93/01288; McCafferty et al. International Publication No. WO 92/01047; Garrard et al. International Publication No. WO 92/09690; Ladner et al. International Publication No. WO 90/02809; Fuchs et al. (1991) Bio/Technology 9:1370-1372; Hay et al. (1992) Hum Antibod Hybridomas 3:81-85; Huse et al. (1989) Science 246:1275-1281; Griffths et al. (1993) EMBO J 12:725-734; Hawkins et al. (1992) J Mol Biol 226:889-896; Clackson et al. (1991) Nature 352:624-628; Gram et al. (1992) PNAS 89:3576-3580; Garrad et al. (1991) Bio/Technology 9:1373-1377; Hoogenboom et al. (1991) Nuc Acid Res 19:4133-4137; and Barbas et al. (1991) PNAS 88:7978-7982, the contents of all of which are incorporated by reference herein).

[00179] In some embodiments, antibodies described herein can be fully human antibodies (*e.g.*, antibodies made in a mouse which has been genetically engineered to produce antibodies from a human immunoglobulin sequence), or non-human antibodies, *e.g.*, a rodent (mouse or rat), goat, primate (*e.g.*, monkey), or camel antibodies. In some embodiments, non-human antibodies can

be rodent antibodies (mouse or rat antibodies). Methods of producing rodent antibodies are known in the art.

[00180] In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can be humanized antibodies or humanized antigen-binding fragments. As used herein, "humanized" antibodies refer to forms of non-human (e.g., murine) antibodies that are specific chimeric immunoglobulins, immunoglobulin chains, or fragments thereof that contain minimal sequence derived from non-human immunoglobulin. In some embodiments, humanized antibodies can be human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and biological activity. In some embodiments, humanized antibodies can have at least one or two, but generally all three, recipient CDRs (of heavy and or light immuoglobulin chains) replaced with a donor CDR. In some embodiments, antibodies may be replaced with at least a portion of a non-human CDR or only some of the CDRs may be replaced with non-human CDRs. In some embodiments, a minimal number of CDRs required for binding to the antigen can be replaced. In some embodiments, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine or optimize antibody performance. In general, a humanized antibody can comprise at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. Humanized antibodies optimally also can comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Antibodies can have Fc regions modified as described in, for example, WO 99/58572. Other forms of humanized antibodies have one or more CDRs (one, two, three, four, five, or six) which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody. Humanized antibodies can be produced, for example, by modeling the antibody variable domains and producing the antibodies using genetic engineering techniques, such as CDR grafting or CDR substitution, wherein one, two, or all CDRs of an immunoglobulin chain can be replaced. A description of various techniques for the production of humanized antibodies is found, for example, in U.S. Patent 5,225,539; Morrison et al., (1984) Proc. Nat'l Acad. Sci. USA 81:6851-55; Whittle et al., (1987) Prot. Eng. 1:499-505; Co et al., (1990) J. Immunol. 148:1149-1154; Co et al., (1992) Proc. Nat'l Acad. Sci. USA 88:2869-2873; Carter et al., (1992) Proc. Nat'l Acad.

Sci. USA 89:4285-4289; Routledge et al., (1991) Eur. J. Immunol. 21:2717-2725 and PCT Patent Publication Nos. WO 91/09967; WO 91/09968 and WO 92/113831. For example, human monoclonal antibodies can be generated using transgenic mice carrying the human immunoglobulin genes rather than the mouse system. Splenocytes from these transgenic mice immunized with the antigen of interest can be used to produce hybridomas that secrete human mAbs with specific affinities for epitopes from a human protein (see, e.g., Wood et al. International Application WO 91/00906, Kucherlapati et al. PCT publication WO 91/10741; Lonberg et al. International Application WO 92/03918; Kay et al. International Application 92/03917; Lonberg, N. et al. 1994 Nature 368:856-859; Green, L.L. et al. 1994 Nature Genet. 7:13-21; Morrison, S.L. et al. 1994 Proc. Natl. Acad. Sci. USA 81:6851-6855; Bruggeman et al. 1993 Year Immunol 7:33-40; Tuaillon et al. 1993 PNAS 90:3720-3724; Bruggeman et al. 1991 Eur J Immunol 21:1323-1326). In some embodiments, immunocompetent transgenic mice can be used. In some embodiments, immunocompetent transgenic mice can comprise human antibody heavy chains, human antibody light chains, or combinations thereof. In some embodiments, immunocompetent transgenic mice can comprise human antibody heavy chains, human antibody lamda light chains, human antibody kappa light chains or combinations thereof. In some embodiments, one or more specific amino acids can be substituted, deleted, or added in humanized antibodies. Criteria for selecting amino acids from the donor are described in US 5,585,089, e.g., columns 12-16 of US 5,585,089, e.g., columns 12-16 of US 5,585,089, the contents of which are hereby incorporated by reference. Other techniques for humanizing antibodies are described in Padlan et al. EP 519596 A1, published on December 23, 1992.

[00181] In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can comprise a CDR-grafted scaffold domain. In some embodiments, the scaffold domain can be based on a fibronectin domain, e.g., fibronectin type III domain. In some embodiments, the overall fold of the fibronectin type III (Fn3) domain can be closely related to that of the smallest functional antibody fragment, the variable domain of the antibody heavy chain. There are three loops at the end of Fn3; the positions of BC, DE and FG loops approximately correspond to those of CDR1, 2 and 3 of the VH domain of an antibody. In some embodiments, Fn3 may not have disulfide bonds; and therefore Fn3 can be stable under reducing conditions, unlike antibodies and their fragments (see, e.g., WO 98/56915; WO 01/64942; WO 00/34784). An Fn3 domain can be modified (e.g., using CDRs or hypervariable loops described herein) or varied, e.g., to select domains that bind to an antigen/marker/cell described herein. In some embodiments, a scaffold domain, e.g., a folded domain, can be based on an antibody, e.g., a “minibody” scaffold created by deleting three beta strands from a heavy chain variable domain of a monoclonal antibody (see, e.g., Tramontano et al., 1994, J Mol.

Recognit. 7:9; and Martin et al., 1994, EMBO J. 13:5303-5309). In some embodiments, the minibody can be used to present two hypervariable loops. In some embodiments, the scaffold domain can be a V-like domain (see, e.g., Coia et al. WO 99/45110) or a domain derived from tendamistatin, which is a 74 residue, six-strand beta sheet sandwich held together by two disulfide bonds (see, e.g., McConnell and Hoess, 1995, J Mol. Biol. 250:460). For example, the loops of tendamistatin can be modified (e.g., using CDRs or hypervariable loops) or varied, e.g., to select domains that bind to a marker/antigen/cell described herein. Another exemplary scaffold domain is a beta-sandwich structure derived from the extracellular domain of CTLA-4 (see, e.g., WO 00/60070). Other exemplary scaffold domains can include, but are not limited to, T-cell receptors, MHC proteins, extracellular domains (e.g., fibronectin Type III repeats, EGF repeats), protease inhibitors (e.g., Kunitz domains, ecotin, BPTI, and so forth), TPR repeats; trifoil structures, zinc finger domains, DNA-binding proteins, particularly monomeric DNA binding proteins, RNA binding proteins, enzymes, e.g., proteases (particularly inactivated proteases), RNase, chaperones, e.g., thioredoxin, and heat shock proteins; and intracellular signaling domains (such as SH2 and SH3 domains). See, e.g., US 20040009530 and US 7,501,121, incorporated herein by reference. In some embodiments, a scaffold domain can be evaluated and chosen, e.g., by one or more of the following criteria: (1) amino acid sequence, (2) sequences of several homologous domains, (3) 3-dimensional structure, and/or (4) stability data over a range of pH, temperature, salinity, organic solvent, oxidant concentration. In some embodiments, the scaffold domain can be a small, stable protein domain, e.g., a protein of less than 100, 70, 50, 40 or 30 amino acids. The domain may include one or more disulfide bonds or may chelate a metal, e.g., zinc.

[00182] In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can comprise variable regions, or a portion thereof, e.g., CDRs, generated in a non-human organism (e.g., a rat or mouse). In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can be chimeric, CDR-grafted, or humanized antibodies. In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can be generated in a non-human organism and modified. For example, antibodies, antigen-binding fragments thereof, or functional fragments thereof generated in a non-human organism (e.g., a rat or mouse) can be modified in the variable frame work or constant region, to decrease antigenicity and/or immunogenicity in humans. In some embodiments, chimeric antibodies can be produced by recombinant DNA techniques known in the art (see Robinson et al., International Patent Publication PCT/US86/02269; Akira, et al., European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496; Morrison et al., European Patent Application 173,494;

Neuberger et al., International Application WO 86/01533; Cabilly et al. U.S. Patent No. 4,816,567; Cabilly et al., European Patent Application 125,023; Better et al. (1988 Science 240:1041-1043); Liu et al. (1987) PNAS 84:3439-3443; Liu et al., 1987, J. Immunol. 139:3521-3526; Sun et al. (1987) PNAS 84:214-218; Nishimura et al., 1987, Canc. Res. 47:999-1005; Wood et al. (1985) Nature 314:446-449; and Shaw et al., 1988, J. Natl Cancer Inst. 80:1553-1559).

[00183] In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein that can selectively binds to an antigen of a target protein or an epitope on an antigen of a target protein. In some embodiments, the target can comprise an erythropoietin (EPO) protein, an EPO receptor subunit of a homo-EPOR or a hetero-EPOR, a CD131 subunit of a hetero-EPOR, or a combination thereof. In some embodiments, the target can comprise a hetero-EPOR. For example, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can selectively binds to a hetero-EPOR comprising a EPO receptor subunit and a CD131 subunit. In this embodiment, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can bind to both EPO receptor subunit and CD131 subunit of a hetero-EPOR. In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can be non-naturally occurring. In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can be isolated and/or purified. In some embodiments, antibodies, antigen-binding fragments thereof, or functional fragments thereof described herein can be used in *in vitro* assays (e.g., binding assays, functional assays, etc.).

[00184] In some embodiments, antibodies or functional fragments thereof described herein can bind to a target and can act as an antagonist. In one example, an anti-EPO antibody can bind an EPO protein and can prevent formation of a complex between an EPO protein and a homo-EPOR. In another example, an anti-EPO antibody can bind an EPO protein and can prevent formation of a complex between an EPO protein and a hetero-EPOR. In yet another example, an anti-EPOR antibody can bind an EPO receptor subunit and can prevent complex formation of a homo-EPOR, complex formation of a hetero-EPOR, complex formation between an EPO protein and a homo-EPOR, or complex formation between an EPO protein and a hetero-EPOR. In yet another example, an anti-CDC131 antibody can bind a CDC131 subunit of a hetero-EPOR and can prevent complex formation of a hetero-EPOR or complex formation between an EPO protein and a hetero-EPOR. In some embodiments, preventing complex formation of a homo-EPOR or complex formation between an EPO protein and a homo-EPOR can lead to prevention of homo-EPOR activation or function. In some embodiments, preventing complex formation of a hetero-EPOR or complex formation between an EPO protein and a hetero-EPOR can lead to prevention

of hetero-EPOR activation or function. In some embodiments, an anti-EPO antibody can bind an EPO protein and inhibit or decrease the level of an activity of a homo-EPOR or a hetero-EPOR without affecting binding of the EPO protein to the homo-EPOR or the hetero-EPOR. In some embodiments, an anti-EPOR antibody can bind to an EPO receptor subunit of a homo-EPOR or a hetero-EPOR and inhibit or decrease the level of an activity of the homo-EPOR or the hetero-EPOR without affecting the complex formation of the homo-EPOR or the hetero-EPOR, or complex formation between an EPO protein and the homo-EPOR or an EPO protein and the hetero-EPOR. In some embodiments, an anti-CD131 antibody can bind a CD131 subunit of a hetero-EPOR and inhibit or decrease the level of an activity of the hetero-EPOR without affecting complex formation of the hetero-EPOR or binding of an EPO protein to the hetero-EPOR.

[00185] In some embodiments, antibodies or functional fragments thereof described herein can bind to a target and can act as an agonist. In one example, an anti-EPOR antibody can bind an EPO receptor subunit of a homo-EPOR in a manner that mimics the binding of an EPO to a homo-EPOR. In another example, an anti-EPOR antibody can bind a EPO receptor subunit of a hetero-EPOR in a manner that mimics the binding of an EPO to a hetero-EPOR. In yet another example, an anti-CD131 antibody can bind a CD131 subunit of a hetero-EPOR in a manner that mimics the binding of an EPO to a hetero-EPOR. In some embodiments, mimicking the binding of an EPO to a homo-EPOR can lead to activation of the homo-EPOR. In some embodiments, mimicking the binding of an EPO to a hetero-EPOR can lead to activation of the hetero-EPOR. In some embodiments, an anti-EPO antibody can promote or increase an activity of a homo-EPOR or a hetero-EPOR without affecting the binding affinity of the EPO protein to the homo-EPOR or the hetero-EPOR. In some embodiments, an anti-EPOR antibody can promote or increase an activity of a homo-EPOR or a hetero-EPOR without affecting the binding affinity of the EPO protein to the homo-EPOR or the hetero-EPOR, or the binding affinity of the homo-EPOR (e.g., between the two EPO receptor subunits of the homo-EPOR) or the hetero-EPOR (e.g., between the EPO receptor subunit and CD131 subunit of the hetero-EPOR). In some embodiments, an anti-CD131 antibody can promote or increase an activity of a hetero-EPOR without affecting the binding affinity of the EPO protein to the hetero-EPOR or the binding affinity of the hetero-EPOR (e.g., between the EPO receptor subunit and CD131 subunit of the hetero-EPOR).

[00186] In some embodiments, a homo-EPOR activity or a hetero-EPOR activity can include, but are not limited to, phosphorylation of an intracellular domain of a homo-EPOR, a hetero-EPOR, Janus tyrosine kinase 2 (Jak2), or Signal transducer and activator of transcription 5 (Stat5). In some embodiments, a homo-EPOR activity or a hetero-EPOR activity can include,

but are not limited to, activation of Jak2, Jak2 pathway, Stat5 pathway, mitogen-activated protein kinase (MAPK), MAPK pathway, extracellular signal-regulated kinase (ERK), ERK pathway, phosphatidylinositol 3-kinase (PI3K), PI3K pathway, v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), Akt/PKB pathway, Mammalian Target of rapamycin (mTOR), or mTOR pathway. In some embodiments, antibodies or functional fragments thereof described herein can inhibit activation or phosphorylation of homo-EPOR, hetero-EPOR, Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR. In some embodiments, antibodies or functional fragments thereof described herein can inhibit activation of Jak2, Jak2 pathway, Stat5, Stat5 pathway, MAPK, MAPK pathway, ERK, ERK pathway, PI3K, PIK3 pathway, Akt/PKB, Akt/PKB pathway, mTOR, or mTOR pathway. In some embodiments, antibodies or functional fragments thereof described herein can promote activation or phosphorylation of homo-EPOR, hetero-EPOR, Jak2, Stat5, or mTOR. In some embodiments, antibodies or functional fragments thereof described herein can promote activation of Jak2, Jak2 pathway, Stat5, Stat5 pathway, MAPK, MAPK pathway, ERK, ERK pathway, PI3K, PIK3 pathway, Akt/PKB, Akt/PKB pathway, mTOR, or mTOR pathway. In some embodiments, antibodies or functional fragments thereof described herein may not affect activation or phosphorylation of homo-EPOR, hetero-EPOR, Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR. In some embodiments, antibodies or functional fragments thereof described herein may not affect activation of Jak2, Jak2 pathway, Stat5, Stat5 pathway, MAPK, MAPK pathway, ERK, ERK pathway, PI3K, PIK3 pathway, Akt/PKB, Akt/PKB pathway, mTOR, or mTOR pathway. In some embodiments, activation or phosphorylation of homo-EPOR, hetero-EPOR, Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR can be measured using any methods known in the art. Examples of methods to measure Jak2, Stat5, MAPK, ERK, PI3K, Akt/PKB, or mTOR activation level include, but are not limited to, western blotting, a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or enzyme-linked immunosorbant assay (ELISA).

[00187] In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can bind to a target and can act as agonists for hetero-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be agonists for hetero-EPOR and can selectively bind to hetero-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be agonists for hetero-EPOR and can have a higher binding affinity to hetero-EPOR than to homo-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be agonists for hetero-EPOR and can have a hetero-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about

8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a homo-EPOR binding affinity.

[00188] In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be agonists for hetero-EPOR and can have binding specificity or selectivity for a hetero-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be agonists for hetero-EPOR and can have a higher specificity or selectivity to hetero-EPOR than to homo-EPOR. For example, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be agonists for hetero-EPOR and can have a hetero-EPOR binding specificity or selectivity that is higher than a homo-EPOR binding specificity or selectivity. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be agonists for hetero-EPOR and have a hetero-EPOR binding specificity or selectivity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a homo-EPOR binding specificity or selectivity.

[00189] In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can bind to a target and can act as antagonists for hetero-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be antagonists for hetero-EPOR and can selectively bind to hetero-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be antagonists for hetero-EPOR and can have a higher binding affinity to hetero-EPOR than to homo-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be antagonists for hetero-EPOR and can have a hetero-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a homo-EPOR binding affinity.

[00190] In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be antagonists for hetero-EPOR and can have binding specificity or selectivity for a hetero-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be antagonists for hetero-EPOR and can have a higher specificity or selectivity to hetero-EPOR than to homo-EPOR. For example, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be antagonists for hetero-EPOR and can have a hetero-EPOR binding specificity or selectivity that is higher than a homo-EPOR binding specificity or selectivity. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be antagonists for hetero-EPOR and have a hetero-EPOR binding specificity or selectivity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at

least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a homo-EPOR binding specificity or selectivity.

[00191] In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can bind to a target and can act as agonists for homo-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be agonists for homo-EPOR and can selectively bind to homo-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be agonists for homo-EPOR and can have a higher binding affinity to homo-EPOR than to hetero-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be agonists for homo-EPOR and can have a homo-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a hetero-EPOR binding affinity.

[00192] In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be agonists for homo-EPOR and can have binding specificity or selectivity for homo-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be agonists for homo-EPOR and can have a higher specificity or

selectivity to homo-EPOR than to hetero-EPOR. For example, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be agonists for homo-EPOR and can have a homo-EPOR binding specificity or selectivity that is higher than a hetero-EPOR binding specificity or selectivity. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be agonists for homo-EPOR and have a homo-EPOR binding specificity or selectivity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a hetero-EPOR binding specificity or selectivity.

[00193] In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can bind to a target and can act as antagonists for homo-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be antagonists for homo-EPOR and can selectively bind to homo-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be antagonists for homo-EPOR and can have a higher binding affinity to homo-EPOR than to hetero-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be antagonists for homo-EPOR and can have a homo-EPOR binding affinity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least

about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a hetero-EPOR binding affinity.

[00194] In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be antagonists for homo-EPOR and can have binding specificity or selectivity for homo-EPOR. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be antagonists for homo-EPOR and can have a higher specificity or selectivity to homo-EPOR than to hetero-EPOR. For example, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof can be antagonists for homo-EPOR and can have a homo-EPOR binding specificity or selectivity that is higher than a hetero-EPOR binding specificity or selectivity. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, or functional fragments thereof described herein can be antagonists for homo-EPOR and have a homo-EPOR binding specificity or selectivity that is at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 6%, at least about 7%, at least about 8%, at least about 9%, at least about 10%, at least about 11%, at least about 12%, at least about 13%, at least about 14%, at least about 15%, at least about 16%, at least about 17%, at least about 18%, at least about 19%, at least about 20%, at least about 21%, at least about 22%, at least about 23%, at least about 24%, at least about 25%, at least about 26%, at least about 27%, at least about 28%, at least about 29%, at least about 30%, at least about 31%, at least about 32%, at least about 33%, at least about 34%, at least about 35%, at least about 36%, at least about 37%, at least about 38%, at least about 39%, at least about 40%, at least about 41%, at least about 42%, at least about 43%, at least about 44%, at least about 45%, at least about 46%, at least about 47%, at least about 48%, at least about 49%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 99% higher than a hetero-EPOR binding specificity or selectivity.

[00195] In some aspects, antibodies described herein have specificity for EPO, hetero-EPOR, or homo-EPOR and include all the forms described above. The antibody can be engineered for use in a particular organism. The organism can be a human, canine, or a commercially valuable livestock, such as, for example, pigs, horses, dogs, cats, chickens, or other birds. Such engineering of the antibody can include, for example, CDR splicing, humanization, humaneering, chimerization, or isolating human (or other organism) antibodies using any of the repertoire technologies or monoclonal technologies known in the art.

[00196] Certain examples of antibodies with alternative scaffolds can include, but are not limited to, nanobodies, affibodies, microbodies, evibodies, and domain antibodies. Certain examples of alternative scaffolds useful for creating antibodies can include, but are not limited to, single domain antibodies from camelids; protease inhibitors; human serum transferrin; CTLA-4; fibronectin, including, but not limited to, the fibronectin type III domain; C-type lectin-like domains; lipocalin family proteins; ankyrin repeat proteins; the Z-domain of Protein A; gamma-crystallin; Tendamistat; Neocarzinostatin; CBM4-2; the T-cell receptor; Im9; designed AR proteins; designed TPR proteins; zinc finger domains; pVIII; Avian Pancreatic Polypeptide; GCN4; WW domains; Src Homology 3 (SH3) domains; Src Homology 2 (SH2) domains; PDZ domains; TEM-1 beta-lactamase; GFP; Thioredoxin; Staphylcoccal nuclease; PHD-finger domains; CI-2; BPTI; APPI; HPSTI; Ecotin; LACI-D1; LDTI; MTI-II; scorpion toxins; Insect Defensin A Peptide; EETI-II; Min-23; CBD; PBP; Cytochrome b_{562}; Transferrin; LDL Receptor Domain A; and ubiquitin. Certain examples of alternative scaffolds are discussed in Hey et al., "Artificial, non-antibody binding proteins for pharmaceutical and industrial applications" Trends in Biotechnology, 23:514-22 (2005) and Binz et al., "Engineering novel binding proteins from nonimmunoglobulin domains" Nature Biotechnology, 23:1257-68 (2005), both of which are incorporated by reference in their entirety for all purposes.

[00197] A bispecific or bifunctional antibody can comprise two different heavy/light chain pairs and two different binding sites. Bispecific antibodies may be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai & Lachmann Clin. Exp. Immunol 79: 315-321 (1990), Kostelny et al. J. Immunol. 148:1547-1553 (1992), which is incorporated by reference in its entirety for all purposes.

[00198] Bispecific antibody molecules can be classified into five different structural groups: (i) bispecific immunoglobulin G (BsIgG); (ii) IgG appended with an additional antigen-binding moiety; (iii) bispecific antibody fragments; (iv) bispecific fusion proteins; and (v) bispecific antibody conjugates. BsIgG is a format that is monovalent for each antigen. Exemplary BsIgG formats include but are not limited to crossMab, DAF (two-in-one), DAF (four-in-one), DutaMab, DT-IgG, knobs-in-holes common LC, knobs-in-holes assembly, charge pair, Fab-arm exchange, SEEDbody, triomab, LUZ-Y, Fcab, κλ-body, orthogonal Fab. *See* Spiess et al. Mol. Immunol. 67(2015):95-106. Exemplary BsIgGs include catumaxomab (Fresenius Biotech, Trion Pharma, Neopharm), which contains an anti-CD3 arm and an anti-EpCAM arm; and ertumaxomab (Neovii Biotech, Fresenius Biotech), which targets CD3 and HER2. In some embodiments, BsIgG comprises heavy chains that are engineered for heterodimerization. For example, heavy chains can be engineered for heterodimerization using a "knobs-into-holes" strategy, a SEED platform, a common heavy chain (e.g., in κλ-bodies), and use of heterodimeric

Fc regions. *See* Spiess et al. Mol. Immunol. 67(2015):95-106. Strategies that have been used to avoid heavy chain pairing of homodimers in BsIgG include knobs-in-holes, duobody, azymetric, charge pair, HA-TF, SEEDbody, and differential protein A affinity. *See Id.* BsIgG can be produced by separate expression of the component antibodies in different host cells and subsequent purification/assembly into a BsIgG. BsIgG can also be produced by expression of the component antibodies in a single host cell. BsIgG can be purified using affinity chromatography, e.g., using protein A and sequential pH elution. IgG appended with an additional antigen-binding moiety is another format of bispecific antibody molecules. For example, monospecific IgG can be engineered to have bispecificity by appending an additional antigen-binding unit onto the monospecific IgG, e.g., at the N- or C- terminus of either the heavy or light chain. Exemplary additional antigen-binding units include single domain antibodies (e.g., variable heavy chain or variable light chain), engineered protein scaffolds, and paired antibody variable domains (e.g., single chain variable fragments or variable fragments). *See Id.* Examples of appended IgG formats include dual variable domain IgG (DVD-Ig), IgG(H)-scFv, scFv-(H)IgG, IgG(L)-scFv, scFv-(L)IgG, IgG(L,H)-Fv, IgG(H)-V, V(H)-IgG, IgG(L)-V, V(L)-IgG, KIH IgG-scFab, 2scFv-IgG, IgG-2scFv, scFv4-Ig, zybody, and DVI-IgG (four-in-one). *See* Spiess et al. Mol. Immunol. 67(2015):95-106. An example of an IgG-scFv is MM-141 (Merrimack Pharmaceuticals), which binds IGF-1R and HER3. Examples of DVD-Ig include ABT-981 (AbbVie), which binds IL-1α and IL-1β; and ABT-122 (AbbVie), which binds TNF and IL-17A.

[00199] Bispecific antibody fragments (BsAb) are a format of bispecific antibody molecules that lack some or all of the antibody constant domains. For example, some BsAb lack an Fc region. In some embodiments, bispecific antibody fragments include heavy and light chain regions that are connected by a peptide linker that permits efficient expression of the BsAb in a single host cell. Exemplary bispecific antibody fragments include but are not limited to nanobody, nanobody-HAS, BiTE, Diabody, DART, TandAb, scDiabody, scDiabody-CH3, Diabody-CH3, triple body, miniantibody, minibody, TriBi minibody, scFv-CH3 KIH, Fab-scFv, scFv-CH-CL-scFv, F(ab')2, F(ab')2-scFv2, scFv-KIH, Fab-scFv-Fc, tetravalent HCAb, scDiabody-Fc, Diabody-Fc, tandem scFv-Fc, and intrabody. For example, the BiTE format comprises tandem scFvs, where the component scFvs bind to CD3 on T cells and a surface antigen on cancer cells. Bispecific fusion proteins include antibody fragments linked to other proteins, e.g., to add additional specificity and/or functionality. An example of a bispecific fusion protein is an immTAC, which comprises an anti-CD3 scFv linked to an affinity-matured T-cell receptor that recognizes HLA-presented peptides. In some embodiments, the dock-and-lock (DNL) method can be used to generate bispecific antibody molecules with higher valency. Also, fusions to albumin binding proteins or human serum albumin can be extend the serum half-life of antibody

fragments. In some embodiments, chemical conjugation, e.g., chemical conjugation of antibodies and/or antibody fragments, can be used to create BsAb molecules. An exemplary bispecific antibody conjugate includes the CovX-body format, in which a low molecular weight drug is conjugated site-specifically to a single reactive lysine in each Fab arm or an antibody or fragment thereof. In some embodiments, the conjugation improves the serum half-life of the low molecular weight drug. An exemplary CovX-body is CVX-241 (NCT01004822), which comprises an antibody conjugated to two short peptides inhibiting either VEGF or Ang2. In some instances, bispecific antibodies can further comprise a linker. In some instances, bispecific antibodies can further comprise a Fc domain. The Fc domain can be, for example, a human IgG1 Fc domain. The Fc domain can comprise a knob-in-hole. In some instances, bispecific antibodies can further comprise a linker and an Fc domain. In some embodiments, a linker can be a peptide linker. Non-limiting examples of peptide linkers can include $(GS)_n$, $(GGS)_n$, $(GGGS)_n$, $(GGSG)_n$, $(GGSGG)_n$, or $(GGGGS)_n$, wherein n can be 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. For example, a linking peptide can be $(GGGGS)_3$ or $(GGGGS)_4$. Linkers described herein can be used for multispecific antibodies. In this embodiment, multispecific antibodies can have more than one linker. In this embodiment, the linker can be the same. Alternatively, the linkers can be different.

[00200] The antibody molecules can be produced by recombinant expression, e.g., of at least one or more component, in a host system. Exemplary host systems include eukaryotic cells (e.g., mammalian cells, e.g., CHO cells, or insect cells, e.g., SF9 or S2 cells) and prokaryotic cells (e.g., *E. coli*). Bispecific antibody molecules can be produced by separate expression of the components in different host cells and subsequent purification/assembly. Alternatively, the antibody molecules can be produced by expression of the components in a single host cell. Purification of bispecific antibody molecules can be performed by various methods such as affinity chromatography, e.g., using protein A and sequential pH elution. In other embodiments, affinity tags can be used for purification, e.g., histidine-containing tag, myc tag, or streptavidin tag.

[00201] In an aspect, an antibody may be part of a conjugate molecule comprising all or part of the antibody and a prodrug. The term "prodrug" refers to a precursor or derivative form of a pharmaceutically active substance. A prodrug can be less cytotoxic to cells compared to the parent drug and capable of being enzymatically activated or converted into the more active cytotoxic parent form. Exemplary prodrugs can include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, beta-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs and

optionally substituted phenylacetamide-containing prodrugs, 5-fluorocytosine and other 5-fluorouridine prodrugs which can be converted into a more active cytotoxic free drug. Examples of cytotoxic drugs that can be derivatized into a prodrug form can include, but are not limited to, those cytotoxic agents described above. See, e.g., U.S. Pat. No. 6,702,705.

[00202] In some aspect, an anti-EPOR, anti-CD131, or anti-EPO antibody can comprise an antigen binding domain or an antigen binding fragment. In some embodiments, an antigen binding domain or an antigen binding fragment can comprise a heavy chain variable region (VH), a light chain variable region (VL), or a combination thereof. In some embodiments, a heavy chain variable region (VH) can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH sequences listed in Table 5. In some embodiments, a VH can comprise any one of VH sequences listed in Table 5. In some embodiments, a VH can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH sequences listed in Table 7. In some embodiments, a VH can comprise any one of VH sequences listed in Table 7. In some embodiments, a VH can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH sequences listed in Table 9. In some embodiments, a VH can comprise any one of VH sequences listed in Table 9.

[00203] In some embodiments, a light chain variable region (VL) can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL sequences listed in Table 5. In some embodiments, a VL can comprise any one of VL sequences listed in Table 5. In some embodiments, a VL can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL sequences listed in Table 7. In some embodiments, a VL can comprise any one of VL sequences listed in Table 7. In some embodiments, a VL can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%,

85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL sequences listed in Table 9. In some embodiments, a VL can comprise any one of VL sequences listed in Table 9.

[00204] In some embodiments, a VH can comprise a VH complementarity determining region 1 (VH-CDR1), a VH-CDR2, or a VH-CDR3. In some embodiments, a VH can comprise a VH complementarity determining region 1 (VH-CDR1), a VH-CDR2, and a VH-CDR3.

[00205] In some embodiments, a VH-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR1 sequences listed in Table 14. In some embodiments, a VH-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2068-2255. In some embodiments, a VH-CDR1 can comprise a sequence of any one of SEQ ID NOs: 2068-2255. In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit can comprise a VH-CDR1 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR1 sequences listed in Table 14.

[00206] In some embodiments, a VH-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR1 sequences listed in Table 15. In some embodiments, a VH-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2820-2948. In some embodiments, a VH-CDR1 can comprise a sequence of any one of SEQ ID NOs: 2820-2948. In some embodiments, an anti-CD131 antibody that binds to EPO receptor subunit can comprise a VH-CDR1 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR1 sequences listed in Table 15.

[00207] In some embodiments, a VH-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR1 sequences listed in Table 16. In some embodiments, a VH-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3336-3471. In some embodiments, a VH-CDR1 can comprise a sequence of any one of SEQ ID NOs: 3336-3471. In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit of a hetero-EPOR can comprise a VH-CDR1 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR1 sequences listed in Table 16.

[00208] In some embodiments, a VH-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR2 sequences in Table 14. In some embodiments, a VH-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2256-2443. In some embodiments, a VH-CDR2 can comprise a sequence of any one of SEQ ID NOs: 2256-2443. In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit can comprise a VH-CDR2 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR2 sequences listed in Table 14.

[00209] In some embodiments, a VH-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR2 sequences listed in Table 15. In some embodiments, a VH-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%,

95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2949-3077. In some embodiments, a VH-CDR2 can comprise a sequence of any one of SEQ ID NOs: 2949-3077. In some embodiments, an anti-CD131 antibody that binds to EPO receptor subunit can comprise a VH-CDR2 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR2 sequences listed in Table 15.

[00210] In some embodiments, a VH-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR2 sequences listed in Table 16. In some embodiments, a VH-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3472-3607. In some embodiments, a VH-CDR2 can comprise a sequence of any one of SEQ ID NOs: 3472-3607. In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit of a hetero-EPOR can comprise a VH-CDR2 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR2 sequences listed in Table 16.

[00211] In some embodiments, a VH-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR3 sequences listed in Table 4. In some embodiments, a VH-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 63-250. In some embodiments, a VH-CDR3 can comprise a sequence of any one of SEQ ID NOs: 63-250. In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit can comprise a VH-CDR3 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%,

65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR3 sequences listed in Table 4.

[00212] In some embodiments, a VH-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR3 sequences listed in Table 6. In some embodiments, a VH-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 815-943. In some embodiments, a VH-CDR3 can comprise a sequence of any one of SEQ ID NOs: 815-943. In some embodiments, an anti-CD131 antibody that binds to CD131 subunit of a hetero-EPOR can comprise a VH-CDR3 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR3 sequences listed in Table 6.

[00213] In some embodiments, a VH-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR3 sequences listed in Table 8. In some embodiments, a VH-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 1331-1466. In some embodiments, a VH-CDR3 can comprise a sequence of any one of SEQ ID NOs: 1331-1466. In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit of a hetero-EPOR can comprise a VH-CDR3 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR3 sequences listed in Table 8.

[00214] In some embodiments, a VL can comprise a VL complementarity determining region 1 (VL-CDR1), a VL-CDR2, or a VL-CDR3. In some embodiments, a VL can comprise a VL complementarity determining region 1 (VL-CDR1), a VL-CDR2, and a VL-CDR3.

[00215] In some embodiments, a VL-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR1 sequences listed in Table 14. In some embodiments, a VL-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2444-2631. In some embodiments, a VL-CDR1 can comprise a sequence of any one of SEQ ID NOs: 2444-2631. In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit can comprise a VL-CDR1 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR1 sequences listed in Table 14.

[00216] In some embodiments, a VL-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR1 sequences listed in Table 15. In some embodiments, a VL-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3078-3206. In some embodiments, a VL-CDR1 can comprise a sequence of any one of SEQ ID NOs: 3078-3206. In some embodiments, an anti-CD131 antibody that binds to EPO receptor subunit can comprise a VL-CDR1 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR1 sequences listed in Table 15.

[00217] In some embodiments, a VL-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR1 sequences listed in Table 16. In some embodiments, a VL-CDR1 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%,

35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3608-3743. In some embodiments, a VL-CDR1 can comprise a sequence of any one of SEQ ID NOs: 3608-3743. In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit of a hetero-EPOR can comprise a VL-CDR1 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR1 sequences listed in Table 16.

[00218] In some embodiments, a VL-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR2 sequences in Table 14. In some embodiments, a VL-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2632-2819. In some embodiments, a VL-CDR2 can comprise a sequence of any one of SEQ ID NOs: 2632-2819. In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit can comprise a VL-CDR2 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR2 sequences listed in Table 14.

[00219] In some embodiments, a VL-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR2 sequences listed in Table 15. In some embodiments, a VL-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3207-3335. In some embodiments, a VL-CDR2 can comprise a sequence of any one of SEQ ID NOs: 3207-3335. In some embodiments, an anti-CD131 antibody that binds to EPO receptor subunit can comprise a VL-CDR2 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%,

80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR2 sequences listed in Table 15.

[00220] In some embodiments, a VL-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR2 sequences listed in Table 16. In some embodiments, a VL-CDR2 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3744-3879. In some embodiments, a VL-CDR2 can comprise a sequence of any one of SEQ ID NOs: 3744-3879. In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit of a hetero-EPOR can comprise a VL-CDR2 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR2 sequences listed in Table 16.

[00221] In some embodiments, a VL-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH-CDR3 sequences listed in Table 4. In some embodiments, a VL-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 251-438. In some embodiments, a VL-CDR3 can comprise a sequence of any one of SEQ ID NOs: 251-438. In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit can comprise a VL-CDR3 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR3 sequences listed in Table 4.

[00222] In some embodiments, a VL-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR3 sequences listed in

Table 6. In some embodiments, a VL-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 944-1072. In some embodiments, a VL-CDR3 can comprise a sequence of any one of SEQ ID NOs: 944-1072. In some embodiments, an anti-CD131 antibody that binds to CD131 subunit of a hetero-EPOR can comprise a VL-CDR3 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR3 sequences listed in Table 6.

[00223] In some embodiments, a VL-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR3 sequences listed in Table 8. In some embodiments, a VL-CDR3 can comprise a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 1467-1602. In some embodiments, a VL-CDR3 can comprise a sequence of any one of SEQ ID NOs: 1467-1602. In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit of a hetero-EPOR can comprise a VL-CDR3 sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL-CDR3 sequences listed in Table 8.

[00224] In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit of a hetero-EPOR can comprise a VH-CDR1 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2068-2255, a VH-CDR2 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2256-2443, and a VH-CDR3 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%,

93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 63-250. In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit of a hetero-EPOR can comprise a VL-CDR1 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2444-2631, a VL-CDR2 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2632-2819, and a VL-CDR3 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to a sequence of SEQ ID NO: 251-438.

[00225] In some embodiments, an anti-CD131 antibody can comprise a VH-CDR1 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2820-2948, a VH-CDR2 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 2949-3077, and a VH-CDR3 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to a sequence of SEQ ID NO: 815-943. In some embodiments, an anti-CD131 antibody can comprise a VL-CDR1 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3078-3206, a VL-CDR2 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3207-3335, and a VL-CDR3 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%,

85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to a sequence of SEQ ID NO: 944-1072.

[00226] In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit of a hetero-EPOR can comprise a VH-CDR1 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3336-3471, a VH-CDR2 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3472-3607, and a VH-CDR3 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 1331-1466. In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit can comprise a VL-CDR1 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3608-3743, a VL-CDR2 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of SEQ ID NOs: 3744-3879, and a VL-CDR3 comprising a sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to a sequence of SEQ ID NO: 1467-1602.

[00227] In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit of a hetero-EPOR can comprise a VH comprising an amino acid sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH sequences listed in Table 5. In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit of a hetero-EPOR can comprise a VL comprising an amino acid sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%,

91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL sequences listed in Table 5. In some embodiments, an anti-EPOR antibody that binds to EPO receptor subunit of a hetero-EPOR can comprise a VH comprising an amino acid sequence of any one of SEQ ID NOs: 439-626 and a VL comprising an amino acid sequence of any one of SEQ ID NOs: 627-814.

[00228] In some embodiments, an anti-CD131 antibody can comprise a VH comprising an amino acid sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH sequences listed in Table 7. In some embodiments, an anti-CD131 antibody can comprise a VL comprising an amino acid sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL sequences listed in Table 7. In some embodiments, an anti-CD131 antibody can comprise a VH comprising an amino acid sequence of any one of SEQ ID NOs: 1073-1201 and a VL comprising an amino acid sequence of any one of SEQ ID NOs: 1202-1330.

[00229] In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit of a hetero-EPOR can comprise a VH comprising an amino acid sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH sequences listed in Table 9. In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit of a hetero-EPOR can comprise a VL comprising an amino acid sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VL sequences listed in Table 9. In some embodiments, an anti-EPOR antibody that binds to both EPO receptor subunit and CD131 subunit of a hetero-EPOR EPO receptor subunit of a hetero-EPOR can comprise a VH comprising an amino acid sequence of any one of SEQ ID NOs: 1603-1738 and a VL comprising an amino acid sequence of any one of SEQ ID NOs: 1739-1874.

[00230] In some embodiments, an anti-EPOR antibody, anti-CD131 antibody, or anti-EPO antibody can comprise a VH sequence and a kappa chain variable regions (VK) sequence. In some embodiments, an anti-EPOR antibody, anti-CD131 antibody, or anti-EPO antibody can comprise a VH sequence and a lamda chain variable regions. In some embodiments, an anti-EPOR

antibody, anti-CD131 antibody, or anti-EPO antibody can comprise a VH sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH sequences listed in Table 10. In some embodiments, an anti-EPOR antibody, anti-CD131 antibody, or anti-EPO antibody can comprise a VH sequence of any one of SEQ ID NOs: 1739-1955. For example, an anti-EPOR antibody, anti-CD131 antibody, or anti-EPO antibody can comprise a VH sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VH sequences of any one of SEQ ID NOs: 1739-1955. In some embodiments, an anti-EPOR antibody, anti-CD131 antibody, or anti-EPO antibody can comprise a VK sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VK sequences listed in Table 10. In some embodiments, an anti-EPOR antibody, anti-CD131 antibody, or anti-EPO antibody can comprise a VK sequence of any one of SEQ ID NOs: 1956-1972. For example, an anti-EPOR antibody, anti-CD131 antibody, or anti-EPO antibody can comprise a VK sequence with at least 100%, 99.9%, 99.8%, 99.7%, 99.6%, 99.5%, 99.4%, 99.3%, 99.2%, 99.1%, 99%, 98%, 97%, 96%, 95%, 94%, 93%, 92%, 91%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, or at least 20% sequence identity to any one of VK sequences of any one of SEQ ID NOs: 1956-1972.

[00231] In some aspects, an anti-EPOR antibody, anti-CD131 antibody, or an anti-EPO antibody can bind to the hetero-EPOR or homo-EPOR or EPO (respectively)with an affinity of from about 1 pM to about 100 nM, from about 2.0 to about 5.1 nM, from about 45 nM to about 300 nM, or from about 2.0 to about 300 nM. In some embodiments, an anti-EPOR antibody, anti-CD131 antibody, or an anti-EPO antibody can bind with an affinity of at least about 300 nM, at least about 140 nM, at least about 100 nM, at least about 5.1 nm, at least about 3.8 nM, or at least about 2.4 nM. In some aspects, a binding affinity can be measured using any method known in the art. For example, a binding affinity can be measure using surface plasmon resonance (SPR; Biacore), Kinexa Biocensor, scintillation proximity assays, enzyme linked immunosorbent assay (ELISA), ORIGEN immunoassay (IGEN), fluorescence quenching, fluorescence transfer, yeast display, or any combination thereof. In some embodiments, a binding affinity can be screened using a suitable bioassay.

[00232] In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a binding affinity of less than about 600 nM, about 590 nM, about 580 nM, about 570 nM, about 560 nM, about 550 nM, about 540 nM, about 530 nM, about 520 nM, about 510 nM, about 500 nM, about 490 nM, about 480 nM, about 470 nM, about 460 nM, about 450 nM, about 440 nM, about 430 nM, about 420 nM, about 410 nM, about 400 nM, about 390 nM, about 380 nM, about 370 nM, about 360 nM, about 350 nM, about 340 nM, about 330 nM, about 320 nM, about 310 nM, about 300 nM, about 290 nM, about 280 nM, about 270 nM, about 260 nM, about 250 nM, about 240 nM, about 230 nM, about 220 nM, about 210 nM, about 200 nM, about 190 nM, about 180 nM, about 170 nM, about 160 nM, about 150 nM, about 140 nM, about 130 nM, about 120 nM, about 110 nM, about 100 nM, about 90 nM, about 80 nM, about 70 nM, about 50 nM, about 50 nM, about 49 nM, about 48 nM, about 47 nM, about 46 nM, about 45 nM, about 44 nM, about 43 nM, about 42 nM, about 41 nM, about 40 nM, about 39 nM, about 38 nM, about 37 nM, about 36 nM, about 35 nM, about 34 nM, about 33 nM, about 32 nM, about 31 nM, about 30 nM, about 29 nM, about 28 nM, about 27 nM, about 26 nM, about 25 nM, about 24 nM, about 23 nM, about 22 nM, about 21 nM, about 20 nM, about 19 nM, about 18 nM, about 17 nM, about 16 nM, about 15 nM, about 14 nM, about 13 nM, about 12 nM, about 11 nM, about 10 nM, about 9 nM, about 8 nM, about 7 nM, about 6 nM, about 5 nM, about 4 nM, about 3 nM, about 2 nM, about 1 nM, about 990 pM, about 980 pM, about 970 pM, about 960 pM, about 950 pM, about 940 pM, about 930 pM, about 920 pM, about 910 pM, about 900 pM, about 890 pM, about 880 pM, about 870 pM, about 860 pM, about 850 pM, about 840 pM, about 830 pM, about 820 pM, about 810 pM, about 800 pM, about 790 pM, about 780 pM, about 770 pM, about 760 pM, about 750 pM, about 740 pM, about 730 pM, about 720 pM, about 710 pM, about 700 pM, about 690 pM, about 680 pM, about 670 pM, about 660 pM, about 650 pM, about 640 pM, about 630 pM, about 620 pM, about 610 pM, about 600 pM, about 590 pM, about 580 pM, about 570 pM, about 560 pM, about 550 pM, about 540 pM, about 530 pM, about 520 pM, about 510 pM, about 500 pM, about 490 pM, about 480 pM, about 470 pM, about 460 pM, about 450 pM, about 440 pM, about 430 pM, about 420 pM, about 410 pM, about 400 pM, about 390 pM, about 380 pM, about 370 pM, about 360 pM, about 350 pM, about 340 pM, about 330 pM, about 320 pM, about 310 pM, about 300 pM, about 290 pM, about 280 pM, about 270 pM, about 260 pM, about 250 pM, about 240 pM, about 230 pM, about 220 pM, about 210 pM, about 200 pM, about 190 pM, about 180 pM, about 170 pM, about 160 pM, or any integer therebetween. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a binding affinity of less than 150 pM, about 140 pM, about 130 pM, about 120 pM, about 110 pM, about 100 pM, about 95 pM, about 90 pM, about 85 pM, about 80 pM, about 75 pM, about 70 pM, about 65 pM, about 60 pM, about 55 pM, about 50 pM about 45

pM, about 40 pM, about 35 pM, about 30 pM, about 25 pM, about 20 pM, about 15 pM, about 10 pM, about 9 pM, about 8 pM, about 7 pM, about 6 pM, about 5 pM, about 4 pM, about 3 pM, about 2 pM, about 1 pM, about 0.9 pM, about 0.8 pM, about 0.7 pM, about 0.6 pM, about 0.5 pM, about 0.4 pM, about 0.3 pM, about 0.2pM, about 0.1 pM, about 0.09 pM, about 0.08, about 0.07 pM, about 0.06 pM, about 0.05 pM, about 0.04 pM, about 0.03 pM, about 0.02 pM, about 0.01 pM, or any integer therebetween.

[00233] In some instances, anti-EPO antibodies, anti-EPOR antibodies, or anti-CD131 antibodies described herein can have antagonistic effects. In some embodiments, anti-EPO antibodies described herein can bind EPOs and inhibit or block EPO/EPOR interaction. For example, anti-EPO antibodies can bind EPOs and inhibit EPOs from binding to homo-EPORs or hetero-EPORs. In some embodiments, the level of inhibition is at least about 1%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100%.

[00234] In some embodiments, anti-EPOR antibodies described herein can bind EPOR subunits of homo-EPORs or hetero-EPORs and inhibit or block homo-EPOR complex formation, hetero-EPOR complex formation, EPO/homo-EPOR interaction, or EPO/hetero-EPOR interaction. For example, anti-EPOR antibodies can bind EPOR subunits and inhibit formation of homo-EPORs or hetero-EPORs. For example, anti-EPOR antibodies can bind EPOR subunits of homo-EPORs or hetero-EPORs and inhibit homo-EPORs or hetero-EPORs from binding to EPOs. In some embodiments, the level of inhibition is at least about 1%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100%.

[00235] In some embodiments, anti-CD131 antibodies described herein can bind CD131 and inhibit or block hetero-EPOR complex formation or EPO/hetero-EPOR interaction. For example, anti-CD131 antibodies can bind CD131 and inhibit formation of hetero-EPORs. For example, anti-CD131 antibodies can bind CD131 subunits of hetero-EPORs and inhibit hetero-EPORs from binding to EPOs. In some embodiments, the level of inhibition is at least about 1%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100%.

[00236] In some instances, anti-EPO antibodies, anti-EPOR antibodies, or anti-CD131 antibodies described herein can have agonistic effects. In some embodiments, anti-EPO antibodies described herein can bind EPOs and enhance or promote EPO/EPOR interaction. In some embodiments, EPO/EPOR interaction is enhanced by at least about 1%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100% with anti-EPO antibodies.

[00237] In some embodiments, anti-EPOR antibodies described herein can bind EPOR subunits of homo-EPORs or hetero-EPORs and enhance or promote homo-EPOR complex formation, hetero-EPOR complex formation, EPO/homo-EPOR interaction, or EPO/hetero-EPOR interaction. In some embodiments, the homo-EPOR complex formation, hetero-EPOR complex formation, EPO/homo-EPOR interaction, or EPO/hetero-EPOR interaction is enhanced by at least about 1%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at

least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100% with anti-EPOR antibodies.

[00238] In some embodiments, anti-CD131 antibodies described herein can bind CD131 and enhance or promote hetero-EPOR complex formation or EPO/hetero-EPOR interaction. In some embodiments, hetero-EPOR complex formation or EPO/hetero-EPOR interaction is enhanced by at least about 1%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 71%, at least about 72%, at least about 73%, at least about 74%, at least about 75%, at least about 80%, at least about 81%, at least about 82%, at least about 83%, at least about 84%, at least about 85%, at least about 86%, at least about 87%, at least about 88%, at least about 89%, at least about 90%, at least about 91%, at least about 92%, at least about 93%, at least about 94%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100% with anti-CD131 antibodies.

[00239] In some embodiments, affinity maturation can be used with an antibody disclosed herein to obtain an anti-EPOR antibody, anti-CD131, or an anti-EPO antibody of a desired affinity. When an anti-EPOR antibody, anti-CD131, or anti-EPO antibody is obtained from an animal (e.g., a transgenic animal carrying a human antibody repertoire), the antibodies made in the transgenic animal can undergo affinity maturation. Alternatively, antibodies from a transgenic animal, or from other technologies (such as a display technology) can be affinity matured using chain shuffling approaches and/or mutation of the nucleic acids encoding VH and VL followed by screening and/or selecting for antibodies with greater affinity.

[00240] The most widely used methods for minimizing the immunogenicity of non-human antibodies while retaining specificity and affinity can involve grafting the CDRs of the non-human antibody onto human frameworks typically selected for their structural homology to the non-human framework (Jones et al., 1986, Nature 321:522-5; U.S. Pat. No. 5,225,539, both of which are hereby incorporated by reference in their entirety). The inclusion of some non-human residues at key positions in the framework can improve the affinity of the CDR grafted antibody (Bajorath et al., 1995, J Biol Chem 270:22081-4; Martin et al., 1991, Methods Enzymol. 203:121-53; Al-Lazikani, 1997, J Mol Biol 273:927-48, all of which are hereby incorporated by reference in their entirety). Exemplary methods for humanization of antibodies by CDR grafting

are disclosed, for example, in U.S. Pat. No. 6,180,370, which is hereby incorporated by reference in its entirety.

[00241] Improvements to the traditional CDR-grafting approaches can use various hybrid selection approaches, in which portions of the non-human antibody have been combined with libraries of complementary human antibody sequences in successive rounds of selection for antigen binding, in the course of which most of the non-human sequences are gradually replaced with human sequences. For example, in the chain-shuffling technique (Marks, et al., 1992, Biotechnology 10:779-83, which is hereby incorporated by reference in its entirety for all purposes) one chain of the non-human antibody can be combined with a naive human repertoire of the other chain on the rationale that the affinity of the non-human chain will be sufficient to constrain the selection of a human partner to the same epitope on the antigen. Selected human partners can then be used to guide selection of human counterparts for the remaining non-human chains.

[00242] Other methodologies can include chain replacement techniques where the non-human CDR3s were retained and only the remainder of the V-regions, including the frameworks and CDRs 1 and 2, were individually replaced in steps performed sequentially (e.g., U.S. Patent Application No. 20030166871; Rader, et al., Proc Natl Acad Sci USA 95:8910-15, 1998; Steinberger, et al., J. Biol. Chem. 275:36073-36078, 2000; Rader, et al., J. Biol. Chem. 275:13668-13676, 2000, all of which are hereby incorporated by reference in their entirety for all purposes).

[00243] These technologies can be used to make antibodies suitable for use in non-human subjects by engineering the CDRs into framework regions of the subject species using analogous approaches to the CDR grafting methods used for making antibodies for use in humans.

[00244] The disclosure encompasses pharmaceutically acceptable salts of anti-EPOR antibodies, anti-CD131antibodies, or anti-EPO antibodies, including those with a positive net charge, those with a negative net charge, and those with no net charge, and including, without limitation, salts of anti-EPOR antibodies, anti-CD131 antibodies, or anti-EPO antibodies including fragments thereof as compounds, in pharmaceutical compositions, in their therapeutic and diagnostic uses, and in their production.

[00245] In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life of from 1 minute to 1 hour in human plasma. In some embodiments,, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life of about 1 minute to 2 minutes, about 1 minute to about 4 minutes, about 1 minute to about 5 minutes, about 1 minute to about 10 minutes, about 1 minute to about 15 minutes, about 1 minute to about 20 minutes, about 1 minute to about 25 minutes,

about 1 minute to about 30 minutes, about 1 minute to about 35 minutes, about 1 minute to about 40 minutes, about 1 minute to about 45 minutes, about 1 minute to about 50 minutes, about 1 minute to about 55 minutes, or about 1 minute to about 1 hour. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life of about 1 minute, about 2 minutes, about 3 minutes, about 4 minutes, about 5 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 25 minutes, about 30 minutes, about 35 minutes, about 40 minutes, about 45 minutes, about 50 minutes, about 55 minutes, or about 1 hour.. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life of from 1 hour to 5 days in human plasma. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life about 1 hour to about 120 hours. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life about 1 hour to about 5 hours, about 1 hour to about 10 hours, about 1 hour to about 12 hours, about 1 hour to about 24 hours, about 1 hour to about 36 hours, about 1 hour to about 48 hours, about 1 hour to about 60 hours, about 1 hour to about 72 hours, about 1 hour to about 84 hours, about 1 hour to about 96 hours, about 1 hour to about 120 hours, about 5 hours to about 10 hours, about 5 hours to about 12 hours, about 5 hours to about 24 hours, about 5 hours to about 36 hours, about 5 hours to about 48 hours, about 5 hours to about 60 hours, about 5 hours to about 72 hours, about 5 hours to about 84 hours, about 5 hours to about 96 hours, about 5 hours to about 120 hours, about 10 hours to about 12 hours, about 10 hours to about 24 hours, about 10 hours to about 36 hours, about 10 hours to about 48 hours, about 10 hours to about 60 hours, about 10 hours to about 72 hours, about 10 hours to about 84 hours, about 10 hours to about 96 hours, about 10 hours to about 120 hours, about 12 hours to about 24 hours, about 12 hours to about 36 hours, about 12 hours to about 48 hours, about 12 hours to about 60 hours, about 12 hours to about 72 hours, about 12 hours to about 84 hours, about 12 hours to about 96 hours, about 12 hours to about 120 hours, about 24 hours to about 36 hours, about 24 hours to about 48 hours, about 24 hours to about 60 hours, about 24 hours to about 72 hours, about 24 hours to about 84 hours, about 24 hours to about 96 hours, about 24 hours to about 120 hours, about 36 hours to about 48 hours, about 36 hours to about 60 hours, about 36 hours to about 72 hours, about 36 hours to about 84 hours, about 36 hours to about 96 hours, about 36 hours to about 120 hours, about 48 hours to about 60 hours, about 48 hours to about 72 hours, about 48 hours to about 84 hours, about 48 hours to about 96 hours, about 48 hours to about 120 hours, about 60 hours to about 72 hours, about 60 hours to about 84 hours, about 60 hours to about 96 hours, about 60 hours to about 120 hours, about 72 hours to about 84 hours, about 72 hours to about 96 hours, about 72 hours to about 120 hours, about 84 hours to about 96 hours, about 84 hours to

about 120 hours, or about 96 hours to about 120 hours. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life about 1 hour, about 5 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours, about 72 hours, about 84 hours, about 96 hours, or about 120 hours. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life at least about 1 hour, about 5 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours, about 72 hours, about 84 hours, or about 96 hours. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life at most about 5 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours, about 72 hours, about 84 hours, about 96 hours, or about 120 hours. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life at least about 10 days, about 11 days, about 11 days, 12 days, 13 days, 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, or 20 days. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life at about 10 days to about 11 days, about 10 to about 12 days, about 10 days to about 13 days, 10 days to about 14 days, about 10 days to about 15 days, about 10 days to about 16 days, about 10 days to about 17 days, about 10 days to about 18 days, about 10 days to about 19 days, or about 10 days to about 20 days. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can have a half-life at about 14 days to about 17 days.

[00246] The disclosure also encompasses bispecific or multispecific antibodies that can have specificity for at least two antigens. For example, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can be generated as bispecific antibodies that can also bind another target. In some embodiments, anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies described herein can be generated as bispecific antibodies that can also bind a cell surface marker associated with immune cells, a signaling molecule associated with immune cells, or an antigen associated with tumor. In some embodiments, bispecific antibodies described herein can enhance specificity and/or selectivity of anti-EPO, anti-EPOR, anti-CD131 antibodies described herein. For example, bispecific antibodies that can bind a cell surface marker of immune cells and any of EPO, homo-EPOR, hetero-EPOR can be used to target EPO, homo-EPOR, or hetero-EPOR in immune cells. For example, bispecific antibodies that can bind a signaling molecule of immune cells and any of EPO, homo-EPOR, hetero-EPOR can be used to target EPO, homo-EPOR, or hetero-EPOR in immune cells. For example, bispecific antibodies that can bind an antigen associated with tumor and any of EPO, homo-EPOR, hetero-EPOR can be used to target EPO, homo-EPOR, or hetero-EPOR in tumor or cancer cells.

[00247] In some embodiments, a bispecific antibody can bind (i) EPO, EPO receptor subunit of a homo-EPOR or a hetero-EPOR, CD131 subunit of a hetero-EPOR, a homo-EPOR, a hetero EPOR; and (ii) a cell surface marker associated with immune cells. Examples of cell surface markers associated with immune cells can include, but are not limited to, lymphocyte antigen 75 (DEC205), X-C motif chemokine receptor 1 (XCR1), or X-C motif chemokine ligand 1 (XCL1). In some embodiments, bispecific antibodies described herein can enhance specificity and/or selectivity of anti-EPO, anti-EPOR, anti-CD131 antibodies described herein for targeting immune cells. For example, bispecific antibodies that can bind a cell surface marker associated with immune cells and any of EPO, homo-EPOR, hetero-EPOR can be used to target EPO, homo-EPOR, or hetero-EPOR in immune cells. In some embodiments, bispecific antibodies described herein can specifically and/or selectively target EPO, homo-EPOR, or hetero-EPOR in immune cells and specifically and/or selectively increase or decrease homo-EPOR activity or hetero-EPOR activity described herein in immune cells. In some embodiments, bispecific antibodies described herein can be used to enhance specificity and/or selectivity of agonistic anti-EPO, anti-EPOR, anti-CD131 binding described herein in immune cells to promote immune tolerance before/after organ transplant (e.g., bone marrow, kidney, heart, lung, liver, etc.). In some embodiments, immune cells can comprise macrophages, dendritic cells, T-cells, natural killer cells, or B cells.

[00248] In some embodiments, a bispecific antibody can bind (i) EPO, EPO receptor subunit of a homo-EPOR or a hetero-EPOR, CD131 subunit of a hetero-EPOR, a homo-EPOR, a hetero EPOR; and (ii) a signaling molecule associated with immune cells. Examples of signaling molecules associated with immune cells can include, but are not limited to, Programmed Death Ligand 1 (PD-L1), T-cell immunoglobulin and mucin-domain containing 3 (Tim3), or Triggering receptor expressed on myeloid cells 2 (TREM2). In some embodiments, bispecific antibodies described herein can enhance specificity and/or selectivity of anti-EPO, anti-EPOR, anti-CD131 antibodies described herein for targeting immune cells. For example, bispecific antibodies that can bind a signaling molecule associated with immune cells and any of EPO, homo-EPOR, hetero-EPOR can be used to target EPO, homo-EPOR, or hetero-EPOR in immune cells and can have synergistic anti-cancer effect. In some embodiments, bispecific antibodies described herein can specifically and/or selectively target EPO, homo-EPOR, or hetero-EPOR in immune cells and specifically and/or selectively increase or decrease homo-EPOR activity or hetero-EPOR activity described herein in immune cells. For example, bispecific antibodies described herein can be used to specifically and/or selectively target EPO, homo-EPOR, or hetero-EPOR in immune cells and specifically and/or selectively increase hetero-EPOR activity to stimulate

immune response in cancer. In some embodiments, immune cells can comprise macrophages, dendritic cells, T-cells, natural killer cells, or B cells.

[00249] In some embodiments, a bispecific antibody can bind (i) EPO, EPO receptor subunit of a homo-EPOR or a hetero-EPOR, CD131 subunit of a hetero-EPOR, a homo-EPOR, a hetero EPOR; and (ii) a tumor marker or an antigen associated with tumor. Examples of tumor markers or antigens associated with tumor can include, but are not limited to, PD1, HER2, CEA, CEACAM5, CD19, CD20, CD22, prostate specific antigen (PSA), CD123, CLL-1, B cell maturation antigen, CD138, CD133 (PROM1), CD44, ALDH1A1, CD34, CD24, EpCAM (ESA), CD117 (KIT), CD90 (THY1), CD166 (ALCAM), PDXL-1, PTCH, CD87 (PLAUR), SSEA-1, EGFR, SP, ALDH, CD49, CD326, LGR5, ALDH1A, LETM1, NANOG, POU5F1, SALL4, SOX2, LINGO2, AFP, NOTCH1, NOTCH2, NOTCH3, CTNNBL1, CD29, CD25, CD61, PROCR, TSPAN8, BMI1, FOXO1, FOXO3, FOXO4, CD15 (FUT4), CHL1, KLF4, NES, TACSTD2, TGM2, CD36, IL1RAP, GLI2, TET2, DNMT3A, KRAS, LDHB, LDHC, LDHD, NPM1, CD33, CD49f, CD171, ABCG2, FZD, CXCR4, OCT4, ALDH, E-cadherin, CD200, ABCB5, vimentin, CD146, CD31, CD144, or CD201 (PROCR). In some embodiments, bispecific antibodies described herein can enhance specificity and/or selectivity of anti-EPO, anti-EPOR, anti-CD131 antibodies described herein for targeting tumors. For example, bispecific antibodies that can bind a tumor associated antigen and any of EPO, homo-EPOR, hetero-EPOR can be used to target EPO, homo-EPOR, or hetero-EPOR in cancer or tumor cells. In some embodiments, tumor associated antigens can be on cancer or tumor cells (e.g., on cell membrane) or secreted by cancer or tumor cells. In some embodiments, bispecific antibodies described herein can specifically and/or selectively target EPO, homo-EPOR, or hetero-EPOR in cancer or tumor cells and specifically and/or selectively increase or decrease homo-EPOR activity or hetero-EPOR activity described herein in cancer or tumor cells.

[00250] The disclosure also encompasses a composition comprising a combination or a population of antibodies or functional fragments thereof described herein. For example, a composition can comprise one, two, three, four, five, six, seven, eight, nine, ten, or more different antibodies or functional fragments thereof. In one embodiment, a composition can comprise one antibody or a functional fragment thereof described herein. In another embodiment, a composition can comprise a combination or a population of antibodies or functional fragments comprising two different antibodies or functional fragments thereof. In another embodiment, a composition can comprise a combination or a population of antibodies or functional fragments thereof comprising three different antibodies or functional fragments thereof. In yet another embodiment, a composition can comprise a combination or a population of antibodies or functional fragments thereof comprising four, five, six, seven, eight, nine, ten, or

more than ten different antibodies or functional fragments thereof. In some embodiments, each of the one, two, three, four, five, six, seven, eight, nine, ten, or more different antibodies or functional fragments thereof can bind to the same target (e.g., EPO protein, a EPO receptor subunit, or a CD131 subunit, etc.). In some embodiments, each of the one, two, three, four, five, six, seven, eight, nine, ten, or more different antibodies or functional fragments thereof can bind to a different part of the same target (e.g., EPO protein, a EPO receptor subunit, or a CD131 subunit, etc.). In some embodiments, each of the one, two, three, four, five, six, seven, eight, nine, ten, or more different antibodies or functional fragments thereof can bind to a different target (e.g., EPO protein, a EPO receptor subunit, a CD131 subunit, or a combination thereof). In some embodiments, at least two of the one, two, three, four, five, six, seven, eight, nine, ten, or more different antibodies or functional fragments thereof can bind to the same target (e.g., EPO protein, a EPO receptor subunit, or a CD131 subunit, etc.) and at least two of the one, two, three, four, five, six, seven, eight, nine, ten, or more different antibodies or functional fragments thereof can bind to a different target (e.g., EPO protein, a EPO receptor subunit, a CD131 subunit, or a combination thereof). In some embodiments, at least two of the one, two, three, four, five, six, seven, eight, nine, ten, or more different antibodies or functional fragments thereof can bind to the same target (e.g., EPO protein, a EPO receptor subunit, or a CD131 subunit, etc.), wherein each of the at least two of the one, two, three, four, five, six, seven, eight, nine, ten, or more different antibodies or functional fragments thereof can bind to a different part of the same target, and at least two of the one, two, three, four, five, six, seven, eight, nine, ten, or more different antibodies or functional fragments thereof can bind to a different target (e.g., EPO protein, a EPO receptor subunit, a CD131 subunit, or a combination thereof).

Modifications of Antibodies and Analogs

[00251] Antibodies and analogs described herein can have one or more modifications that can enhance their activity, binding, specificity, selectivity, or another feature. In some aspects, an anti-EPOR antibody, and/or an anti-CD131 antibody, and/or an anti-EPO antibody, and/or an EPO-analog, and/or an engineered EPO can include a moiety that extends a half-life ($T_{1/2}$) or/and the duration of action of the antibody or analog. In some embodiments, the moiety can extend the circulation $T_{1/2}$, blood $T_{1/2}$, plasma $T_{1/2}$, serum $T_{1/2}$, terminal $T_{1/2}$, biological $T_{1/2}$, elimination $T_{1/2}$ or functional $T_{1/2}$, or any combination thereof, of the antibody or analog. In some embodiments, an Fc portion of an antibody or an analog described herein can be modified to extend half-life of the antibody.

[00252] In one aspect, an anti-EPOR antibody and/or anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or an engineered EPO may be modified by a single moiety. In another aspect, an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO

antibody and/or an EPO analog and/or an engineered EPO may be modified by two or more substantially similar or identical moieties or two or more moieties of the same type. In some embodiments, an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or an engineered EPO may include two or more moieties of different types, or two or more different types of moieties. In some embodiments, two or more anti-EPOR antibodies and/or anti-CD131 antibodies and/or anti-EPO antibodies and/or EPO analogs and/or engineered EPOs can also be attached to one moiety. In some embodiments, the attachment between the anti-EPOR antibody and/or anti-CD131 antibody and/or anti-EPO antibody and/or EPO analog and/or engineered EPO and the moiety can be covalent or noncovalent.

[00253] In some aspects, a polypeptide moiety can be recombinantly fused to the N-terminus or the C-terminus of the heavy chain or the light chain of an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or an engineered EPO, optionally via a linker. In some embodiments, the linker may comprise about 4-30 amino acid residues. For example, the linker may comprise from about 6 or 8 amino acid residues to about 20 amino acid residues, or from about 6 or 8 amino acid residues to about 15 amino acid residues.

[00254] In some aspects, a protracting moiety can be human serum albumin (HSA) or a portion thereof (e.g., domain III) that binds to the neonatal Fc receptor (FcRn). The HSA or FcRn-binding portion thereof can optionally have one or more mutations that confer a beneficial property or effect. In some embodiments, the HSA or FcRn-binding portion thereof can comprise one or more mutations that can enhance pH-dependent HSA binding to FcRn or/and increase HSA half-life, such as K573P or/and E505G/V547A. In some embodiments, a protracting moiety can be an unstructured polypeptide.

[00255] In some aspects, a protracting moiety can be a carboxy-terminal peptide (CTP) derived from the β-subunit of human chorionic gonadotropin (hCG). In the human body, the fourth, fifth, seventh and eight serine residues of the 34-aa CTP of hCG-β typically are attached to *O*-glycans terminating with a sialic acid residue.

[00256] In some aspects, a protracting moiety can be 1, 2, 3, 4, 5, or more moieties of a synthetic polymer. In some embodiments, the synthetic polymer can be biodegradable or non-biodegradable. Biodegradable polymers useful as protracting moieties can include, but are not limited to, poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC) and poly[oligo(ethylene glycol) methyl ether methacrylate] (POEGMA). Non-biodegradable polymers useful as protracting moieties include without limitation poly(ethylene glycol)(PEG), polyglycerol, poly(*N*-(2-hydroxypropyl)methacrylamide) (PHPMA), polyoxazolines and poly(*N*-

vinylpyrrolidone) (PVP). In some embodiments, a synthetic polymer can be polyethylene glycol (PEG). PEGylation can be done by chemical or enzymatic, site-specific coupling or by random coupling.

[00257] In some embodiments, the individual mass (e.g., average molecular weight), or the total mass, of the one or more synthetic polymer moieties can be about 10-50 kDa, about 10-20 kDa, about 20-30 kDa, about 30-40 kDa, or kDa 40-50 kDa. In some embodiments, the individual mass (e.g., average molecular weight), or the total mass, of the one or more synthetic polymer moieties can be about 10 kDa, about 20 kDa, about 30 kDa, about 40 kDa, or 50 kDa. In some embodiments, the individual mass (e.g., average MW), or the total mass, of the one or more synthetic polymer moieties can be greater than about 50 kDa, such as about 50-100 kDa, about 50-60 kDa, about 60-70 kDa, about 70-80 kDa, about 80-90 kDa, or about 90-100 kDa. In some embodiments, the individual mass (e.g., average molecular weight), or the total mass, of the one or more synthetic polymer moieties can be about 60 kDa, about 70 kDa, about 80 kDa, about 90 kDa , or about 100 kDa. In some embodiments, the mass (e.g., average MW) of an individual synthetic polymer moiety can be less than about 10 kDa, such as about 1-5 kDa, about 5-10 kDa, or about 5 kDa. In some embodiments, the individual mass (e.g., average MW), or the total mass, of the one or more synthetic polymer (e.g., PEG) moieties can be about 20 kDa or about 40 kDa.

[00258] In some aspects, modified antibodies can comprise a human modified antibody. In some aspects, also provided herein are amino acid sequence variants of modified antibodies which can be prepared by introducing appropriate nucleotide changes into the DNA sequence of modified antibodies, or by synthesis of the desired modified antibody polypeptides. In some embodiments, such variants can include, for example, a deletion, an insertion, or a substitution of one or more residues within the amino acid sequence of an antibody. In some embodiments, any combinations of deletion, insertion, and substitution can be made to generate an antibody that can have desired antigen-binding characteristics. The amino acid changes of a modified antibody can also alter post-translational processes of the modified antibody, including, but are not limited to, changing the number or position of glycosylation sites. In some embodiments, alanine scanning mutagenesis can be used to identify one or more residues or regions of a modified antibody that may be preferred locations for mutagenesis. In some embodiments, a residue or a group of target residues can be identified (e.g., charged residues such as Arg, Asp, His, Lys, and Glu) and replaced by a neutral or negatively charged amino acid (e.g., alanine or polyalanine) to affect an interaction of the amino acids with the surrounding aqueous environment in or outside a cell. In some embodiments, one or more domains demonstrating functional sensitivity to amino acid substitutions can be refined by introducing further amino acid substitution or other substitutions.

In some embodiments, amino acid substitutions can include one or more conservative amino acid replacements in non-functional regions of an modified antibody.

[00259] In some aspects, modifications of antibodies or analogs described herein can be covalent modifications. In some embodiments, covalent modifications can be introduced by reacting one or more targeted amino acid residues of an antibody or functional fragment thereof with an organic derivatizing agent that can be capable of reacting with selected side chains or the N- or C-terminal residues. In some embodiments, covalent modifications can be introduced by altering the native glycosylation pattern of an antibody or an analog. For example, one or more carbohydrate moieties can be deleted from an antibody or an analog. For example, one or more glycosylation sites that are not present in an antibody or an analog can be added. In some embodiments, addition of glycosylation sites to an antibody or an analog can be accomplished by altering the amino acid sequence such that it contains one or more N-linked glycosylation sites. In some embodiments, addition of glycosylation sites to an antibody or an analog can be accomplished by adding or substituting one or more serine or threonine residues of an antibody or an analog (for O-linked glycosylation sites). In some embodiments, a number of carbohydrate moieties on an antibody or an analog can be increased by chemical or enzymatic coupling of glycosides to the antibody or the analog. In some embodiments, carbohydrate moieties present on an antibody or an analog can be removed chemically or enzymatically. In some embodiments, one or more of non-proteinaceous polymers (e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes) can be covalently added to an antibody or an analog.

[00260] In some embodiments, antibodies described herein can be attached at their C-terminal end to all, or part, of an immunoglobulin heavy chain derived from any antibody isotype, e.g., IgG, IgA, IgE, IgD, or IgM, or any of the isotype sub-classes, e.g., IgG1, IgG2b, IgG2a, IgG3, or IgG4. In some embodiments, antibodies, analogs, or functional fragments thereof may be glycosylated. In some embodiments, glycosylation at a variable domain framework residue can alter the binding interaction of the antibody with antigen. In some embodiments, antibodies, analogs, or functional fragments thereof may be modified by adding polyethylene glycol (PEG). In some embodiments, addition of PEG can lead to one or more of improved circulation time, improved solubility, improved resistance to proteolysis, reduced antigenicity and immunogenicity, improved bioavailability, reduced toxicity, improved stability, and/or easier formulation. In some embodiments, antibodies, analogs, or functional fragments thereof can be conjugated to, or recombinantly engineered with, an affinity tag (e.g., a purification tag).

RNAi and Small Molecules

[00261] RNAi and small molecules that reduce expression or activity of EPO, EPOR, and/or CD131 can be used to overcome tumor suppressive microenvironments in certain tumors. RNAi includes, for example, siRNA, miRNA, antisense RNA, lncRNA, etc.

[00262] RNA interference is a method of post-transcriptional gene regulation that is conserved throughout many eukaryotic organisms. RNAi can be induced by short (i.e., <30 nucleotide) double stranded RNA ("dsRNA") molecules which are present in the cell. These short dsRNA molecules, called "short interfering RNA" or "siRNA," cause the destruction of target RNAs which share sequence homology with the siRNA. It is believed that the siRNA and the targeted RNA bind to an "RNA-induced silencing complex" or "RISC," which cleaves the targeted RNA. The siRNA can be recycled much like a multiple-turnover enzyme, with a single siRNA molecule capable of inducing cleavage of approximately 1000 target RNA molecules.

[00263] In an aspect, the disclosure relates to regulatory RNAs for inhibiting the expression of EPO (erythropoietin), EPOR (erythropoietin receptor) and/or CD131.

[00264] Regulatory RNAs (e.g., siRNAs) described herein can target EPO mRNA to reduce the half-life and/or function of the EPO mRNA. Regulatory RNAs (e.g., siRNAs) can target exons and UTRs of the EPO mRNA. The cDNA sequence of human EPO (NCBI Reference Sequence: NM_000799.4) is:

```
   1 cctttcccag atagcacgct ccgccagtcc caagggtgcg caaccggctg cactcccctc
  61 ccgcgaccca gggcccggga gcagccccca tgacccacac gcacgtctgc agcagccccg
 121 ctcacgcccc ggcgagcctc aacccaggcg tcctgcccct gctctgaccc cgggtggccc
 181 ctacccctgg cgacccctca cgcacacagc ctctccccca cccccacccg cgcacgcaca
 241 catgcagata acagccccga cccccggcca gagccgcaga gtccctgggc caccccggcc
 301 gctcgctgcg ctgcgccgca ccgcgctgtc ctcccggagc cggaccgggg ccaccgcgcc
 361 cgctctgctc cgacaccgcg ccccctggac agccgccctc tcctccaggc ccgtggggct
 421 ggccctgcac cgccgagctt cccgggatga gggcccccgg tgtggtcacc cggcgcgccc
 481 caggtcgctg agggaccccg gccaggcgcg gagatggggg tgcacgaatg tcctgcctgg
 541 ctgtggcttc tcctgtccct gctgtcgctc cctctgggcc tcccagtcct gggcgcccca
 601 ccacgcctca tctgtgacag ccgagtcctg gagaggtacc tcttggaggc caaggaggcc
 661 gagaatatca cgacgggctg tgctgaacac tgcagcttga atgagaatat cactgtccca
 721 gacaccaaag ttaatttcta tgcctggaag aggatggagg tcgggcagca ggccgtagaa
 781 gtctggcagg gcctggccct gctgtcggaa gctgtcctgc ggggccaggc cctgttggtc
 841 aactcttccc agccgtggga gcccctgcag ctgcatgtgg ataaagccgt cagtggcctt
 901 cgcagcctca ccactctgct tcgggctctg ggagcccaga aggaagccat ctcccctcca
 961 gatgcggcct cagctgctcc actccgaaca atcactgctg acactttccg caaactcttc
1021 cgagtctact ccaatttcct ccggggaaag ctgaagctgt acacagggga ggcctgcagg
1081 acaggggaca gatgaccagg tgtgtccacc tgggcatatc caccacctcc ctcaccaaca
1141 ttgcttgtgc cacaccctcc cccgccactc ctgaaccccg tcgaggggct ctcagctcag
1201 cgccagcctg tcccatggac actccagtgc cagcaatgac atctcagggg ccagaggaac
1261 tgtccagaga gcaactctga gatctaagga tgtcacaggg ccaacttgag ggcccagagc
1321 aggaagcatt cagagagcag ctttaaactc agggacagag ccatgctggg aagacgcctg
1381 agctcactcg gcaccctgca aaatttgatg ccaggacacg ctttggaggc gatttacctg
1441 ttttcgcacc taccatcagg gacaggatga cctggataac ttaggtggca agctgtgact
1501 tctccaggtc tcacgggcat gggcactccc ttggtggcaa gagccccctt gacaccgggg
1561 tggtgggaac catgaagaca ggatgggggc tggcctctgg ctctcatggg gtccaagttt
1621 tgtgtattct tcaacctcat tgacaagaac tgaaaccacc aa
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(SEQ ID NO: 3).

[00265] Exemplary nucleic acids encoding RNAi targeting mRNA encoding EPO include siRNA targeting the sequences (these sequences will have U instead of T in the mRNA):

CTTGAATGAGAATATCACTGTCCCA (SEQ ID NO: 4)

GCAGCTTGAATGAGAATATCACTGT (SEQ ID NO: 5)

GCATGTGGATAAAGCCGTCAGTGGC (SEQ ID NO: 6)

CCGAACAATCACTGCTGACACTTTC (SEQ ID NO: 7)

CTTTCCGCAAACTCTTCCGAGTCTA (SEQ ID NO: 8)

AAACTCTTCCGAGTCTACTCCAATT (SEQ ID NO: 9)

GAGAGCAACTCTGAGATCTAAGGAT (SEQ ID NO: 10)

AGAGCAACTCTGAGATCTAAGGATG (SEQ ID NO: 11)

GAGCAACTCTGAGATCTAAGGATGT (SEQ ID NO: 12)

CAGGAAGCATTCAGAGAGCAGCTTT (SEQ ID NO: 13)

AGGAAGCATTCAGAGAGCAGCTTTA (SEQ ID NO: 14)

GAAGCATTCAGAGAGCAGCTTTAAA (SEQ ID NO: 15)

GAGAGCAGCTTTAAACTCAGGGACA (SEQ ID NO: 16)

CAGGACACGCTTTGGAGGCGATTTA (SEQ ID NO: 17)

CATCAGGGACAGGATGACCTGGATA (SEQ ID NO: 18)

GGGACAGGATGACCTGGATAACTTA (SEQ ID NO: 19)

[00266] Regulatory RNAs (e.g., siRNAs) described herein can target EPOR mRNA to reduce the half-life and/or function of the EPOR mRNA. Regulatory RNAs (e.g., siRNAs) can target exons and UTRs of the EPOR mRNA. The cDNA sequence of human EPOR (NCBI Reference Sequence: NM_000121.4) is:

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   1 ggtcagctgc gtccggcgga ggcagctgct gacccagctg tggactgtgc cgggggcggg
  61 ggacggaggg gcaggagccc tgggctcccc gtggcggggg ctgtatcatg gaccacctcg
 121 gggcgtccct ctggccccag gtcggctccc tttgtctcct gctcgctggg gccgcctggg
 181 cgcccccgcc taacctcccg gaccccaagt tcgagagcaa agcggccttg ctggcggccc
 241 gggggcccga agagcttctg tgcttcaccg agcggttgga ggacttggtg tgtttctggg
 301 aggaagcggc gagcgctggg gtgggcccgg gcaactacag cttctcctac cagctcgagg
 361 atgagccatg gaagctgtgt cgcctgcacc aggctcccac ggctcgtggt gcggtgcgct
 421 tctggtgttc gctgcctaca gccgacacgt cgagcttcgt gcccctagag ttgcgcgtca
 481 cagcagcctc cggcgctccg cgatatcacc gtgtcatcca catcaatgaa gtagtgctcc
 541 tagacgcccc cgtggggctg gtggcgcggt tggctgacga gagcggccac gtagtgttgc
 601 gctggctccc gccgcctgag acacccatga cgtctcacat ccgctacgag gtggacgtct
 661 cggccggcaa cggcgcaggg agcgtacaga gggtggagat cctggagggc cgcaccgagt
 721 gtgtgctgag caacctgcgg ggccggacgc gctacacctt cgccgtccgc gcgcgtatgg
 781 ctgagccgag cttcggcggc ttctggagcg cctggtcgga gcctgtgtcg ctgctgacgc
 841 ctagcgacct ggacccccctc atcctgacgc tctccctcat cctcgtggtc atcctggtgc
 901 tgctgaccgt gctcgcgctg ctctcccacc gccgggctct gaagcagaag atctggcctg
 961 gcatcccgag cccagagagc gagtttgaag gcctcttcac cacccacaag ggtaacttcc
1021 agctgtggct gtaccagaat gatggctgcc tgtggtggag cccctgcacc cccttcacgg
1081 aggacccacc tgcttccctg gaagtcctct cagagcgctg ctgggggacg atgcaggcag
1141 tggagccggg gacagatgat gagggccccc tgctggagcc agtgggcagt gagcatgccc
1201 aggataccta tctggtgctg gacaaatggt tgctgccccg gaacccgccc agtgaggacc
1261 tcccagggcc tggtggcagt gtggacatag tggccatgga tgaaggctca gaagcatcct
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1321 cctgctcatc tgctttggcc tcgaagccca gcccagaggg agcctctgct gccagctttg
1381 agtacactat cctggacccc agctcccagc tcttgcgtcc atggacactg tgccctgagc
1441 tgccccctac cccaccccac ctaaagtacc tgtaccttgt ggtatctgac tctggcatct
1501 caactgacta cagctcaggg gactcccagg gagcccaagg gggcttatcc gatggccccc
1561 actccaaccc ttatgagaac agccttatcc cagccgctga gcctctgccc cccagctatg
1621 tggcttgctc ttaggacacc aggctgcaga tgatcaggga tccaatatga ctcagagaac
1681 cagtgcagac tcaagactta tggaacaggg atggcgaggc ctctctcagg agcaggggca
1741 ttgctgattt tgtctgccca atccatcctg ctcaggaaac cacaaccttg cagtattttt
1801 aaatatgtat agtttttttt tgtatctata tatatatata cacatatgta tgtaagtttt
1861 tctaccatga tttctacaaa cacccttaa gtcccatctt cccctgggca taggccatag
1921 ggatagaagt taaagttctt gagcttattc agaagctgga tctgcaatct gaatgctact
1981 cataacataa caaaatagta tgttaaacag ctcttaaatc ttactggctt accacattaa
2041 atgatttctc tctcctaact cagctcaaat gggcagccat ccatgggatg agtcagaggt
2101 tcagactctt ccagtctgta gctctacctt ctcttagggt acttagatgg atcccctgtt
2161 ctacaaactg ccagtcagca agggaagaaa aagggcagca atgaccctca atgggccatt
2221 tgagggatct ggcctggaaa tgggcttcct ctcttcttct cacacctcac tggctggaaa
2281 cagtcacatg accccagtca catgaaaggc caggaaactt agtttagctg tacacccagg
2341 aagggcaaag ctgtttaagg gccactagct agtctctgcc actaataata ataaaagtaa
2401 ttctgaatca g  (SEQ ID NO: 20)
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[00267] Exemplary nucleic acids encoding RNAi targeting mRNA encoding EPOR include siRNA targeted at the following sequences (these sequence will be in the mRNA with U instead of T):

CACCGAGCGGTTGGAGGACTTGGTG (SEQ ID NO: 21)

CGAGGATGAGCCATGGAAGCTGTGT (SEQ ID NO: 22)

ATGGAAGCTGTGTCGCCTGCACCAG (SEQ ID NO: 23)

CACCAGGCTCCCACGGCTCGTGGTG (SEQ ID NO: 24)

ATATCACCGTGTCATCCACATCAAT (SEQ ID NO: 25)

ACATCAATGAAGTAGTGCTCCTAGA (SEQ ID NO: 26)

ATCAATGAAGTAGTGCTCCTAGACG (SEQ ID NO: 27)

CGTGGGGCTGGTGGCGCGGTTGGCT (SEQ ID NO: 28)

CTGGAGGGCCGCACCGAGTGTGTGC (SEQ ID NO: 29)

ACCACCCACAAGGGTAACTTCCAGC (SEQ ID NO: 30)

CAGAATGATGGCTGCCTGTGGTGGA (SEQ ID NO: 31)

AGCGCTGCTGGGGGACGATGCAGGC (SEQ ID NO: 32)

GAGGGAGCCTCTGCTGCCAGCTTTG (SEQ ID NO: 33)

CCTGTACCTTGTGGTATCTGACTCT (SEQ ID NO: 34)

ATCTGACTCTGGCATCTCAACTGAC (SEQ ID NO: 35)

TCTGGCATCTCAACTGACTACAGCT (SEQ ID NO: 36)

CAGGGGACTCCCAGGGAGCCCAAGG (SEQ ID NO: 37)

AGCCTCTGCCCCCCAGCTATGTGGC (SEQ ID NO: 38)

CTCAAGACTTATGGAACAGGGATGG (SEQ ID NO: 39)

CTTACTGGCTTACCACATTAAATGA (SEQ ID NO: 40)

[00268] Regulatory RNAs (e.g., siRNAs) described herein can target CD131 mRNA to reduce the half-life and/or function of the CD131 mRNA. Regulatory RNAs (e.g., siRNAs) can target exons and UTRs of the CD131 mRNA. The cDNA sequence of CD131 (NCBI Reference Sequence: NM_000395.3) is:

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   1 actctgccta gaggctccag aagaagactg gtctctccca ccacacagag gcctggagga
  61 ggcagaggcc aggagggaga ggtcccaaga gcctgtgaaa tgggtctggc ctggctccca
 121 gctgggcagg aacacaggac ttcaggacac taaggaccct gtcatgccca tggccagcac
 181 ccaccagtgc tggtgcctgc ctgtccagag ctgaccaggg agatggtgct ggcccagggg
 241 ctgctctcca tggccctgct ggccctgtgc tgggagcgca gcctggcagg ggcagaagaa
 301 accatcccgc tgcagaccct gcgctgctac aacgactaca ccagccacat cacctgcagg
 361 tgggcagaca cccaggatgc ccagcggctc gtcaacgtga ccctcattcg ccgggtgaat
 421 gaggacctcc tggagccagt gtcctgtgac ctcagtgatg acatgccctg gtcagcctgc
 481 ccccatcccc gctgcgtgcc caggagatgt gtcattccct gccagagttt tgtcgtcact
 541 gacgttgact acttctcatt ccaaccagac aggcctctgg gcacccggct caccgtcact
 601 ctgacccagc atgtccagcc tcctgagccc agggacctgc agatcagcac cgaccaggac
 661 cacttcctgc tgacctggag tgtggccctt gggagtcccc agagccactg gttgtcccca
 721 ggggatctgg agtttgaggt ggtctacaag cggcttcagg actcttggga ggacgcagcc
 781 atcctcctct ccaacacctc ccaggccacc ctggggccag agcacctcat gcccagcagc
 841 acctacgtgg cccgagtacg gacccgcctg gccccaggtt ctcggctctc aggacgtccc
 901 agcaagtgga gcccagaggt ttgctgggac tcccagccag gggatgaggc ccagccccag
 961 aacctggagt gcttctttga cggggccgcc gtgctcagct gctcctggga ggtgaggaag
1021 gaggtggcca gctcggtctc ctttggccta ttctacaagc ccagcccaga tgcaggggag
1081 gaagagtgct ccccagtgct gagggagggg ctcggcagcc tccacaccag gcaccactgc
1141 cagattcccg tgcccgaccc cgcgacccac ggccaataca tcgtctctgt tcagccaagg
1201 agggcagaga aacacataaa gagctcagtg aacatccaga tggcccctcc atcctcaac
1261 gtgaccaagg atggagacag ctacagcctg cgctgggaaa caatgaaaat gcgatacgaa
1321 cacatagacc acacatttga gatccagtac aggaaagaca cggccacgtg gaaggacagc
1381 aagaccgaga ccctccagaa cgcccacagc atggccctgc cagccctgga gccctccacc
1441 aggtactggg ccagggtgag ggtcaggacc tcccgcaccg gctacaacgg gatctggagc
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1561 ctcatcgtga tcttcctcac catcgctgtg ctcctggccc tccgcttctg tggcatctac
1621 gggtacaggc tgcgcagaaa gtgggaggag aagatcccca accccagcaa gagccacctg
1681 ttccagaacg ggagcgcaga gctttggccc ccaggcagca tgtcggcctt cactagcggg
1741 agtcccccac accaggggcc gtggggcagc cgcttccctg agctggaggg ggtgttccct
1801 gtaggattcg gggacagcga ggtgtcacct ctcaccatag aggaccccaa gcatgtctgt
1861 gatccaccat ctgggcctga cacgactcca gctgcctcag atctacccac agagcagccc
1921 cccagccccc agccaggccc gcctgccgcc tcccacacac ctgagaaaca ggcttccagc
1981 tttgacttca atgggcccta cctggggccg ccccacagcc gctccctacc tgacatcctg
2041 ggccagccgg agcccccaca ggagggtggg agccagaagt ccccacctcc agggtccctg
2101 gagtacctgt gtctgcctgc tgggggggcag gtgcaactgg tccctctggc ccaggcgatg
2161 ggaccaggac aggccgtgga agtggagaga aggccgagcc agggggctgc agggagtccc
2221 tccctggagt ccgggggagg ccctgccccc cctgctcttg ggccaagggt gggaggacag
2281 gaccaaaagg acagccctgt ggctataccc atgagctctg gggacactga ggaccctgga
2341 gtggcctctg gttatgtctc ctctgcagac ctggtattca ccccaaactc aggggcctcg
2401 tctgtctccc tagttccctc tctgggcctc ccctcagacc agacccccag cttatgtcct
2461 gggctggcca gtggaccccc tggagcccca ggccctgtga agtcagggtt tgagggctat
2521 gtggagctcc ctccaattga gggccggtcc cccaggtcac caaggaacaa tcctgtcccc
2581 cctgaggcca aaagccctgt cctgaaccca ggggaacgcc cggcagatgt gtccccaaca
2641 tccccacagc ccgagggcct ccttgtcctg cagcaagtgg gcgactattg cttcctcccc
2701 ggcctggggc ccggccctct ctcgctccgg agtaaacctt cttccccggg acccggtcct
2761 gagatcaaga acctagacca ggcttttcaa gtcaagaagc ccccaggcca ggctgtgccc
2821 caggtgcccg tcattcagct cttcaaagcc ctgaagcagc aggactacct gtctctgccc
2881 ccttgggagg tcaacaagcc tggggaggtg tgttgagacc cccaggccta gacaggcaag
2941 gggatggaga gggcttgcct tccctcccgc ctgaccttcc tcagtcattt ctgcaaagcc
3001 aaggggcagc ctcctgtcaa ggtagctaga ggcctgggaa aggagatagc cttgctccgg
3061 ccccccttgac cttcagcaaa tcacttctct ccctgcgctc acacagacac acacacacac
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3121 acgtacatgc acacattttt cctgtcaggt taacttattt gtaggttctg cattattaga
3181 actttctaga tatactcatt ccatctcccc ctcatttttt taatcaggtt tccttgcttt
3241 tgccattttt cttccttctt ttttcactga tttattatga gagtggggct gaggtctgag
3301 ctgagcctta tcagactgag atgcggctgg ttgtgttgag gacttgtgtg ggctgcctgt
3361 ccccggcagt cgctgatgca catgacatga ttctcatctg ggtgcagagg tgggaggcac
3421 caggtgggca cccgtggggg ttagggcttg gaagagtggc acaggactgg gcacgctcag
3481 tgaggctcag ggaattcaga ctagcctcga ttgtcactcc gagaaatggg catggtattg
3541 ggggtcgggg gggcggtgca agggacgcac atgagagact gtttgggagc ttctggggag
3601 ccctgctagt tgtctcagtg atgtctgtgg gacctccagt cccttgagac cccacgtcat
3661 gtagagaagt taacggccca agtggtgggc aggctggcgg gacctgggga acatcaggag
3721 aggagtccag agcccacgtc tactgcggaa aagtcagggg aaactgccaa acaaaggaaa
3781 atgccccaaa ggcatatatg ctttagggcc tttggtccaa atggcccggg tggccactct
3841 tccagataga ccaggcaact ctccctccca ccggccacag atgaggggct gctgatctat
3901 gcctgggcct gcaccaggga ttatggttct tttaaatctt tgcctttcag atacaggaaa
3961 aataatggca ttaaattgct ttaatttgca ttattttagt tatccagttt gcacatattt
4021 ttataggtat cttaggcatc gattggtatt ttttaactgg gccaagccca ttaaggtctt
4081 tcttctgttg ggtgctatca ttttctgatt aagtcttttt gactattgac atacagtctt
4141 tcacagatgg tggagtgttt ttcccccaaa tctgttgttt gtcttataat gttgtatatg
4201 aggttttatg gtgtatgaat atgaatgctt ctgtaatgtc aaacagatcc ctagtaaact
4261 ccttcttcac ttttactgtc agatttacaa aggtcctccc attgcaaagc agtgtttgtc
4321 ctaatttata tattgttttt ctagttcatt ttgtgtttcc aacttttcat gtaaaatttt
4381 aattattttt gaatgtgtgg atgtgagact gaggtgcctt ttggtactga aattcttttt
4441 ccatgtacct gaagtgttac ttttgtgata taggaaatcc ttgtatatat actttattgg
4501 tccctaggct tcctattttg ttaccttgct ttctctatgg catccaccat tttgattgtt
4561 ctacttttat gatatgtttt cataagtggt taagcaagta ttctcgttac ttttgctctt
4621 aaatccctat tcattacagc aatgttggtg gtcaaagaaa atgataaaca acttgaatgt
4681 tcaatggtcc tgaaatacat aacaacattt tagtacattg taaagtagaa tcctctgttc
4741 ataatgaaca agatgaacca atgtggatta gaaagaagtc cgagatatta attccaaaat
4801 atccagacat tgttaaaggg aaaaaattgc aataaaatat ttgtaacata aaa  (SEQ
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ID NO: 41)

[00269] Exemplary nucleic acids encoding RNAi targeting mRNA encoding CD131 include siRNA that target the following sequences (these sequences will have U instead of T in the mRNA):

GGCTCGTCAACGTGACCCTCATTCG (SEQ ID NO: 42)

CCTGGAGCCAGTGTCCTGTGACCTC (SEQ ID NO: 43)

GCCCAGGAGATGTGTCATTCCCTGC (SEQ ID NO: 44)

GTCGTCACTGACGTTGACTACTTCT (SEQ ID NO: 45)

GACGTTGACTACTTCTCATTCCAAC (SEQ ID NO: 46)

CTCCACACCAGGCACCACTGCCAGA (SEQ ID NO: 47)

ACCCACGGCCAATACATCGTCTCTG (SEQ ID NO: 48)

ATGGCCCCTCCATCCCTCAACGTGA (SEQ ID NO: 49)

ACGTGACCAAGGATGGAGACAGCTA (SEQ ID NO: 50)

GTGACCAAGGATGGAGACAGCTACA (SEQ ID NO: 51)

AAGGATGGAGACAGCTACAGCCTGC (SEQ ID NO: 52)

ATGCGATACGAACACATAGACCACA (SEQ ID NO: 53)

CGATACGAACACATAGACCACACAT (SEQ ID NO: 54)

GTGGGTGCTGGCCCTCATCGTGATC (SEQ ID NO: 55)

AGATCCCCAACCCCAGCAAGAGCCA (SEQ ID NO: 56)

CGGGGACAGCGAGGTGTCACCTCTC (SEQ ID NO: 57)

CTACCCACAGAGCAGCCCCCCAGCC (SEQ ID NO: 58)

AAAGGACAGCCCTGTGGCTATACCC (SEQ ID NO: 59)

CCTGAGATCAAGAACCTAGACCAGG (SEQ ID NO: 60)

TCAAAGCCCTGAAGCAGCAGGACTA (SEQ ID NO: 61)

GTCAAAGAAAATGATAAACAACTTG (SEQ ID NO: 62)

[00270] The regulatory RNA can be complementary to a sequence in the above exons, and can be complementary to about 15 nucleotides to about 30 contiguous nucleotides in the target. The regulatory RNA can have 70%, 75%, 80%, 85%, 90%, 95%, 97%, or 99% sequence identity with the complement to the target sequence. The regulatory RNA can also be one that hybridizes to the target sequence under stringent hybridization conditions. Exemplary regulatory RNAs include, for example a regulatory RNA that is complementary to any 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 contiguous nucleotides of SEQ ID NO: 3, SEQ ID NO: 20, or SEQ ID NO: 41. Exemplary regulatory RNAs include, for example a regulatory RNA that is complementary to any 21 contiguous nucleotides of SEQ ID NO: 3, SEQ ID NO: 20, or SEQ ID NO: 41.

[00271] In an aspect, the disclosure describes isolated siRNA comprising short double-stranded RNA from about 15 nucleotides to about 30 nucleotides in length, or between 18 and 25, or 18, 19, 20, 21, 22, 23, 24, or 25 nucleotides in length and are targeted to the target mRNA. The siRNA comprise a sense RNA strand and a complementary antisense RNA strand annealed together by standard Watson-Crick base-pairing interactions (hereinafter "base-paired"). Each strand of the duplex can be the same length or of different lengths. As is described in more detail below, the sense strand comprises a nucleic acid sequence which is identical to a target sequence contained within the target mRNA. In some cases, the siRNA molecules comprise single-stranded RNAs. In some aspects, the disclosure describes an antisense oligonucleotide (ASO). ASO is an inhibitory polynucleotide that is small (-18-30 nucleotides), synthetic, single-stranded nucleic acid polymers of diverse chemistries, which can be employed to modulate gene expression via various mechanisms. ASOs can be subdivided into two major categories: RNase H competent and steric block. The endogenous RNase H enzyme RNASEH1 recognizes RNA-DNA heteroduplex substrates that are formed when DNA-based oligonucleotides bind to their cognate mRNA transcripts and catalyzes the degradation of RNA. Cleavage at the site of ASO binding results in destruction of the target RNA, thereby silencing target gene expression. This approach has been widely used as a means of downregulating disease-causing or disease-modifying genes.

[00272] The sense and antisense strands of a siRNA can comprise two complementary, single-stranded RNA molecules or can comprise a single molecule in which two complementary portions are base-paired and are covalently linked, for example, by a single-stranded hairpin loop. Without wishing to be bound by any theory, it is believed that the hairpin loop of the latter type of siRNA molecule is cleaved intracellularly by the Dicer protein (or its equivalent) to form an siRNA of two individual base-paired RNA molecules.

[00273] siRNA can comprise partially purified RNA, substantially pure RNA, synthetic RNA, recombinantly produced RNA, as well as altered RNA that differs from naturally-occurring RNA by the addition, deletion, substitution and/or alteration of one or more nucleotides, or combinations of one or more of the foregoing. Alterations can include addition of non-nucleotide material, such as to the end(s) of the siRNA or to one or more internal nucleotides of the siRNA, including modifications that make the siRNA resistant to nuclease digestion. One or both strands of the siRNA can also comprise a 3' overhang. As used herein, a 3' overhang refers to at least one unpaired nucleotide extending from the 3'-end of a duplexed RNA strand. The 3' overhang can have 1 to about 6 nucleotides (which includes ribonucleotides or deoxynucleotides) in length, or from 1 to about 5 nucleotides in length, or from 1 to about 4 nucleotides in length, or from about 2 to about 4 nucleotides in length. The 3' overhang can be present on both strands of the siRNA, and can be 2 nucleotides in length. For example, each strand of an siRNA can have 3' overhangs of dithymidylic acid (TT) or diuridylic acid (UU).

[00274] In order to enhance the stability of a siRNA, the 3' overhangs can be stabilized against degradation. For example, the overhangs can be stabilized by including purine nucleotides, such as adenosine or guanosine nucleotides. The overhangs can also be stabilized by substitution of pyrimidine nucleotides with modified analogues, e.g., substitution of uridine nucleotides in the 3' overhangs with 2'-deoxythymidine, is tolerated and does not affect the efficiency of RNAi degradation. In particular, the absence of a 2' hydroxyl in the 2'-deoxythymidine significantly enhances the nuclease resistance of the 3' overhang in tissue culture medium.

[00275] The siRNA can have the sequence AA(N19)TT or NA(N21), where N is any nucleotide. These siRNA can have approximately 30-70% G/C content, and can comprise approximately 50% G/C content. The sequence of the sense siRNA strand can correspond to (N19)TT or N21 (i.e., positions 3 to 23), respectively. In the latter case, the 3' end of the sense siRNA can be converted to TT. The rationale for this sequence conversion is to generate a symmetric duplex with respect to the sequence composition of the sense and antisense strand 3' overhangs. The antisense RNA strand can then synthesized as the complement to positions 1 to 21 of the sense strand.

[00276] When Position 1 of the 23-nt sense strand is not recognized in a sequence-specific manner by the antisense strand, the 3'-most nucleotide residue of the antisense strand can be chosen deliberately. However, in this case the penultimate nucleotide of the antisense strand (complementary to position 2 of the 23-nt sense strand in either embodiment) is generally complementary to the targeted sequence.

[00277] The siRNA can also have the sequence NAR(N17)YNN, where R is a purine (e.g., A or G) and Y is a pyrimidine (e.g., C or U/T). The respective 21-nt sense and antisense RNA strands therefore generally begin with a purine nucleotide. Such siRNA can be expressed from pol III expression vectors without a change in targeting site, as expression of RNAs from pol III promoters is only believed to be efficient when the first transcribed nucleotide is a purine.

[00278] The siRNA usually has a sequence having no more than five (5) consecutive purines or pyrimidines. The siRNA also usually comprises a sequence having no more than five (5) consecutive nucleotides having the same nucleobase (i.e., A, C, G, or U/T).

[00279] The siRNA can be targeted to any stretch of approximately 19-25 contiguous nucleotides in any of the target mRNA sequences (the "target sequence"). Techniques for selecting target sequences for siRNA are given, for example, in Fakhr et al., Precise and efficient siRNA design: a key point in competent gene silencing, Cancer Gene Therapy 23:73-82 (2016), which is hereby incorporated by reference in its entirety for all purposes. Thus, the sense strand of the present siRNA comprises a nucleotide sequence identical to any contiguous stretch of about 19 to about 25 nucleotides in the target mRNA.

[00280] The siRNA can be obtained using a number of techniques known to those of skill in the art. For example, the siRNA can be chemically synthesized or recombinantly produced using methods known in the art, such as the Drosophila in vitro system described in U.S. published application 2002/0086356, which is hereby incorporated by reference in its entirety for all purposes. siRNA can be chemically synthesized using appropriately protected ribonucleoside phosphoramidites and a conventional DNA RNA synthesizer. The siRNA can be synthesized as two separate, complementary RNA molecules, or as a single RNA molecule with two complementary regions. Commercial suppliers of synthetic RNA molecules or synthesis reagents are well known in the art.

[00281] siRNA can also be expressed from recombinant circular or linear DNA plasmids using any suitable promoter. Suitable promoters for expressing siRNA from a plasmid include, for example, the U6 or H1 RNA pol III promoter sequences and the cytomegalovirus promoter. Selection of other suitable promoters is within the skill in the art. Recombinant plasmids can also comprise inducible or regulatable promoters for expression of the siRNA in a particular tissue or in a particular intracellular environment.

[00282] The siRNA expressed from recombinant plasmids can either be isolated from cultured cell expression systems by standard techniques, or can be expressed intracellularly at or near a target tissue or cells in vivo. siRNA can be expressed from a recombinant plasmid either as two separate, complementary RNA molecules, or as a single RNA molecule with two complementary regions. Selection of plasmids suitable for expressing siRNA, methods for inserting nucleic acid sequences for expressing the siRNA into the plasmid, and methods of delivering the recombinant plasmid to the cells of interest are within the skill in the art. See, for example Tuschl, T. (2002), Nat. Biotechnol, 20: 446-448; Brummelkamp T R et al. (2002), Science 296: 550-553; Miyagishi M et al. (2002), Nat. Biotechnol. 20: 497-500; Paddison P J et al. (2002), Genes Dev. 16: 948-958; Lee N S et al. (2002), Nat. Biotechnol. 20: 500-505; and Paul C P et al. (2002), Nat. Biotechnol. 20: 505-508, all of which are incorporated by reference in their entirety for all purposes.

[00283] siRNA can also be expressed from recombinant viral vectors intracellularly at or near the target tissue or cells in vivo. The recombinant viral vectors can comprise sequences encoding the siRNA and any suitable promoter for expressing the siRNA sequences. Suitable promoters include, for example, the U6 or H1 RNA pol III promoter sequences and the cytomegalovirus promoter. Selection of other suitable promoters is within the skill in the art. The recombinant viral vectors can also comprise inducible or regulatable promoters for expression of the siRNA in a particular tissue or in a particular intracellular environment. siRNA can be expressed from a recombinant viral vector either as two separate, complementary RNA molecules, or as a single RNA molecule with two complementary regions.

[00284] Any viral vector capable of accepting the coding sequences for the siRNA molecule(s) to be expressed can be used for example vectors derived from adenovirus (AV); adeno-associated virus (AAV); retroviruses (e.g., lentiviruses (LV), Rhabdoviruses, murine leukemia virus); herpes virus, and the like. The tropism of the viral vectors can also be modified by pseudotyping the vectors with envelope proteins or other surface antigens from other viruses. For example, an AAV vector of the invention can be pseudotyped with surface proteins from vesicular stomatitis virus (VSV), rabies, Ebola, Mokola, and the like.

[00285] The siRNA can be chemically modified to enhance stability. The siRNA may be synthesized and/or modified by methods well established in the art, such as those described in "Current protocols in nucleic acid chemistry," Beaucage, S. L. et al. (Eds.), John Wiley & Sons, Inc., New York, N.Y., USA, which is hereby incorporated herein by reference. Specific examples of siRNA compounds include siRNAs containing modified backbones or no natural intemucleoside linkages. siRNAs having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone.

Modified siRNAs that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides.

[00286] Modified siRNA backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those) having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.

[00287] Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; and 5,625,050, each of which is incorporated by reference in its entirety for all purposes.

[00288] Modified siRNA backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl intemucleoside linkages, mixed heteroatoms and alkyl or cycloalkyl intemucleoside linkages, or one or more short chain heteroatomic or heterocyclic intemucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH_2 component parts.

[00289] Representative U.S. patents that teach the preparation of the above oligonucleosides include, but are not limited to, U.S. Pat. Nos. 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and, 5,677,439, each of which is herein incorporated by reference in its entirety for all purposes.

[00290] In other suitable siRNA mimetics, both the sugar and the internucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such

oligomeric compound, a dsRNA mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar backbone of a siRNA is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative U.S. patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference in its entirety for all purposes. Further teaching of PNA compounds can be found in Nielsen et al., Science, 1991, 254, 1497-1500, which is incorporated by reference in its entirety for all purposes.

[00291] In another aspect, siRNAs can have phosphorothioate backbones and oligonucleosides with heteroatom backbones, and in particular --CH_2--NH--CH_2--, --CH_2--$N(CH_3)$--O--CH_2-- [known as a methylene (methylimino) or MMI backbone], --CH_2--O--$N(CH_3)$--CH_2--, --CH_2--$N(CH_3)$--$N(CH_3)$--CH_2-- and --$N(CH_3)$--CH_2--CH_2--[wherein the native phosphodiester backbone is represented as --O--P--O--CH_2--] of the above-referenced U.S. Pat. NO: 5,489,677, and the amide backbones of the above-referenced U.S. Pat. NO: 5,602,240. Also preferred are dsRNAs having morpholino backbone structures of the above-referenced U.S. Pat. NO: 5,034,506.

[00292] Modified siRNAs may also contain one or more substituted sugar moieties. siRNAs can comprise one of the following at the 2' position: OH; F; O--, S--, or N-alkyl; O--, S--, or N-alkenyl; O--, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Particularly preferred are $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3)]_2$, where n and m are from 1 to about 10. Other preferred dsRNAs comprise one of the following at the 2' position: C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, SO_2CH_3, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an dsRNA, or a group for improving the pharmacodynamic properties of an dsRNA, and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy (2'-O--$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., Helv. Chim. Acta, 1995, 78, 486-504) i.e., an alkoxy-alkoxy group. A further preferred modification includes 2'-dimethylaminooxyethoxy, i.e., a $O(CH_2)_2ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples herein below, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O--CH_2--O--CH_2--$N(CH_2)_2$, also described in examples herein below.

[00293] Other modifications can include 2'-methoxy (2'-OCH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the siRNA, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked siRNAs and the 5' position of 5' terminal nucleotide. siRNAs may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, each of which is incorporated by reference in its entirety for all purposes.

[00294] siRNAs may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl uracil and cytosine, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl anal other 8-substituted adenines and guanines, 5-halo, particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-daazaadenine and 3-deazaguanine and 3-deazaadenine. Further nucleobases include those disclosed in U.S. Pat. NO: 3,687,808, those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. L, ed. John Wiley & Sons, 1990, these disclosed by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y S., Chapter 15, DsRNA Research and Applications, pages 289-302, Crooke, S. T. and Lebleu, B., Ed., CRC Press, 1993, each of which is incorporated by reference in its entirety for all purposes. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds featured in the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and 0-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2 °C. (Sanghvi, Y. S., Crooke, S. T. and Lebleu, B., Eds., DsRNA Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278, which is incorporated by

reference in its entirety for all purposes) and are exemplary base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications.

[00295] Representative U.S. patents that teach the preparation of certain of the above noted modified nucleobases as well as other modified nucleobases include, but are not limited to, the above noted U.S. Pat. NO: 3,687,808, as well as U.S. Pat. Nos. 4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941, and U.S. Pat. NO: 5,750,692, each of which is incorporated by reference in its entirety for all purposes.

[00296] Another modification of the siRNAs can involve chemically linking to the siRNA one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the siRNA. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acid. Sci. USA, 1989, 86: 6553-6556), cholic acid (Manoharan et al., Biorg. Med. Chem. Let., 1994, 4:1053-1060), a thioether, e.g., beryl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660:306-309; Manoharan et al., Biorg. Med. Chem. Let., 1993, 3:2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20:533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J, 1991, 10:1111-1118; Kabanov et al., FEBS Lett., 1990, 259:327-330; Svinarchuk et al., Biochimie, 1993, 75:49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-Hphosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654; Shea et al., Nucl. Acids Res., 1990, 18:3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14:969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264:229-237), or an octadecylamine or hexylamino-carbonyloxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277:923-937), each of the foregoing references are incorporated by reference in its entirety for all purposes.

[00297] Representative U.S. patents that teach the preparation of such siRNA conjugates include, but are not limited to, U.S. Pat. Nos. 4,828,979; 4,948,882; 5,218,105; 5,525,465; 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025; 4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481;

5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941, each of which is herein incorporated by reference in its entirety for all purposes.

[00298] It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within a siRNA. The present invention also includes dsRNA compounds which are chimeric compounds. "Chimeric" siRNA compounds or "chimeras," in the context of this invention, are siRNA compounds, particularly siRNAs, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of a siRNA compound. These siRNAs typically contain at least one region wherein the siRNA is modified so as to confer upon the siRNA increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the siRNA may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of siRNA inhibition of gene expression. Consequently, comparable results can often be obtained with shorter siRNAs when chimeric siRNAs are used, compared to phosphorothioate deoxysiRNAs hybridizing to the same target region.

[00299] In certain instances, the siRNA may be modified by a non-ligand group. A number of non-ligand molecules have been conjugated to siRNAs in order to enhance the activity, cellular distribution or cellular uptake of the siRNA, and procedures for performing such conjugations are available in the scientific literature. Such non-ligand moieties have included lipid moieties, such as cholesterol (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86:6553), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4:1053), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660:306; Manoharan et al., Bioorg. Med. Chem. Let., 1993, 3:2765), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20:533), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10:111; Kabanov et al., FEBS Lett., 1990, 259:327; Svinarchuk et al., Biochimie, 1993, 75:49), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethylammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36:3651; Shea et al., Nucl. Acids Res., 1990, 18:3777), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14:969), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36:3651), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264:229), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277:923), each of the foregoing references

is incorporated by reference in its entirety for all purposes. Representative United States patents that teach the preparation of such siRNA conjugates have been listed above. Typical conjugation protocols involve the synthesis of siRNAs bearing an aminolinker at one or more positions of the sequence. The amino group is then reacted with the molecule being conjugated using appropriate coupling or activating reagents. The conjugation reaction may be performed either with the siRNA still bound to the solid support or following cleavage of the siRNA in solution phase. Purification of the siRNA conjugate by HPLC typically affords the pure conjugate.

[00300] In some embodiments, the disclosed siRNA molecules are used for reducing EPO and/or EpoR activity to reduce tumor mass and increase survival in a subject with cancer or suspected of . having cancer.

[00301] In certain embodiments the disclosed siRNA is a composition that comprises RNA interference (RNAi) molecules. In some embodiments, said RNAi binds to an RNA molecule that is selected from the group consisting of an mRNA molecule that encodes an erythropoietin (EPO) protein, an mRNA molecule that encodes an EPO receptor subunit, an mRNA molecule that encodes a CD131 subunit, and any combination thereof. In some embodiments, such composition is administered to a subject to treat cancer. In some embodiments, upon administering the subject with said RNAi, tumor mass is reduced. In some embodiments, upon administering the subject with said RNAi, the immune response is increased. In some embodiments, the immune response is increased through the production of effector T (T_{eff}) cells.

[00302] In some embodiments the RNAi is a composition administered to a subject having cancer, wherein said RNAi binds to an RNA molecule that is selected from a group consisting of an mRNA molecule that encodes a erythropoietin (EPO) protein, an mRNA molecule that encodes a EPO receptor subunit, an mRNA molecule that encodes a CD131 subunit, and any combination thereof; wherein upon administering said RNAi to said subject, the subject's tumor mass is reduced. In some embodiments, the tumor mass is reduced by at least 10%. In some embodiments, the tumor mass is reduced by at least 20%. In some embodiments, the tumor mass is reduced by at least 30%. In some embodiments, the tumor mass is reduced by at least 40%. In some embodiments, the tumor mass is reduced by at least 50%. In some embodiments, the tumor mass is reduced by at least 60%. In some embodiments, the tumor mass is reduced by at least 70%. In some embodiments, the tumor mass is reduced by at least 80%.

[00303] In some embodiments, the tumor mass is reduced to less than 0.8 cm^3. In some embodiments, the tumor mass is reduced to less than 0.7 cm^3. In some embodiments, the tumor mass is reduced to less than 0.6 cm^3. In some embodiments, the tumor mass is reduced to less than 0.5 cm^3. In some embodiments, the tumor mass is reduced to less than 0.4 cm^3. In some

embodiments, the tumor mass is reduced to less than 0.3 cm^3. In some embodiments, the tumor mass is reduced to less than 0.2 cm^3.

[00304] In some embodiments, the tumor mass is reduced to about 0.8 cm^3. In some embodiments, the tumor mass is reduced to about 0.7 cm^3. In some embodiments, the tumor mass is reduced to about 0.6 cm^3. In some embodiments, the tumor mass is reduced to less than 0.5 cm^3. In some embodiments, the tumor mass is reduced to less than 0.4 cm^3. In some embodiments, the tumor mass is reduced to less than 0.3 cm^3. In some embodiments, the tumor mass is reduced to less than 0.2 cm^3.

[00305] In some embodiments the RNAi is a composition administered to a subject having cancer, wherein said RNAi binds to an RNA molecule that is selected from a group consisting of an mRNA molecule that encodes an erythropoietin (EPO) protein, an mRNA molecule that encodes an EPO receptor subunit, an mRNA molecule that encodes a CD131 subunit, and any combination thereof; wherein upon administering said RNAi to said subject, the subject's immune response is increased through the production of more effector T (T_{eff}) cells.

[00306] In some embodiments, the targeted cancer is selected from hepatocarcinoma, colon cancer, breast cancer, lung cancer, brain cancer, or melanoma.

[00307] In some embodiments, the RNAi molecules reduce EPO half-life in a subject. In some embodiments, the RNAi molecules reduce EPO levels in a subject. In some embodiments, reduced EPO levels increases survival. In some embodiments, the survival rate is increased two-fold. In some embodiments, the survival rate is increased three-fold. In some embodiments, the survival rate is increased five-fold. In some embodiments, the survival rate is increased by about half a year to about 5 years. In some embodiments, the survival rate is increased by about half a year to about 3 years. In some embodiments, the survival rate is increased by about half a year to about a year.

[00308] In some embodiments, the RNAi is in a nanoparticle. Any suitable nanoparticle described herein will be a useful nanoparticle carrier. In some embodiments, the nanoparticle is a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises about 20-70% cationic lipid: about 5-45% neutral lipid: about 20-55% cholesterol: and/or about 0.5-15% PEG-modified lipid. In some embodiments, the lipid nanoparticle comprises about 20-60% cationic lipid: about 5-25% neutral lipid: about 25-55% cholesterol: and/or about 0.5-15% PEG-modified lipid. In some embodiments, the lipid nanoparticle comprises about 35 to 45% cationic lipid, about 40% to 50% cationic lipid, about 50% to 60% cationic lipid, and/or about 55% to 65% cationic lipid.

[00309] In some embodiments, the ratio of the RNAi to lipid nanoparticles is about 5:1 to about 20:1. In some embodiments, the ratio of the RNAi to lipid nanoparticles is about 10:1 to about 25:1. In some embodiments, the ratio of the RNAi to lipid nanoparticles is about 15:1 to

about 30:1. In some embodiments, the ratio of the RNAi to lipid nanoparticles is at least about 30:1.

[00310] In some embodiments, the RNAi is a siRNA, or a miRNA, or an antisense RNA, or a lncRNA. In some embodiments, the RNAi is a siRNA. In some embodiments the RNAi is miRNA. In some embodiments, the RNAi is antisense RNA. In some embodiments, the RNAi is lncRNA.

[00311] In some embodiments, a siRNA has a sequence length of about 3 to about 90 nucleotides. In some embodiments, a siRNA has a sequence length of about 3 to about 60 nucleotides. In some embodiments, a siRNA has a sequence length of about 3 to about 45 nucleotides. In some embodiments, a siRNA has a sequence length of about 9 to about 42 nucleotides. In some embodiments, a siRNA has a sequence length of about 15 to about 30 nucleotides. In some embodiments, a siRNA has a sequence length of about 21 to about 30 nucleotides.

[00312] In some embodiments, a siRNA molecule comprises a nucleic acid that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, 100% identical to any of the following sequences: SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, or SEQ ID NO: 62.

[00313] In some embodiments, the siRNA targets the following sequences: SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, or SEQ ID NO: 19.

[00314] In some embodiments, the siRNA comprises a nucleic acid that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, 100% identical to any the following sequences: SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID

NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, or SEQ ID NO: 40.

[00315] In some embodiments, the siRNA comprises a nucleic acid that is at least 70%, 75%, 80%, 85%, 90%, 95%, 97%, 99%, 100% identical to any of the following sequences: SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, or SEQ ID NO: 62

[00316] Small molecules can also be used to upregulate or downregulate EPO and/or EPOR, so as to induce immunotolerance or immunosuppression (collectively negative immune modulation), or increase immune activity. For example, inhibitors of hypoxia-inducible factor (HIF) can reduce EPO/EPOR mediated immunosuppression, and inhibitors of HIF-prolyl hydroxylase (PHD) can stimulate immune tolerance or immunosuppression.

[00317] Hypoxia-inducible factor (HIF) is a helix-loop-helix transcription factor that acts as a master regulator of hypoxia activated gene expression, allowing adaptation to hypoxia. HIF is a heterodimer complex composed by two subunits, α-subunit (oxygen sensitive) and a β-subunit (constitutively expressed, and also called aryl hydrocarbon receptor nuclear translocator (ARNT)). HIF-prolyl hydroxylase (PHD) leads to degradation of HIF and is a O2-sensitive negative regulator of HIF. Hence PHD inhibitors lead to activation of HIF signaling. PHD inhibitors can increase HIF activity and this can stimulate erythropoiesis.

[00318] The HIF pathway along with the HIF-prolyl hydroxylase domain (PHD) are transcription factors that are important oxygen-sensing pathways for mediating tissue adaptation to low oxygen environments primarily by the transcription regulation of gene expression. Inhibitors of HIF can reduce EPO/EPOR mediated immunosuppression, and inhibitors of PHD can stimulate the immune tolerance or immunosuppression. EPO is typically present in low amounts in circulation under homeostatic conditions. When erythropoietic stress occurs through hypoxia or anemia, it can result in a dramatic increase in EPO production. Since hypoxia is a significant feature in many cancers and some chronic conditions, inhibition of the HIF transcription factor can promote reduction of tumor growth or alleviating and or treating chronic conditions.

[00319] The HIF transcription factor has an oxygen-sensitive α-subunit and a constantly expressed β-subunit. Three HIF- α subunits are currently known: HIF-1α, HIF-2α, and HIF-3α. Under hypoxic conditions, the α-subunit no longer degrades, and will form a heterodimer with the β-subunit, which activates gene transcription. By inhibiting the heterodimer formation, gene

transcription is not activated, which can result in inhibiting the cellular response to hypoxia including inhibition of EPO production.

[00320] The inhibitor of HIF inhibits HIF activity by inhibiting the HIF pathway activity indirectly by a variety of mechanisms. The inhibitors of HIF can inhibit HIF-1α protein synthesis, HIF-1α protein stabilization, HIF-1α-HIF-1β dimerization, and HIF-1 dimer DNA binding and interactions with other proteins. In some embodiments, the inhibitor of HIF is a HIF-1 inhibitor.

[00321] The HIF and PHD pathways coordinate the hypoxia responses for cells and tissues. PHD is a 2-oxoglutarate (2OG)-dependent oxygenase which utilizes molecular oxygen for various cellular processes including HIF regulation and hypoxia response.

[00322] Inhibitors of PHD are useful for activating the HIF pathway by impairing HIF-α degradation, which leads to HIF signaling. The HIF signaling can stimulate the erythropoiesis protein (EPO), which can enhance apoptotic cell clearance and immune tolerance.

[00323] Other pathways that can regulate EPO include interleukin pathways (such as IL-1α, IL-1β, and IL-6), tumor necrosis factor (TNF- α), estrogen receptors, Phospholipase C, gamma 1 (phospholipase C-γ1), and Cbl/p85/Episin-1 pathway.

[00324] Interleukins are cytokines expressed and secreted by white blood cells that regulate immune responses, inflammatory responses, and hematopoiesis. The inhibition of certain interleukins can suppress the actions of interleukins for the immune system, which results in antagonistic effects of EPO production, and inhibiting hetero-EPOR activity.

[00325] TNF- α is an adipokine and cytokine which regulates immune cells. Inhibitors of TNF- α can reduce the levels of EPO induced cell proliferation and inhibit hetero EPOR activity.

[00326] Estrogen receptors are proteins found inside cells and activated by the hormone estrogen. After estrogen activation, the estrogen receptors can translocate to the nucleus and bind DNA to regulate the activity of different genes. Activation of estrogen receptors has also been found to promote cell proliferation, and in breast cancer cells with estrogen receptors, there have been found functional EPO receptors as well. Inhibitors and antagonists of estrogen receptors can inhibit cellular proliferation and inhibit EPOR promotion of cell growth.

[00327] Phospholipase C-γ1 is a cell growth factor protein that is involved in cell growth, migration, proliferation, and apoptosis. Mutations of this cell growth factor can lead to tumor growth via cancer cell proliferation. Additionally, EPO can induce activation of Phospholipase C-γ1. Inhibitors of phospholipase C-γ1 can inhibit the activation of phospholipase C-γ1, thereby inhibiting hetero-EPOR activity to reduce tumor growth.

[00328] The Cbl/p85/Episin-1 pathway can mediate EPO-induced EPOR internalization, and thereby reduce EPO signaling. EPO can induce Cbl- dependent ubiquination of the p85

regulatory subunit, which results in binding of phosphotyrosinases on EPOR. This results in endocytosis of EPOR. Cbl is an E3 ligase which plays a role in endocytic downregulation of receptor tyrosine kinases. Promotion of Cbl/p85 activation can result in endocytosis of EPOR, which reduces EPOR activity.

[00329] In some embodiments, small molecules are used to downregulate EPO, so as to induce immunosuppression (collectively negative immune modulation) or increase immune activity.

[00330] In some embodiments a composition is administered to a subject having cancer or chronic diseases, comprising a compound, a pharmaceutically acceptable salt, solvate, or steroisomer thereof, wherein said compound inhibits a hetero-erythropoietin (EPO) receptor activity in a myeloid cell in said subject.

[00331] In some embodiments a composition is administered to a subject having cancer or chronic infection condition, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound inhibits a hetero-erythropoietin (EPO) receptor activity in a myeloid cell in said subject.

[00332] Chronic diseases are diseases which persist with long-lasting effects on a subject. Chronic diseases may have remission periods, wherein the disease temporarily goes away, or reappears. Chronic diseases can be alleviated by altering dietary, lifestyle and metabolic risk factors of a subject. These are behavioral changes which can be performed by the subject. Chronic diseases can also be treated using the compounds described herein. Chronic diseases can be broadly categorized into two categories, chronic infectious diseases or conditions and chronic-non-communicable diseases.

[00333] Chronic infectious diseases are chronic conditions which are caused by transmissible infections. Examples of chronic infection diseases include, but is not limited to human immunodeficiency virus infection and acquired immunodeficiency syndrome (HIV/AIDS), tuberculosis (TB), Lyme diseases, and graft-versus-host disease.

[00334] Chronic non-communicable diseases include, but is not limited to cancers, cardiovascular diseases, chronic respiratory diseases, and diabetes mellitus. Other diseases include but are not limited to Alzheimer's disease, Huntington's disease, Parkinson's disease, autoimmune diseases, chronic hepatitis, and chronic kidney diseases.

[00335] In some embodiments a composition is administered to a subject having cancer or chronic infection condition, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound inhibits a hetero-erythropoietin (EPO) receptor activity so that resistance to immune-checkpoint blockade is reversed in said subject.

[00336] In some embodiments, the hetero-EPO receptor comprises an EPO subunit and a CD131 subunit. In some embodiments, the hetero-EPO receptor is on a macrophage, monocyte, dendritic cell, basophil, neutrophil, or eosinophil.

[00337] In some embodiments, a composition comprised of a compound, or pharmaceutically acceptable salt, solvate, or stereoisomer thereof, inhibits hetero-erythropoietin (EPO) receptor's activity. In some embodiments, such composition can treat cancer or chronic infection condition in a subject. In some embodiments, the cancer is selected from hepatocarcinoma, colon cancer, breast cancer, lung cancer, brain cancer, or melanoma. In another embodiment, the chronic infectious condition develops in patients with an organ transplant or skin grafting.

[00338] In some embodiments, the inhibitory activity occurs in a myeloid cell. In another embodiment, the inhibitory activity results in reversal of resistance to immune-checkpoint blockade. In some embodiments, an inhibitory activity leads to a decrease of a cancer cell population.

[00339] In some embodiments, the immune-checkpoint blockade is an inhibitor of CTLA-4, PD-1, or PD-L1. In some embodiments, the immune-checkpoint blockade is an inhibitor of PD-1 or PD-L1. In some embodiments, the immune-checkpoint blockade is an inhibitor of CTLA-4. In some embodiments, the inhibitor of CTLA-4, PD-1, or PD-L1 is Nivolumab, Pembrolizumab, Cemiplimab, Atezolizumab, Avelumab, Durvalumab, Ipilimumab, Lirilumab, and BMS-986016.

[00340] In some embodiments, the compound is an inhibitor of hypoxia-inducible factor (HIF), IL-1α, IL-1β, TNF-α, IL-6, estrogen receptors, phospholipase C-γ1, or Cbl/p85/Episin-1 pathway. In some embodiments, the compound is an inhibitor of hypoxia-inducible factor (HIF), IL-1α, IL-1β, TNF-α, IL-6, or estrogen receptors. In some embodiments, the compound is an inhibitor of hypoxia-inducible factor (HIF).

[00341] In some embodiments, the compound is selected from CAY10585 (LW6), Chetomin, Chrysin, Dimethyl-bisphenol A, Echinomycin, 2-Methoxyestradiol (2ME2), SYP-5, PX-478 2HCl, KC7F2, GN44028, Verucopeptin, FM19G11, PT2399, PT2385, Belzutifan, HIF-2a-IN-1, HIF-2a-IN-2, HIF-2a-IN-3, HIF-2a-IN-4, TC-S 700, IDF-11774, Paeoniflorin, Emetine hydrochloride, Glucosamine, PX12, Vitexin, BAY 87-2243, Lificiguat (YC-1), Vorinostat, Tanespimycin, Silibinin, diallyl trisulfide (DATS), Herboxidiene (GEX1A), Celastrol, Phenethyl isothiocyanate (PEITC), Gliotoxin, Sulforaphane, Acriflavin, Emodin, Cardenolide, 3,3'-Diindolylmethane (DIM), Pseudolaric acid-B (PAB), Bavachinin, Andrographolide, Isoliquiritigenin, Wondonin, Thymoquinone, or Curcumin.

[00342] In some embodiments, the compound is CAY10585 (LW6), Chetomin, Chrysin, Dimethyl-bisphenol A, Echinomycin, 2-Methoxyestradiol (2ME2), SYP-5, PX-478 2HCl, KC7F2, GN44028, Verucopeptin, FM19G11, PT2399, PT2385, Belzutifan, HIF-2a-IN-1, HIF-2a-IN-2, HIF-2a-IN-3, HIF-2a-IN-4, TC-S 700, IDF-11774, Paeoniflorin, Emetine hydrochloride, Glucosamine, PX12, Vitexin, BAY 87-2243, Lificiguat (YC-1), Vorinostat, or Tanespimycin.

[00343] In certain embodiments, the compound is Chetomin, Echinomycin, PT2399, Belzutifan, Vorinostat, or Tanespimycin.

[00344] In some embodiments, said compound is selected from Silibinin, diallyl trisulfide (DATS), Herboxidiene (GEX1A), Celastrol, Phenethyl isothiocyanate (PEITC), Gliotoxin, Sulforaphane, Acriflavin, Emodin, Cardenolide, 3,3'-Diindolylmethane (DIM), Pseudolaric acid-B (PAB), Bavachinin, Andrographolide, Isoliquiritigenin, Wondonin, Thymoquinone, or Curcumin.

[00345] In some embodiments, small molecules can also be used to upregulate EPOR, so as to induce immunotolerance.

[00346] In some embodiments, a composition comprising of a compound, or pharmaceutically acceptable salt, solvate, or stereoisomer thereof, promotes hetero-erythropoietin (EPO) receptor's activity. In some embodiments, immune tolerance to an antigen is increased in a subject exposed to such a composition. In certain embodiments, a compound has no substantial effect on EPO receptor activity. In some embodiments, the EPO receptor comprises at least two EPO receptor subunits.

[00347] In some embodiments is a composition for administering to a subject, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound promotes a hetero-erythropoietin (EPO) receptor activity, wherein said hetero-EPO receptor comprises a EpoR subunit and CD131 subunit, so that immune tolerance to an antigen is increased in said subject; and wherein said compound has no substantial effect on a homo-EPO receptor activity, wherein said homo-EPO receptor comprises at least two EPO receptor subunits.

[00348] In some embodiments, the compound is an inhibitor of HIF-Prolyl Hydroxylase (PHD), NHF-4, GATA factor, IL-17, AKT/NFkB/HIF1 pathway, estrogen receptor, Angiotensin II receptor, Topoisomerase II, or Epithelial membrane protein 1 (EMP-1).

[00349] In some embodiments, the compound is an inhibitor of HIF-Prolyl Hydroxylase (PHD), NHF-4, GATA factor, Angiotensin II receptor, Topoisomerase II, or IL-17.

[00350] In some embodiments, the compound is an inhibitor of HIF-Prolyl Hydroxylase (PHD).

[00351] In some embodiments, the compound is selected from Roxadustat, Vadadustat, Enarodustat, Desidustat, Molidustat, Dimethyloxaloylglycine, Daprodustat, Prolyl Hydroxylase inhibitor 1, TM6089, TRC160334, PHD-1-IN-1, MK-8617, JNJ-42041935, TP0463518, IOX

(JICL38), IOX4, IOX3 (FG-2216), Dencichin, HIF-PHD-IN-1, AKB-6899, VH298, M1001, ML228, Dimethyloxalylglycine (DMOG), Mitoxantrone, Angiotensin II (Ang II), or 17β-estradiol.

[00352] In another embodiments, the compound is selected from Roxadustat, Vadadustat, Enarodustat, Desidustat, Molidustat, Dimethyloxaloylglycine, Daprodustat, Prolyl Hydroxylase inhibitor 1, TM6089, TRC160334, PHD-1-IN-1, MK-8617, JNJ-42041935, TP0463518, IOX (JICL38), IOX4, IOX3 (FG-2216), Dencichin, HIF-PHD-IN-1, AKB-6899, VH298, M1001, ML228, Dimethyloxalylglycine (DMOG).

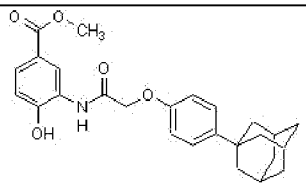
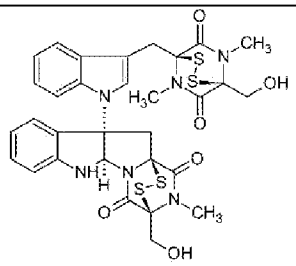
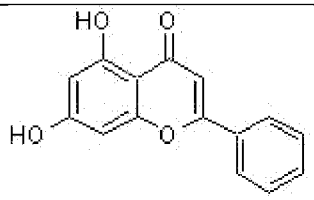
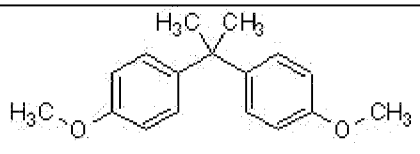
[00353] In some embodiments, the compound is Mitoxantrone, Angiotensin II (Ang II), or 17β-estradiol.

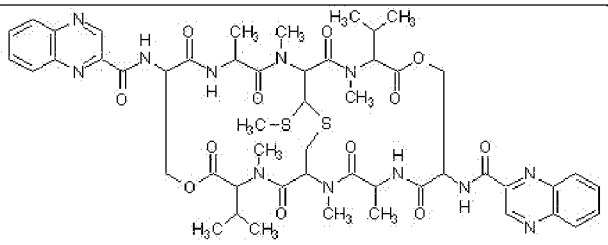
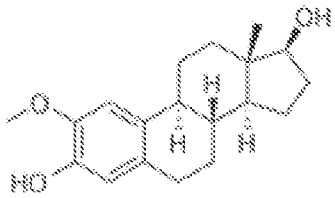
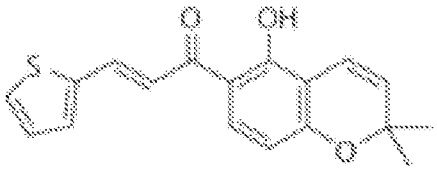
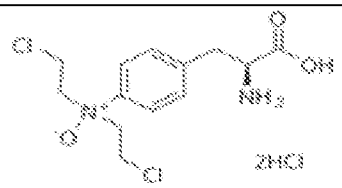
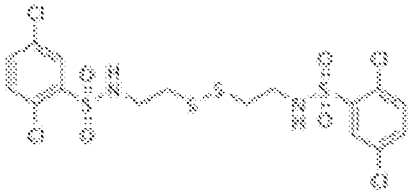
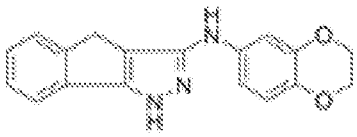
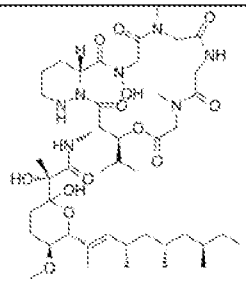
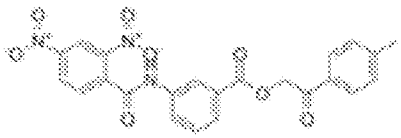
[00354] In certain embodiments, the compound is an EPOR agonist. In certain embodiments, a compound is LG5640.

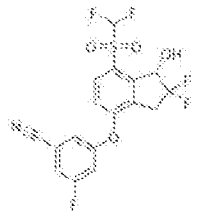
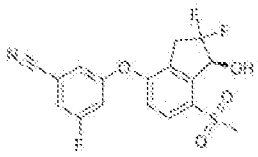
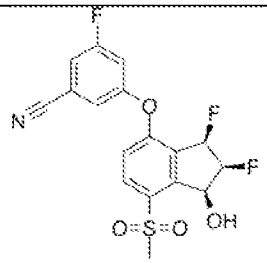
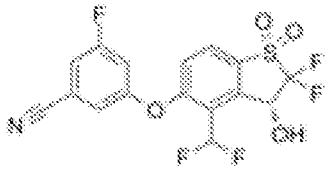
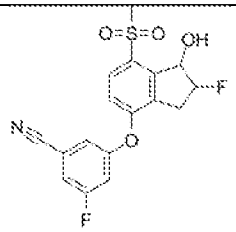
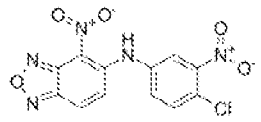
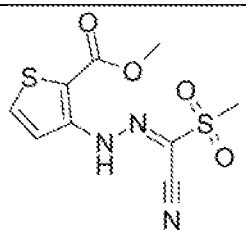
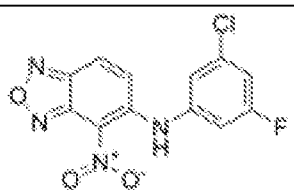
[00355] In some embodiments, the immune tolerance is to a transplanted organ or a self-antigen.

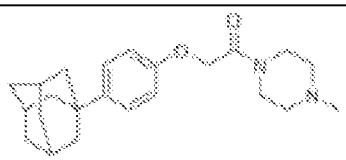
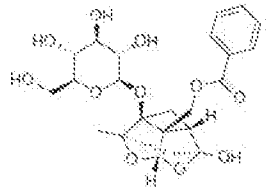
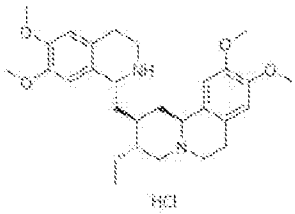
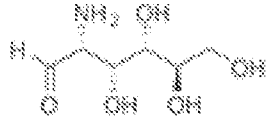
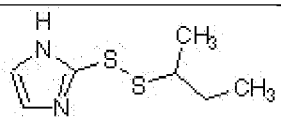
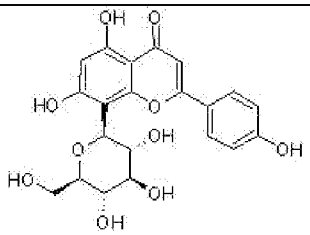
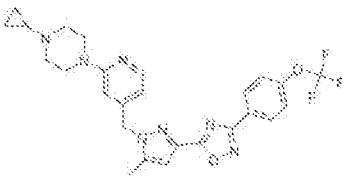
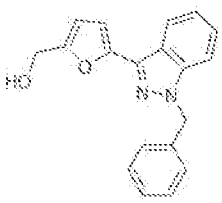
[00356] Exemplary inhibitors of HIF are in Table 1 below.

Table 1A. Inhibitors of Hypoxia-Inducible Factor (HIF)

HIF inhibitors	CAS Number	Target	IC50	Chemical structure
CAY10585 (LW6)	934593-90-5	HIF-1a	0.7-2.6 uM	
Chetomin	1403-36-7	HIF-1a	10 nM	
Chrysin	480-40-0	HIF-1a		
Dimethyl-bisphenol A	1568-83-8	HIF-1a		

Echinomycin	512-64-1	HIF-1a	1.2 nM	
2-Methoxyestradiol (2ME2)	362-07-2	HIF-1a		
SYP-5	1384268-04-5	HIF-1a		
PX-478 2HCl	685898-44-6	HIF-1a		
KC7F2	927822-86-4	HIF-1a	20 uM	
GN44028	1421448-26-1	HIF-1a	14 nM	
Verucopeptin	138067-14-8	HIF-1a	0.22 uM	
FM19G11	329932-55-0	HIF-1a	80 nM	

PT2399	1672662-14-4	HIF-2a	6 nM	
PT2385	1672665-49-4	HIF-2a	27 nM	
Belzutifan (PT2977)	1672668-24-4	HIF-2a	9 nM	
HIF-2α-IN-1	1799948-06-3	HIF-2a	0.5 uM	
HIF-2α-IN-2	1672666-82-8	HIF-2a	16 nM	
HIF-2α-IN-3	313964-19-1	HIF-2a	0.4 uM	
HIF-2α-IN-4	882268-69-1	HIF-2a	5 uM	
TC-S 700	1422955-31-4	HIF-2a	81 nM	

IDF-11774	1429054-28-3		3.65 uM	
Paeoniflorin	23180-57-6			
Emetine hydrochloride	14198-59-5			
Glucosamine	3416-24-8			
PX12	141400-58-0	Thioredoxin-1		
Vitexin	3681-93-4	Glucosidase	48 nM	
BAY 87-2243	1227158-85-1	Mitochondrial complex I		
Lificiguat (YC-1)	170632-47-0	Soluble guanylyl cyclase(sGC) activator and HIF-1a inhibitor		

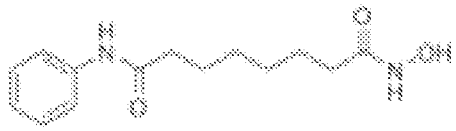
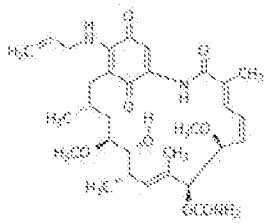
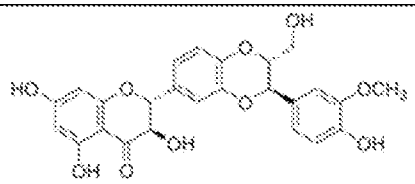
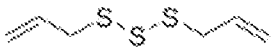
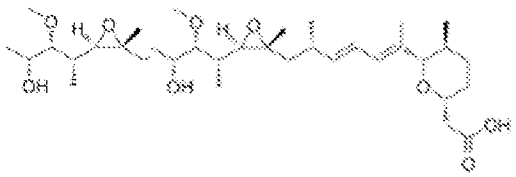
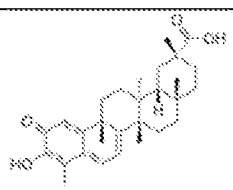
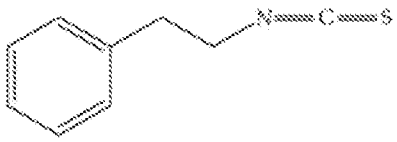
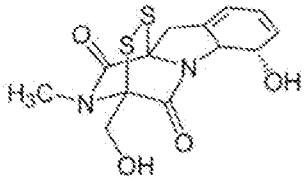
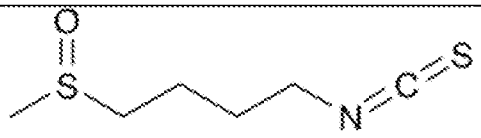
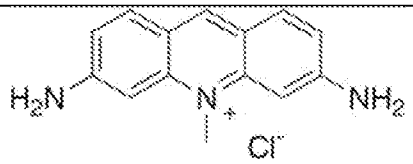
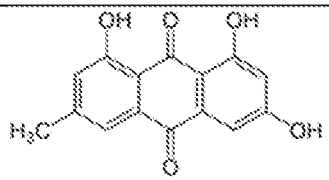
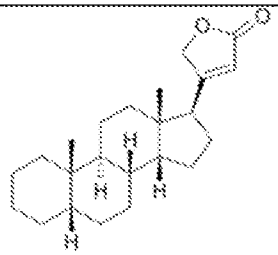
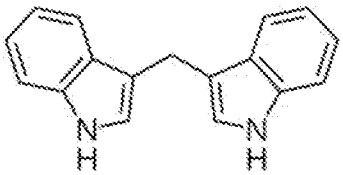
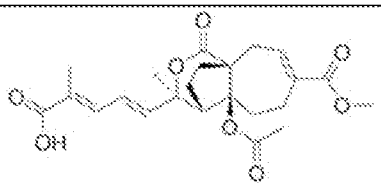
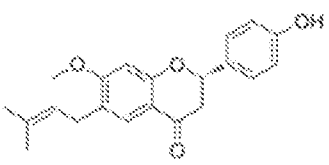
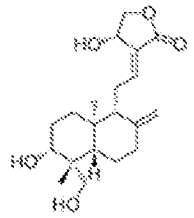
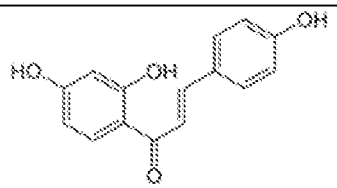
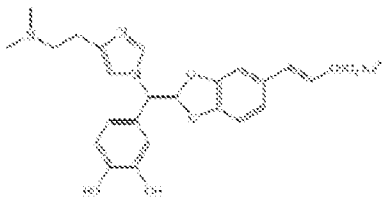
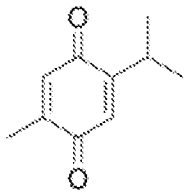
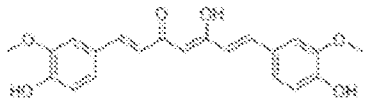
Vorinostat (SAHA, MK0683, Zolinza)	149647-78-9	HDAC	10 nM	
Tanespimycin (17-AAG, CP127374, NSC-330507, KOS 953)	75747-14-7	HSP90	5 nM	

Table 1B. Inhibitors of Hypoxia-Inducible Factor (HIF) (continued)

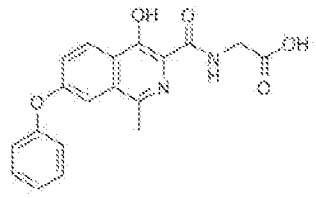
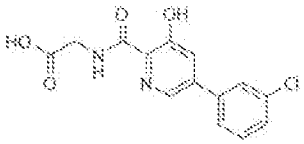
HIF inhibitors	CAS Number	Target	Chemical structure
Silibinin	22888-70-6	HIF-1*	
Diallyl trisulfide (DATS)	2050-87-5	HIF-1*	
Herboxidiene (GEX1A)	142861-00-5	HIF-1*	
Celastrol (Tripterin)	34157-83-0	HIF-1*	

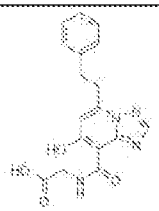
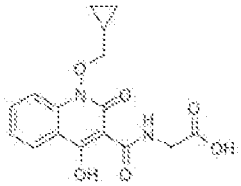
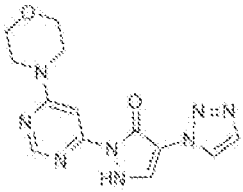
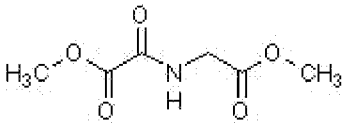
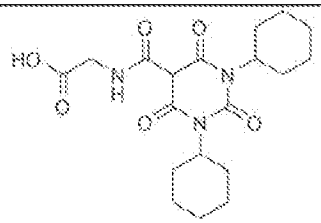
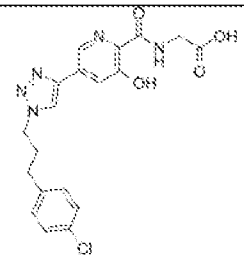
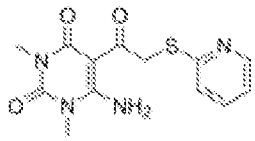
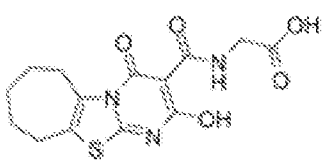
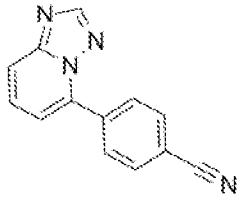
Phenethyl isothiocyanate (PEITC)	2257-09-2	HIF-1*	
Gliotoxin	67-99-2	HIF-1*	
Sulforaphane	4478-93-7	HIF-1*	
Acriflavin	65589-70-0	HIF-1*	
Emodin	518-82-1	HIF-1*	
Cardenolides	52085-71-9	HIF-1*	
DIM (3, 3'-diindolylmethane)	1968-05-4	HIF-1*	
Pseudolaric acid B (PAB)	82508-31-4	HIF-1*	
Bavachinin	19879-30-2	HIF-1*	

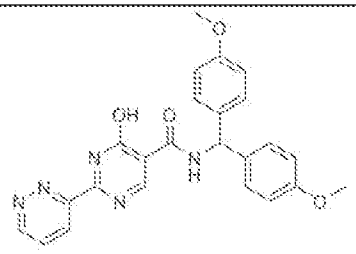
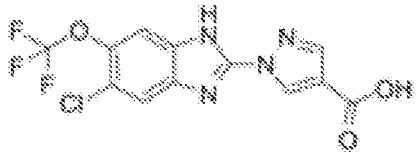
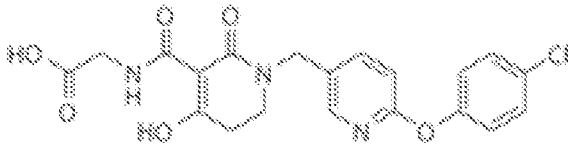
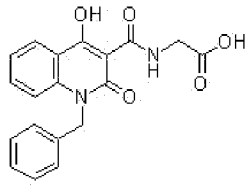
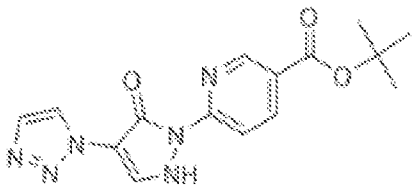
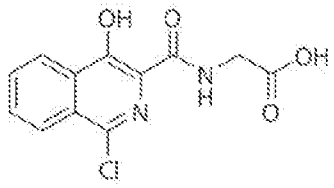
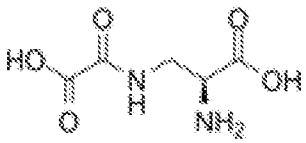
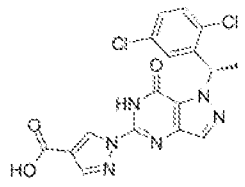
Andrographolide	5508-58-7	HIF-1*	
Isoliquiritigenin (ILTG)	961-29-5	HIF-1*	
Wondonin	336825-31-1	HIF-1*	
Thymoquinone	490-91-5	HIF-1*	
Curcumin	458-37-7	HIF-1*	

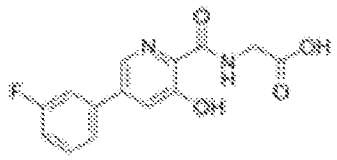
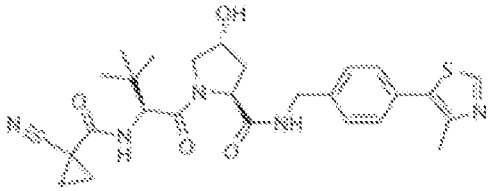
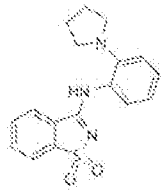
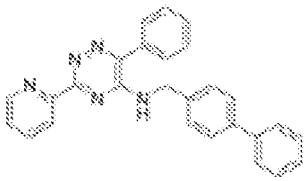
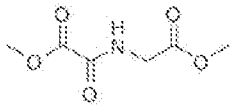
[00357] Exemplary inhibitors of PHD are in Table 2 below.

Table 2. Inhibitors of HIF-Prolyl Hydroxylase (PHD)

PHD inhibitors	CAS Number	Target	IC50	Chemical structure
Roxadustat (FG-4592)	808118-40-3	PHD		
Vadadustat (AKB-6548, B-506, PG-1016548)	1000025-07-9	PHD		

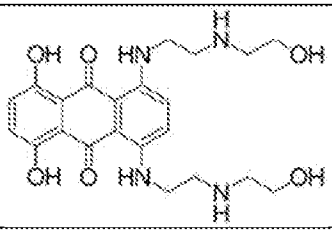
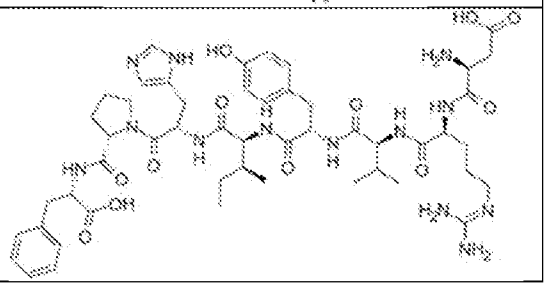
Enarodustat (JTZ-951)	1262132-81-9	PHD2	0.22-5.7 uM	
Desidustat (ZYAN1, ZYAN1-1001)	1616690-16-4	PHD		
Molidustat (BAY 85-3934	1154028-82-6	PHD	450 nM	
Dimethyloxaloylglycine	89464-63-1	PHD		
Daprodustat (GSK1278863)	960539-70-2	PHD		
Prolyl Hydroxylase inhibitor 1 (Compound 15i)	2205125-60-4	PHD	62.23 nM	
TM6089	863421-32-3	PHD		
TRC160334	1293289-69-6	PHD		
PHD-1-IN-1	2009343-14-8	PHD1	34 nM	

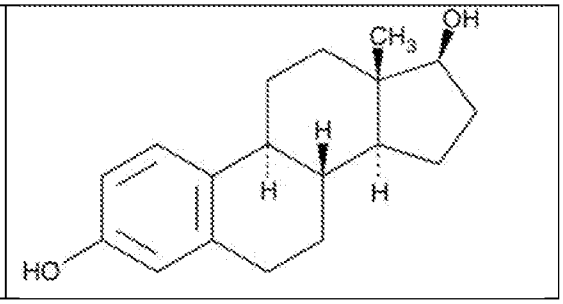
MK-8617	1187990-87-9	PHD1-3	1-14 nM	
JNJ-42041935	1193383-09-3	PHD1-3		
TP0463518	1558021-37-6	PHD1-3	5.3-63 nM	
IOX2 (JICL38)	931398-72-0	PHD2	21 nM	
IOX4	1154097-71-8	PHD2	1.6 nM	
IOX3 (FG-2216)	223387-75-5	PHD2	3.9 nM	
Dencichin	5302-45-4	PHD2		
HIF-PHD-IN-1	1567657-46-8	PHD2	54 nM	

AKB-6899	1007377-55-0	PHD3		
VH298	2097381-85-4	VHL (Von Hippel-Lindau, the E3 ligase)	80-90 nM	
M1001	874590-32-6	HIF-2a agonist	0.67 uM	
ML228 (CID-46742353)	1357171-62-0		1 uM	
DMOG (Dimethyloxalylglycine)	89464-63-1	α-KGDH antagonist and PHD inhibitor		

[00358] Exemplary factors upregulate EPO are in Table 3 below.

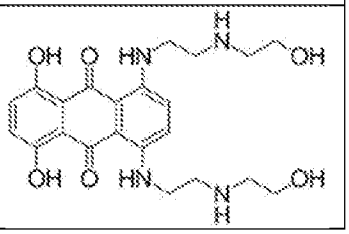
Table 3. Factors upregulate EPO

Factors	CAS Number	Chemical structure
Mitoxantrone	65271-80-9	
Ang II (Angiotensin II)	4474-91-3	

17beta-estradiol (E2-β)	50-28-2	

[00359] Exemplary factors downregulate EPO are in Table 4 below.

Table 4. Factors downregulate EPO

Factors	CAS Number	Target	Chemical structure
Mitoxantrone	65271-80-9	Topoisomerase II inhibitor	

[00360] HIF inhibitors can be used to reduce immunosuppression or immunotolerance (collectively negative immune modulation). PHD inhibitors can be used to induce an immunosuppressive state or immunotolerance.

Pharmaceutical Compositions

[00361] Additional embodiments of the disclosure relate to pharmaceutical compositions comprising an anti-EPOR antibody and/or anti-CD131 antibody and/or anti-EPO antibody and/or EPO analog and/or engineered EPOs, or a pharmaceutically acceptable salt, solvate or hydrate thereof, and one or more pharmaceutically acceptable excipients or carriers. The compositions can optionally contain an additional therapeutic agent. In general, a pharmaceutical composition comprises a therapeutically effective amount of an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or an engineered EPO, one or more pharmaceutically acceptable excipients or carriers and optionally a therapeutically effective amount of an additional therapeutic agent, and is formulated for administration to a subject for therapeutic use.

[00362] Pharmaceutical compositions generally can be prepared according to current good manufacturing practice (GMP), as recommended or required by, e.g., the Federal Food, Drug, and Cosmetic Act §501(a)(2)(B) and the International Conference on Harmonisation Q7 Guideline.

[00363] Pharmaceutical compositions/formulations can be prepared in sterile forms. For example, pharmaceutical compositions/formulations for parenteral administration by injection or infusion generally are sterile. Sterile pharmaceutical compositions/formulations can be compounded or manufactured according to pharmaceutical-grade sterilization standards known to those of skill in the art, such as those disclosed in or required by the United States Pharmacopeia Chapters 797, 1072 and 1211, and 21 Code of Federal Regulations 211.

[00364] Pharmaceutically acceptable excipients and carriers can include pharmaceutically acceptable substances, materials and/or vehicles. Non-limiting examples of types of excipients can include liquid and solid fillers, diluents, binders, lubricants, glidants, surfactants, dispersing agents, disintegration agents, emulsifying agents, wetting agents, suspending agents, thickeners, solvents, isotonic agents, buffers, pH adjusters, absorption-delaying agents, stabilizers, antioxidants, preservatives, antimicrobial agents, antibacterial agents, antifungal agents, chelating agents, adjuvants, sweetening agents, flavoring agents, coloring agents, encapsulating materials, and coating materials. The use of such excipients in pharmaceutical formulations is known in the art. For example, conventional vehicles and carriers can include, but are not limited to, oils (e.g., vegetable oils such as olive oil and sesame oil), aqueous solvents {e.g., saline, buffered saline (e.g., phosphate-buffered saline [PBS]) and isotonic solutions (e.g., Ringer's solution)}, and organic solvents (e.g., dimethyl sulfoxide [DMSO] and alcohols [e.g., ethanol, glycerol and propylene glycol]). Except insofar as any conventional excipient or carrier is incompatible with an anti-EPOR antibody, an anti-CD131 antibody, an anti-EPO antibody, an EPO analog, or an engineered EPO, or a fragment thereof, the disclosure encompasses the use of conventional excipients and carriers in formulations containing an anti-EPOR antibody, an anti-CD131 antibody, an anti-EPO antibody, an EPO analog, an engineered EPO, or a fragment thereof. See, e.g., Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (Philadelphia, Pennsylvania) (2005); Handbook of Pharmaceutical Excipients, 5th Ed., Rowe et al., Eds., The Pharmaceutical Press and the American Pharmaceutical Association (2005); Handbook of Pharmaceutical Additives, 3rd Ed., Ash and Ash, Eds., Gower Publishing Co. (2007); and Pharmaceutical Pre-formulation and Formulation, Gibson, Ed., CRC Press (Boca Raton, Florida) (2004).

[00365] Appropriate formulation can depend on various factors, such as the route of administration chosen. Potential routes of administration of a pharmaceutical composition comprising an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or engineered EPOs can include, but are not limited to, oral, parenteral (including intradermal, subcutaneous, intramuscular, intravascular, intravenous, intraarterial, intraperitoneal, intramedullary, intrathecal and topical), intracavitary, and topical (including

dermal/epicutaneous, transdermal, mucosal, transmucosal, intranasal [e.g., by nasal spray or drop], intraocular [e.g., by eye drop], pulmonary [e.g., by oral or nasal inhalation], buccal, sublingual, rectal [e.g., by suppository], and vaginal [e.g., by suppository]). Topical formulations can be designed to produce a local or systemic therapeutic effect. In certain embodiments, an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or engineered EPOs, or a fragment thereof can be administered parenterally (e.g., intravenously, subcutaneously, intramuscularly or intraperitoneally) by injection (e.g., as a bolus) or by infusion over a period of time.

[00366] Excipients and carriers that can be used to prepare parenteral formulations can include, but are not limited to, solvents (e.g., aqueous solvents such as water, saline, physiological saline, buffered saline [e.g., phosphate-buffered saline], balanced salt solutions [e.g., Ringer's BSS] and aqueous dextrose solutions), isotonic/iso-osmotic agents (e.g., salts [e.g., NaCl, KCl and $CaCl_2$] and sugars [e.g., sucrose]), buffering agents and pH adjusters (e.g., sodium dihydrogen phosphate [monobasic sodium phosphate]/disodium hydrogen phosphate [dibasic sodium phosphate], citric acid/sodium citrate and L-histidine/L-histidine HCl), and emulsifiers (e.g., non-ionic surfactants such as polysorbates [e.g., polysorbate 20 and 80] and poloxamers [e.g., poloxamer 188]). Protein formulations and delivery systems are discussed in, e.g., A. J. Banga, Therapeutic Peptides and Proteins: Formulation, Processing, and Delivery Systems, 3rd Ed., CRC Press (Boca Raton, Florida) (2015).

[00367] The excipients can optionally include one or more substances that increase protein stability, increase protein solubility, inhibit protein aggregation, or reduce solution viscosity, or any combination or all thereof. Examples of such substances can include, but are not limited to, hydrophilic amino acids (e.g., arginine and histidine), polyols (e.g., *myo*-inositol, mannitol and sorbitol), saccharides {e.g., glucose (including D-glucose [dextrose]), lactose, sucrose and trehalose}, osmolytes (e.g., trehalose, taurine, amino acids [e.g., glycine, sarcosine, alanine, proline, serine, β-alanine and γ-aminobutyric acid], and betaines [e.g., trimethylglycine and trimethylamine *N*-oxide]), and non-ionic surfactants {e.g., alkyl polyglycosides, ProTek® alkylsaccarides (e.g., a monosaccharide [e.g., glucose] or a disaccharide [e.g., maltose or sucrose] coupled to a long-chain fatty acid or a corresponding long-chain alcohol), and polypropylene glycol/polyethylene glycol block co-polymers (e.g., poloxamers [e.g., Pluronic™ F-68], and Genapol® PF-10 and variants thereof)}. Because such substances can increase protein solubility, these substances can be used to increase protein concentration in a formulation. Higher protein concentration in a formulation can be advantageous for subcutaneous administration, which has a limited volume of bolus administration (e.g., ≤ about 1.5 mL). In addition, such substances can

be used to stabilize proteins during the preparation, storage and reconstitution of lyophilized proteins.

[00368] For parenteral (e.g., intravenous, subcutaneous or intramuscular) administration, a sterile solution or suspension of an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or an engineered EPO in an aqueous solvent containing one or more excipients can be prepared beforehand and can be provided in, e.g., a pre-filled syringe. Alternatively, an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or an engineered EPO can be dissolved or suspended in an aqueous solvent that can optionally comprise one or more excipients prior to lyophilization (freeze-drying). Shortly prior to parenteral administration, the lyophilized anti-EPOR antibody and/or anti-CD131 antibody and/or anti-EPO antibody and/or EPO analog and/or engineered EPO stored in a suitable container (e.g., a vial) can be reconstituted with, e.g., sterile water that can optionally comprise one or more excipients. If the anti-EPOR antibody and/or anti-CD131 antibody and/or anti-EPO antibody and/or EPO analog and/or engineered EPO is to be administered by infusion (e.g., intravenously), the solution or suspension of the reconstituted anti-EPOR antibody and/or anti-CD131 antibody and/or anti-EPO antibody and/or EPO analog and/or engineered EPO can be added to and diluted in an infusion bag containing, e.g., sterile saline (e.g., about 0.9% NaCl).

[00369] Excipients that can enhance transmucosal penetration of smaller proteins include, but are not limited to, cyclodextrins, alky saccharides (e.g., alkyl glycosides and alkyl maltosides [e.g., tetradecylmaltoside]), and bile acids (e.g., cholic acid, glycocholic acid, taurocholic acid, deoxycholic acid, glycodeoxycholic acid, chenodeoxycholic acid and dehydrocholic acid).

[00370] Excipients that can enhance transepithelial or transdermal penetration of smaller proteins include, but are not limited to, chemical penetration enhancers (CPEs, including fatty acids [e.g., oleic acid]), cell-penetrating peptides {CPPs, including arginine-rich CPPs [e.g., polyarginines such as R_6-R_{11} (e.g., R_6 and R_9) and TAT-related CPPs such as TAT(49-57)] and amphipathic CPPs [e.g., Pep-1 and penetratin]}, and skin-penetrating peptides (SPPs, such as the skin-penetrating and cell-entering [SPACE] peptide). Transdermal penetration of smaller proteins can be further enhanced by use of a physical enhancement technique, such as iontophoresis, cavitational or non-cavitational ultrasound, electroporation, thermal ablation, radio frequency, microdermabrasion, microneedles or jet injection. US 2007/0269379 provides an extensive list of CPEs. F. Milletti, *Drug Discov. Today*, **17**:850-860 (2012) is a review of CPPs. R. Ruan *et al.*, *Ther. Deliv.*, **7**:89-100 (2016) discuss CPPs and SPPs for transdermal delivery of macromolecules, and M. Prausnitz and R. Langer, *Nat. Biotechnol.*, **26**:1261-1268 (2008) discuss a variety of transdermal drug-delivery methods.

[00371] An anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or an engineered EPO can be delivered from a sustained-release composition. As used herein, the term "sustained-release composition" can encompass sustained-release, prolonged-release, extended-release, slow-release and controlled-release compositions, systems and devices. Protein delivery systems are discussed in, e.g., Banga (*supra*). A sustained-release composition can deliver a therapeutically effective amount of an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or an engineered EPO over a prolonged time period. In some embodiments, a sustained-release composition can deliver an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or EPO analog and/or an engineered EPO over a period of at least about 3 days, 1 week, 2 weeks, 3 weeks, 1 month (4 weeks), 6 weeks, 2 months, 3 months or longer. A sustained-release composition can be administered, e.g., parenterally (e.g., intravenously, subcutaneously or intramuscularly).

[00372] A sustained-release composition of an anti-EPOR antibody and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or an engineered EPO can be in the form of, e.g., a particulate system, a lipid or oily composition, or an implant. Particulate systems can include, but are not limited to, nanoparticles, nanospheres, nanocapsules, microparticles, microspheres, and microcapsules. Nanoparticulate systems generally can have a diameter or an equivalent dimension smaller than about 1 μm. In certain embodiments, a nanoparticle, a nanosphere or a nanocapsule can have a diameter or an equivalent dimension of no more than about 500 nm, about 400 nm, or about 300 nm, or no more than about 200 nm, about 150 nm, or about 100 nm. In an aspect, a microparticle, a microsphere or a microcapsule can have a diameter or an equivalent dimension of about 1-200 μm, about 100-200 μm, or about 50-150 μm, or about 1-100 μm, about 1-50 μm, or about 50-100 μm. A nano- or a microcapsule can typically comprise a therapeutic agent in the central core, while the therapeutic agent typically can be dispersed throughout a nano- or a microparticle, or a sphere. In an aspect, a nanoparticulate system can be administered intravenously, while a microparticulate system can be administered subcutaneously or intramuscularly.

[00373] In an aspect, a sustained-release particulate system or implant can be made of a biodegradable polymer and/or a hydrogel. In certain embodiments, the biodegradable polymer can comprise lactic acid and/or glycolic acid [e.g., an L-lactic acid-based copolymer, such as poly(L-lactide-co-glycolide) or poly(L-lactic acid-co-D,L-2-hydroxyoctanoic acid)]. Non-limiting examples of polymers of which a hydrogel can be composed can include polyvinyl alcohol, acrylate polymers (e.g., sodium polyacrylate), and other homopolymers and copolymers having a relatively large number of hydrophilic groups (e.g., hydroxyl or/and carboxylate

groups). The biodegradable polymer of the particulate system or implant can be selected so that the polymer substantially completely degrades around the time the period of treatment is expected to end, and so that the byproducts of the polymer's degradation, like the polymer, are biocompatible.

[00374] Alternatively, a sustained-release composition of a protein can be composed of a non-biodegradable polymer. Non-limiting examples of non-biodegradable polymers can include poloxamers (e.g., poloxamer 407). Sustained-release compositions of a protein can be composed of other natural or synthetic substances or materials, such as hydroxyapatite.

[00375] Sustained-release lipid or oily compositions of a protein can be in the form of, e.g., liposomes, micelles (e.g., those composed of biodegradable natural or/and synthetic polymers, such as lactosomes), or emulsions in an oil.

[00376] A sustained-release composition can be formulated or designed as a depot, which can be injected or implanted, e.g., subcutaneously or intramuscularly. A depot can be in the form of, e.g., a polymeric particulate system, a polymeric implant, or a lipid or oily composition. A depot formulation can comprise a mixture of a protein and, e.g., a biodegradable polymer [e.g., poly(lactide-co-glycolide)] or a semi-biodegradable polymer (e.g., a block copolymer of lactic acid and PEG) in a biocompatible solvent system, whether or not such a mixture forms a particulate system or implant.

[00377] A pharmaceutical composition can be presented in unit dosage form as a single dose wherein all active and inactive ingredients are combined in a suitable system, and components do not need to be mixed to form the composition to be administered. The unit dosage form can generally comprise an effective dose of the therapeutic agent. A representative example of a unit dosage form is a single-use pen comprising a pre-filled syringe, a needle and a needle cover for parenteral (e.g., intravenous, subcutaneous or intramuscular) injection of the therapeutic agent.

[00378] Alternatively, a pharmaceutical composition can be presented as a kit in which the therapeutic agent, excipients and carriers (e.g., solvents) are provided in two or more separate containers (e.g., ampules, vials, tubes, bottles or syringes) and need to be combined to form the composition to be administered. The kit can comprise instructions for storing, preparing and administering the composition (e.g., a solution to be injected intravenously or subcutaneously).

[00379] A kit can comprise all active and inactive ingredients in unit dosage form or the active ingredient and inactive ingredients in two or more separate containers, and can contain instructions for administering or using the pharmaceutical composition to treat a medical condition.

[00380] RNA, RNAi, small molecules and other agents described herein can be formulated as nanoparticles. A nanoparticle can have a mean diameter of about 50-200 nm. The nanoparticle

can be a lipid nanoparticle. A lipid nanoparticle can comprise a cationic lipid, a neutral lipid, a PEG-modified lipid, a sterol, or a non-cationic lipid. In some embodiments, the lipid nanoparticle can comprise a molar ratio of about 20-60% cationic lipid, about 0.5-15% PEG-modified lipid, about 25-55% sterol, and about 25% non-cationic lipid. The cationic lipid can be an ionizable cationic lipid and the non-cationic lipid can be a neutral lipid, and/or the sterol can be a cholesterol. The cationic lipid can be selected from 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319).

[00381] A lipid nanoparticle formulation can be composed of a lipid mixture in molar ratios of about 20-70% cationic lipid: about 5-45% neutral lipid: about 20-55% cholesterol: and/or about 0.5-15% PEG-modified lipid. In some embodiments, a lipid nanoparticle formulation can be composed of a lipid mixture in a molar ratio of about 20-60% cationic lipid: about 5-25% neutral lipid: about 25-55% cholesterol: and/or about 0.5-15% PEG-modified lipid. In some embodiments, a lipid nanoparticle formulation can be composed of about 35 to 45% cationic lipid, about 40% to 50% cationic lipid, about 50% to 60% cationic lipid, and/or about 55% to 65% cationic lipid. In some embodiments, the ratio of lipid to RNA (e.g., mRNA) in lipid nanoparticles can be about 5:1 to about 20:1, about 10:1 to about 25:1, about 15:1 to about 30:1, and/or at least about 30:1.

[00382] A lipid nanoparticle formulation can include about 0.5% to about 15% on a molar basis of the neutral lipid, e.g., about 3 to 12%, about 5 to 10% or about 15%, about 10%, or about 7.5% on a molar basis. Examples of neutral lipids can include, but are not limited to, DSPC, POPC, DPPC, DOPE and SM.

[00383] The formulation can include from about 5% to about 50% on a molar basis of the sterol (e.g., about 15 to 45%, about 20 to 40%, about 40%, about 38.5%, about 35%, or about 31% on a molar basis. A non-limiting example of a sterol can include cholesterol.

[00384] A lipid nanoparticle formulation can include from about 0.5% to about 20% on a molar basis of the PEG or PEG-modified lipid (e.g., about 0.5 to 10%, about 0.5 to 5%, about 1.5%, about 0.5%, about 1.5%, about 3.5%, or about 5% on a molar basis. A PEG or PEG modified lipid comprises a PEG molecule of an average molecular weight of about 2,000 Da. A PEG or PEG modified lipid can comprise a PEG molecule of an average molecular weight of less than about 2,000 Da, for example about 1,500 Da, about 1,000 Da, or about 500 Da. Non-limiting examples of PEG-modified lipids can include PEG-distearoyl glycerol (PEG-DMG) (also referred herein as PEG-C14 or C14-PEG), and PEG-cDMA (further discussed in Reyes et al. J. Controlled Release, 107, 276-287 (2005) the contents of which are herein incorporated by reference in their entirety).

[00385] The ratio of PEG in the lipid nanoparticle formulations may be increased or decreased and/or the carbon chain length of the PEG lipid may be modified from C14 to C18 to alter the pharmacokinetics and/or biodistribution of the lipid nanoparticle formulations. As a non-limiting example, lipid nanoparticle formulations may contain from about 0.5% to about 3.0%, from about 1.0% to about 3.5%, from about 1.5% to about 4.0%, from about 2.0% to about 4.5%, from about 2.5% to about 5.0% and/or from about 3.0% to about 6.0% of the lipid molar ratio of PEG-c-DOMG (R-3-[(.omega.-methoxy-poly(ethyleneglycol)2000)carbamoyl)]-1,2-dimyristy-loxypropyl-3-amine) (also referred to herein as PEG-DOMG) as compared to the cationic lipid, DSPC and cholesterol. The PEG-c-DOMG may be replaced with a PEG lipid including, but not limited to, PEG-DSG (1,2-Distearoyl-sn-glycerol, methoxypolyethylene glycol), PEG-DMG (1,2-Dimyristoyl-sn-glycerol) and/or PEG-DPG (1,2-Dipalmitoyl-sn-glycerol, methoxypolyethylene glycol). The cationic lipid may be selected from any lipid known in the art including, but not limited to, DLin-MC3-DMA, DLin-DMA, C12-200 and DLin-KC2-DMA.

[00386] The molar lipid ratio can be 50/10/38.5/1.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG, PEG-DSG or PEG-DPG), 57.2/7.1134.3/1.4 (mol % cationic lipid/neutral lipid, e.g., DPPC/Chol/PEG-modified lipid, e.g., PEG-cDMA), 40/15/40/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 50/10/35/4.5/0.5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DSG), 50/10/35/5 (cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG), 40/10/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA), 35/15/40/10 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA) or 52/13/30/5 (mol % cationic lipid/neutral lipid, e.g., DSPC/Chol/PEG-modified lipid, e.g., PEG-DMG or PEG-cDMA).

[00387] The amino alcohol cationic lipid may be the lipids described in and/or made by the methods described in U.S. Patent Publication No. US20130150625, which is incorporated by reference in its entirety for all purposes. As a non-limiting example, the cationic lipid may be 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z,2Z)-octadeca-9,12- -dien-1-yloxy] methyl}propan-1-ol (Compound 1 in US20130150625); 2-amino-3-[(9Z)-octadec-9-en-1-yloxy]-2-{[(9Z)-octadec-9-en-1-yloxy]methy- 1}propan-1-ol (Compound 2 in US20130150625); 2-amino-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-[(octyloxy)methyl]propa- n-1-ol (Compound 3 in US20130150625); and 2-(dimethylamino)-3-[(9Z,12Z)-octadeca-9,12-dien-1-yloxy]-2-{[(9Z, 12Z)-octadeca-9,12-dien-1-yloxy]methyl}propan-1-ol (Compound 4 in US20130150625); or any pharmaceutically acceptable salt or stereoisomer thereof.

[00388] A lipid nanoparticle formulation can be composed of (i) at least one lipid selected from the group consisting of 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), dilinoleyl-methyl-4-dimethylaminobutyrate (DLin-MC3-DMA), and di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319); (ii) a neutral lipid selected from DSPC, DPPC, POPC, DOPE and SM; (iii) a sterol, e.g., cholesterol; and (iv) a PEG-lipid, e.g., PEG-DMG or PEG-cDMA, in a molar ratio of 20-60% cationic lipid: 5-25% neutral lipid: 25-55% sterol; 0.5-15% PEG-lipid.

[00389] Examples of lipid nanoparticle compositions and methods of making them are described, for example, in Cifuentes-Rius et al., (2021) Nature Nanotechnol. 16:37-46; Hou et al., (2021) Nature Rev. 6:1078-1094; Jang et al., (2021) Int. J. Med. Sci. 22:10009 (doi.org/10.3390/ijms221810009); Semple et al. (2010) Nat. Biotechnol. 28:172-176; Jayarama et al. (2012), Angew. Chem. Int. Ed., 51: 8529-8533; and Maier et al. (2013) Molecular Therapy 21, 1570-1578 (each of which are incorporated by reference in their entirety for all purposes).

[00390] A lipid nanoparticle formulation can be influenced by the selection of the cationic lipid component, the degree of cationic lipid saturation, the nature of the PEGylation, ratio of all components and biophysical parameters such as size. For example, in Semple et al. (Nature Biotech. 2010 28:172-176), the lipid nanoparticle formulation is composed of 57.1% cationic lipid, 7.1% dipalmitoylphosphatidylcholine, 34.3% cholesterol, and 1.4% PEG-c-DMA. As another example, changing the composition of the cationic lipid can more effectively deliver siRNA to various antigen presenting cells (Basha et al. Mol Ther. 2011 19:2186-2200, which is incorporated by reference in its entirety for all purposes).

[00391] A kit can contain an anti-EPOR and/or an anti-CD131 antibody and/or an anti-EPO antibody and/or an EPO analog and/or an engineered EPO or a pharmaceutical composition comprising the same, and instructions for administering or using the anti-EPOR antibody and/or anti-CD131 antibody and/or anti-EPO antibody and/or EPO analog and/or engineered EPO, or the pharmaceutical composition comprising the same to treat an antibody-associated condition.

[00392] In some aspects, provided herein is a cell comprising an anti-EPO antibody, an anti-EPOR antibody, an anti-CD131 antibody, an EPO analog, or an engineered EPO. In some embodiments, a cell can comprise an immune cell. Examples of an immune cell can include, but are not limited to, a macrophage, a dendritic cell, a T-cell, a natural killer cell, or a B cell. In some embodiments, a T-cell can comprise a cytotoxic T-cell. In some embodiments, a cell can comprise a myeloid cell. In some embodiments, a myeloid cell can comprise a granulocyte, a monocyte, a macrophage, or a dendritic cell. In some embodiments, a cell is an erythroid progenitor cell. In some embodiments, a cell can comprise an endothelial cell.

Uses of Anti-EPOR Antibodies, Anti-CD131 Antibodies, Anti-EPO Antibodies, and/or EPO Analogs/Engineered EPOs

[00393] In one aspect, EPO analogs or engineered EPOs that are antagonists for the hetero-EPOR, anti-hetero-EPOR antibodies that are antagonists for the hetero-EPOR, and/or anti-EPO antibodies that inhibit binding to the hetero-EPOR, and/or knocking down EPOR using siRNA targeting EPOR can be used to overcome immunosuppressive or tolerogenic states in a subject. For example, these EPO analogs, engineered EPOs, anti-hetero-EPOR antibodies, and/or anti-EPO antibodies, and/or knocking down EPOR using siRNA targeting EPOR can be used to overcome a tumor immune suppressive microenvironment, to boost immune response to vaccines, to enhance the immune response during an acute inflammatory response to disease (e.g., an infection from a microorganism or a virus), and/or to treat chronic infectious diseases or conditions. In some embodiments, EPO analogs, anti-hetero-EPOR antibodies, anti-CD131 antibodies and/or anti-EPO antibodies that are antagonists for the hetero-EPOR can inhibit immune tolerance. In some embodiments, inhibiting immune tolerance can comprise promoting or increasing immune response. For example, inhibiting immune tolerance can comprise increasing immune response to a vaccine, a viral infection, a bacterial infection, or a tumor antigen (e.g., an antigen produced by cancer).

[00394] In some embodiments, EPO analogs, anti-hetero-EPOR antibodies, anti-CD131 antibodies and/or anti-EPO antibodies that are antagonists for the hetero-EPOR can promote differentiation of naïve T cells into effector T cells. Markers for effector T cells described herein can include, but are not limited to, Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα). In some embodiments, EPO analogs, anti-hetero-EPOR antibodies, anti-CD131 antibodies and/or anti-EPO antibodies that are antagonists for the hetero-EPOR can inhibit differentiation of naïve T cells into regulatory T cells. Markers for regulatory T cells described herein can include, but are not limited to, Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4). In some embodiments, EPO analogs, anti-hetero-EPOR antibodies, anti-CD131 antibodies and/or anti-EPO antibodies that are antagonists for the hetero-EPOR can increase a number of progenitor exhausted T cells. Markers for progenitor exhausted T cells can include, but are not limited to, Cluster of Differentiation 44 (CD44), Signaling lymphocyte activation molecule family member 6 (SLAMF6) or T cell factor 1 (TCF1).

[00395] In some embodiments, EPO analogs, anti-hetero-EPOR antibodies, anti-CD131 antibodies and/or anti-EPO antibodies that are antagonists for the hetero-EPOR can stimulate

immune response in cancer. For example, EPO analogs, anti-hetero-EPOR antibodies, anti-CD131 antibodies and/or anti-EPO antibodies that are antagonists for the hetero-EPOR can render cancer cells sensitive to an immune checkpoint inhibitor. Examples of immune checkpoint inhibitors can include, but are not limited, to PD-1 inhibitors, PD-L1 inhibitors, and/or CTLA-4 inhibitors. In some embodiments, immune checkpoint inhibitors can comprise anti-CTLA-4 antibodies, anti-PD-1 antibodies, anti-PD-L1 antibodies, or functional fragments thereof, or combinations thereof. In some embodiments, immune checkpoint inhibitors can comprise Nivolumab, Pembrolizumab, Cemiplimab, Atezolimumab, Durvalumab, Avelumab, or Ipilimumab. In some embodiments, EPO analogs, anti-hetero-EPOR antibodies, anti-CD131 antibodies and/or anti-EPO antibodies that are antagonists for the hetero-EPOR can attenuate tumor growth. In some embodiments, EPO analogs, anti-hetero-EPOR antibodies, anti-CD131 antibodies and/or anti-EPO antibodies that are antagonists for the hetero-EPOR can reduce the size of a cancer or attenuate the growth of a cancer.

[00396] Tumors are frequently infiltrated with myeloid cells with immune tolerogenic or suppressive functions. Examples of myeloid cells include, but are not limited to, granulocytes, monocytes, macrophages (MΦs), or dendritic cells (DCs). The hetero-EPOR is widely present and upregulated in such tumor-infiltrating myeloid cells including both dendritic cells (DCs) and macrophages (MΦs), and contributes to immune tolerance or suppression. An antagonistic anti-hetero-EPOR antibody, and/or anti-EPO antibody that inhibits binding to the hetero-EPOR, and/or EPO analog/engineered EPO that are antagonists for the hetero-EPOR can block the activation of the hetero-EPOR (e.g., on myeloid cells) and can prevent immune suppression and antigen-specific immune tolerance thereby enabling effective anti-tumor immunity. In some embodiments, the antibody and/or EPO analog/engineered EPO may not bind the homo-EPOR and so will not interfere with erythropoiesis. The binding epitope of such anti-EPO antibody can be in helix B of the EPO. The ability of such blocking antibodies to reverse hetero-EPOR mediated immune tolerance can be validated in a variety of cancer models, e.g., liver hepatocarcinoma, colorectal cancer, breast cancer, brain cancer, liver metastasis, and lymph node metastasis etc. In addition to cancers, in some embodiments, EPO analogs, anti-hetero-EPOR antibodies, anti-CD131 antibodies and/or anti-EPO antibodies that are antagonists for the hetero-EPOR can be used to treat chronic infections. For example, chronic viral infections (e.g., Hepatitis B Virus, Herpes Simplex Virus, Human Papilloma Virus, Covid-19, influenza, Human Immunodeficiency Virus, meningitis, pneumonia, rotavirus, chicken pox, etc.) and/or chronic bacterial infections (e.g., Mycobacterium tuberculosis, fungal, anthrax, tetanus, leptospirosis, cholera, botulism, pseudomonas, pneumonia, *E. Coli*, gonorrhea, bubonic plague, syphilis, methicillin-resistant Staphylococcus aureus, meningitis, etc.) can be treated similarly. These

antibodies and/or analogs/engineered proteins can also be used to reduce an immune tolerogenic and/or immunosuppressive state for T-cells (e.g., cytotoxic T-cells, CAR T-cells, or TCR engineered T-cells) or natural killer cells (e.g., NK cells engineered with CARs or T-cell receptors).

[00397] Neoplasia, tumors and cancers that can be treated with the analogs/engineered proteins and antibodies described herein can include, for example, benign, malignant, metastatic and non-metastatic types, and can include any stage (I, II, Ill, IV or V) or grade (G1, G2, G3, etc.) of neoplasia, tumor, or cancer, or a neoplasia, tumor, cancer or metastasis that is progressing, worsening, stabilized or in remission. Cancers that may be treated according to the invention can include, but are not limited to, cells or neoplasms of the bladder, blood, bone, bone marrow, brain, breast, colon, esophagus, gastrointestines, gum, head, kidney, liver, lung, nasopharynx, neck, ovary, prostate, skin, stomach, testis, tongue, or uterus. In addition, the cancer may specifically be of the following histological type, though it is not limited to the following: neoplasm, malignant; carcinoma; undifferentiated; giant and spindle cell carcinoma; small cell carcinoma; papillary carcinoma; squamous cell carcinoma; lymphoepithelial carcinoma; basal cell carcinoma; pilomatrix carcinoma; transitional cell carcinoma; papillary transitional cell carcinoma; adenocarcinoma; gastrinoma, malignant; cholangiocarcinoma; hepatocellular carcinoma; combined hepatocellular carcinoma and cholangiocarcinoma; trabecular adenocarcinoma; adenoid cystic carcinoma; adenocarcinoma in adenomatous polyp; adenocarcinoma, familial polyposis coli; solid carcinoma; carcinoid tumor, malignant; bronchiolo-alveolar adenocarcinoma; papillary adenocarcinoma; chromophobe carcinoma; acidophil carcinoma; oxyphilic adenocarcinoma; basophil carcinoma; clear cell adenocarcinoma; granular cell carcinoma; follicular adenocarcinoma; papillary and follicular adenocarcinoma; nonencapsulating sclerosing carcinoma; adrenal cortical carcinoma; endometroid carcinoma; skin appendage carcinoma; apocrine adenocarcinoma; sebaceous adenocarcinoma; ceruminous adenocarcinoma; mucoepidermoid carcinoma; cystadenocarcinoma; papillary cystadenocarcinoma; papillary serous cystadenocarcinoma; mucinous cystadenocarcinoma; mucinous adenocarcinoma; signet ring cell carcinoma; infiltrating duct carcinoma; medullary carcinoma; lobular carcinoma; inflammatory carcinoma; Paget's disease, mammary; acinar cell carcinoma; adenosquamous carcinoma; adenocarcinoma with squamous metaplasia; thymoma, malignant; ovarian stromal tumor, malignant; thecoma, malignant; granulosa cell tumor, malignant; androblastoma, malignant; Sertoli cell carcinoma; Leydig cell tumor, malignant; lipid cell tumor, malignant; paraganglioma, malignant; extra-mammary paraganglioma, malignant; pheochromocytoma; glomangiosarcoma; malignant melanoma; amelanotic melanoma; superficial spreading melanoma; malignant melanoma in giant pigmented nevus; epithelioid cell melanoma;

blue nevus, malignant; sarcoma; fibrosarcoma; fibrous histiocytoma, malignant; myxosarcoma; liposarcoma; leiomyosarcoma; rhabdomyosarcoma; embryonal rhabdomyosarcoma; alveolar rhabdomyosarcoma; stromal sarcoma; mixed tumor; Mullerian mixed tumor; nephroblastoma; hepatoblastoma; carcinosarcoma; mesenchymoma, malignant; Brenner tumor, malignant; phyllodes tumor, malignant; synovial sarcoma; mesothelioma, malignant; dysgerminoma; embryonal carcinoma; teratoma, malignant; struma ovarii, malignant; choriocarcinoma; mesonephroma, malignant; hemangiosarcoma; hemangioendothelioma, malignant; Kaposi's sarcoma; hemangiopericytoma, malignant; lymphangiosarcoma; osteosarcoma; juxtacortical osteosarcoma; chondrosarcoma; chondroblastoma, malignant; mesenchymal chondrosarcoma; giant cell tumor of bone; Ewing's sarcoma; odontogenic tumor, malignant; ameloblastic odontosarcoma; ameloblastoma, malignant; ameloblastic fibrosarcoma; pinealoma, malignant; chordoma; glioma, malignant; ependymoma; astrocytoma; protoplasmic astrocytoma; fibrillary astrocytoma; astroblastoma; glioblastoma; oligodendroglioma; oligodendroblastoma; primitive neuroectodermal; cerebellar sarcoma; ganglioneuroblastoma; neuroblastoma; retinoblastoma; olfactory neurogenic tumor; meningioma, malignant; neurofibrosarcoma; neurilemmoma, malignant; granular cell tumor, malignant; malignant lymphoma; Hodgkin's disease; Hodgkin's; paragranuloma; malignant lymphoma, small lymphocytic; malignant lymphoma, large cell, diffuse; malignant lymphoma, follicular; mycosis fungoides; other specified non-Hodgkin's lymphomas; malignant histiocytosis; multiple myeloma; mast cell sarcoma; immunoproliferative small intestinal disease; leukemia; lymphoid leukemia; plasma cell leukemia; erythroleukemia; lymphosarcoma cell leukemia; myeloid leukemia; basophilic leukemia; eosinophilic leukemia; monocytic leukemia; mast cell leukemia; megakaryoblastic leukemia; myeloid sarcoma; and hairy cell leukemia. In some embodiments, the neoplastic disease may be tumors associated with a cancer selected from prostate cancer, liver cancer, renal cancer, lung cancer, breast cancer, colorectal cancer, pancreatic cancer, brain cancer, hepatocellular cancer, lymphoma, leukemia, gastric cancer, cervical cancer, ovarian cancer, thyroid cancer, melanoma, head and neck cancer, skin cancer and soft tissue sarcoma and/or other forms of carcinoma. The tumor may be metastatic or a malignant tumor.

[00398] Effective vaccination can be challenging for a number of pathological conditions. Blocking hetero-EPOR signaling in the presence of specific antigen(s) can be effective at promoting antigen-specific immunity. This can be achieved by targeting hetero-EPOR expressing dendritic cells with the antigen and the above-mentioned antagonistic EPO analogs/engineered EPOs, antagonistic anti-hetero-EPOR antibodies, and/or anti-EPO antibodies that inhibit EPO from interacting with hetero-EPOR to enhance the immune response. It can also be achieved by nanoparticles that encapsulate mRNA of the antigen and an inhibitor of the

hetero-EPOR signaling pathway which acts either on the heterodimeric receptor or its downstream intracellular signaling pathway. Exemplary vaccines can include vaccines for HIV, HCV, HSV, HBV, cancer vaccines, and/or virally caused diseases requiring repeated injections and/or immunity is short-lived, e.g., HBV, COVID, Influenza A, and/or Shingles.

[00399] In another aspect, EPO analogs or engineered EPOs that are agonists for the hetero-EPOR, and/or anti-EPOR antibodies that are agonists for the hetero-EPOR, and/or anti-CD131 antibodies that are agonists for the hetero-EPOR can be used to induce immunosuppressive or tolerogenic states in a subject. For example, these EPO analogs/engineered EPOs, anti-hetero-EPOR antibodies, and/or anti-EPO antibodies can be used to suppress transplant rejection, induce immune tolerance to specific antigens, reduce immune reaction in autoimmune diseases, reduce systemic chronic inflammation, and reduce damage to neural tissue and other tissue during injury or other stress.

[00400] In organ transplantation and bone marrow transplantation, immune tolerance, especially antigen-specific immune tolerance is desired, e.g., promoting survival of the transplanted organ, preventing Graft-versus-host disease (GvHD) and avoiding the use of highly toxic immunosuppressive drugs. An agonistic antibody for the hetero-EPOR or EPO analog/engineered EPO that is an agonist for the hetero-EPOR can promote immune tolerance. For example, anti-EPO antibodies, anti-hetero-EPOR antibodies, EPO analogs, engineered EPOs that can act as agonists for hetero-EPORs can promote immune tolerance in a subject that has been received an organ transplant or a foreign therapeutics protein. Examples of transplanted organ can comprise, but are not limited to, bone marrow, kidney, liver, lung, or heart. In some embodiments, agonistic antibody for the hetero-EPOR or EPO analog/engineered EPO that is an agonist for the hetero-EPOR may not bind the homo-EPOR. In some embodiments, agonistic antibody for the hetero-EPOR or EPO analog/engineered EPO that is an agonist for the hetero-EPOR may not affect a homo-EPO receptor activity. In some embodiments, agonistic antibody for the hetero-EPOR or EPO analog/engineered EPO that is an agonist for the hetero-EPOR may not affect erythropoiesis. The binding epitope of such an antibody can be the ligand-binding site on hetero-EPOR or the hetero-EPOR heterodimerization site.

[00401] Inducing antigen-specific immune tolerance can be beneficial in a number of conditions. It can be achieved by targeting dendritic cells and/or other antigen-presenting cells with the antigen and the agonists of the hetero-EPOR (EPO analogs or antibodies) to induce immune tolerance. It can also be achieved by nanoparticles that encapsulate mRNAs of the antigen and an agonist of the hetero-EPOR. Alternatively, the nanoparticles with the mRNA encoding the antigen can be combined with the agonist of the hetero-EPOR (together or separate administrations). Exemplary antigens for such immune tolerance applications can include, for

example, recombinant therapeutic proteins (e.g., EndoS to reduce effector function driven autoimmunity, IgA degrading proteases (e.g., H. influenzae, N. meningitidis) for IgA nephropathy, Phenylalanine Hydroxylase for PKU, Uricase for chronic refractory gout), antigens responsible for autoimmune diseases, (e.g., T1D (insulin or pre/pro insulin), Pemphigus Vulgaris (Desmoglein-3), Primary Biliary Cirrhosis (PDC-E2), Graves' disease (TSHR), Myasthenia gravis (MuSK), Sjögren's syndrome (M3R), neuromyelitis optica (AQP4), IdeS (for IgG and complement driven autoimmune disease), Goodpasture syndrome (α3(IV)NC1), and hemophilia), and/or allergies induced by specific allergens (e.g., food, inhaled allergens, etc.).

[00402] Autoimmune diseases that can be treated with hetero-EPOR agonists can include, for example, systemic lupus erythematosus (SLE), inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis), rheumatoid arthritis, multiple sclerosis, Grave's disease, CREST syndrome, systemic sclerosis, celiac disease, Achalasia, Addison's disease, Adult Still's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome, Autoimmune angioedema, Autoimmune dysautonomia, Autoimmune encephalomyelitis, Autoimmune hepatitis, Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune oophoritis, Autoimmune orchitis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune urticaria, Axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, Benign mucosal pemphigoid, Bullous pemphigoid, Castleman disease (CD), Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss Syndrome (CSS) or Eosinophilic Granulomatosis (EGPA), Cicatricial pemphigoid, Cogan's syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic esophagitis (EoE), Eosinophilic fasciitis, Erythema nodosum, Essential mixed cryoglobulinemia, Evans syndrome, Fibromyalgia, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Giant cell myocarditis, Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura (HSP), Herpes gestationis or pemphigoid gestationis (PG), Hidradenitis Suppurativa (HS) (Acne Inversa), Hypogammalglobulinemia, IgA Nephropathy, IgG4-related sclerosing disease, Immune thrombocytopenic purpura (ITP), Inclusion body myositis (IBM), Interstitial cystitis (IC), Juvenile arthritis, Juvenile diabetes (Type 1 diabetes), Juvenile myositis (JM), Kawasaki disease, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus, Lyme disease chronic, Meniere's

disease, Microscopic polyangiitis (MPA), Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal Motor Neuropathy (MMN) or MMNCB, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neonatal Lupus, Neuromyelitis optica, Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Palindromic rheumatism (PR), PANDAS, Paraneoplastic cerebellar degeneration (PCD), Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Pars planitis (peripheral uveitis), Parsonage-Turner syndrome, Pemphigus, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia (PA), POEMS syndrome, Polyarteritis nodosa, Polyglandular syndromes type I, II, III, Polymyalgia rheumatica, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progesterone dermatitis, Psoriasis, Psoriatic arthritis, Pure red cell aplasia (PRCA), Pyoderma gangrenosum, Raynaud's phenomenon, Reactive Arthritis, Reflex sympathetic dystrophy, Relapsing polychondritis, Restless legs syndrome (RLS), Retroperitoneal fibrosis, Rheumatic fever, Rheumatoid arthritis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjögren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome (SPS), Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia (SO), Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome (THS), Transverse myelitis, Type 1 diabetes, Type 2 diabetes, Ulcerative colitis (UC), Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vitiligo, and Vogt-Koyanagi-Harada Disease, etc. Other conditions that can be treated can include, for example, allergies (antibody associated allergies), amyloidosis, and certain forms of transplant rejection, etc. These and other conditions can be treated by administering one or more of the EPO analogs/engineered EPOs and/or antibodies described herein to a subject suffering from the undesired condition.

[00403] Activation of the hetero-EPOR with agonists for this receptor is beneficial in a number of neuronal and tissue stressed or injured conditions, e.g., Ischemia stroke, myocardial infarction, and Alzheimer's disease. Above-mentioned agonistic anti-hetero-EPOR, and/or EPO analogs/engineered EPOs that are agonists for the hetero-EPOR can be useful treatments in these conditions. Since EPO crosses the brain blood barrier (BBB), EPO analogs or engineered EPOs can be useful for CNS applications.

[00404] In some aspects, EPO analogs or engineered EPOs that are agonists for the homo-EPOR and do not bind or are antagonists of the hetero-EPOR, and/or anti-EPO antibodies that inhibit binding of EPO to the hetero-EPOR, and/or anti-hetero-EPOR antibodies that are antagonists for the hetero-EPOR can be used with or without erythropoietin-stimulating agents (ESA) for cancer patients in need to an ESA treatment. In this aspect, any cancer patient needing an ESA can be

provided the ESA combined with these EPO analogs/engineered EPOs, and/or anti-EPOR antibodies, and/or anti-EPO antibodies.

[00405] In some embodiments, the use of ESAs in cancer patients can be limited because of the risk of thromboembolic events and accelerated disease progression and shortened survival. In this embodiment, immune tolerance and/or suppression mediated by activation of the hetero-EPOR on tumor infiltrated myeloid cells including both dendritic cells (DCs) and macrophages (MΦs) can be a major contributor to the enhanced tumor growth and shortened survival seen in cancer patients treated with ESA. In this embodiment, a non-immune tolerogenic or non-suppressive ESA can activate the homo-EPOR and not the hetero-EPOR and can be used to treat anemia in cancer patients without promoting immune tolerance or suppression. Since the interaction site between EPO and the hetero-EPOR resides in helix B of EPO, and helix B is not involved in binding to the homo-EPOR, EPO analogs or engineered EPOs with changes in helix B that inhibit binding to the hetero-EPOR may not interfere with binding to the homo-EPOR, resulting in analogs with the desired receptor activity profile for this use of ESAs in cancer patients. Alternatively, an anti-EPO antibody that neutralizes (or inhibits) binding to the hetero-EPOR while not interfering with EPO binding to the homo-EPOR can be combined with EPO (or other potential ESAs) to provide a combination that has the desired profile of activities at the hetero-EPOR and homo-EPOR for treatment of anemia in cancer patients.

[00406] In some embodiments, anti-EPO antibodies, anti-hetero-EPOR antibodies, EPO analogs, engineered EPOs described herein that can act as agonists for homo-EPOR may not affect immune tolerance. In some embodiments, anti-EPO antibodies, anti-hetero-EPOR antibodies, EPO analogs, engineered EPOs described herein that can act as agonists for homo-EPOR may not affect differentiation of naïve T cells into effector T cells. In some embodiments, markers of effector T cells can include Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα). In some embodiments, anti-EPO antibodies, anti-hetero-EPOR antibodies, EPO analogs, engineered EPOs described herein that can act as agonists for homo-EPOR may not affect differentiation of a plurality of naïve T cells into a plurality of regulatory T cells. In some embodiments, markers for regulatory T cells can include Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4). In some embodiments, anti-EPO antibodies, anti-hetero-EPOR antibodies, EPO analogs, engineered EPOs described herein that can act as agonists for homo-EPOR may not affect immune response.

[00407] In some embodiments, anti-EPO antibodies, anti-hetero-EPOR antibodies, EPO analogs, engineered EPOs that can act as agonists for hetero-EPORs can induce antigen-specific

immune tolerance. In some embodiments, anti-EPO antibodies, anti-hetero-EPOR antibodies, EPO analogs, engineered EPOs that can act as agonists for hetero-EPORs can inhibit differentiation of naïve T cells into effector T cells. Examples of markers for effector T cells can include, but are not limited to, Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα). In some embodiments, anti-EPO antibodies, anti-hetero-EPOR antibodies, EPO analogs, engineered EPOs that can act as agonists for hetero-EPORs can promote differentiation of naïve T cells into regulatory T cells. Examples of markers for regulatory T cells can include, but are not limited to, Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4).

[00408] The therapeutically effective amount and the frequency of administration of, and the length of treatment with EPO analogs and/or engineered EPOs and/or anti-hetero-EPOR antibodies, and/or anti-EPO antibodies disclosed herein to treat an antibody-associated condition may depend on various factors, including the nature and severity of the condition, the potency of the antibody, the mode of administration, the age, body weight, general health, gender and diet of the subject, and the response of the subject to the treatment, and can be determined by the treating physician. The therapeutically effective amount of the antibody and/or analog can be from about 1, 5 or 10 mg to about 200 mg, from about 1, 5 or 10 mg to about 150 mg, from about 1, 5 or 10 mg to about 100 mg, or from about 1, 5 or 10 mg to about 50 mg, or as deemed appropriate by the treating physician, which can be administered in a single dose or in divided doses. The therapeutically effective amount of the antibody and/or analog can be about 1-5 mg, about 5-10 mg, about 10-20 mg, about 20-30 mg, about 30-40 mg, about 40-50 mg, about 50-100 mg, about 100-150 mg, or about 150-200 mg. The therapeutically effective amount of the antibody and/or analog can be about 1 mg, about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 150 mg, or about 200 mg. The therapeutically effective amount of the antibody and/or analog can be about 1-5 mg, about 5-10 mg, or about 10-50 mg. The therapeutically effective amount of the antibody and/or analog can be about 0.01-0.1 mg/kg, about 0.1-0.5 mg/kg, about 0.5-1 mg/kg, about 1-2 mg/kg, or about 2-3 mg/kg body weight, or as deemed appropriate by the treating physician. The therapeutically effective amount of the antibody and/or analog can be about 0.01-0.1 mg/kg, about 0.1-0.5 mg/kg, or about 0.5-1 mg/kg body weight.

[00409] In some aspects, an antibody and/or analog can be administered in any suitable frequency to treat a patient. The antibody or analog can be administered once daily, once every 2

days, once every 3 days, twice weekly, once weekly, once every 2 weeks, once every 3 weeks, once monthly, once every 6 weeks, once every 2 months, or once every 3 months, or as deemed appropriate by the treating physician. The antibody and/or analog can be administered once weekly or once every 2 weeks.

[00410] Likewise, an antibody and/or analog can be administered for any suitable length of time, or in any suitable total number of doses, to treat a patient. The antibody and/or analog is administered over a period of at least about 1 week, 2 weeks, 1 month (4 weeks), 6 weeks, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years or longer, or as deemed appropriate by the treating physician. The condition treated can be a chronic condition. A chronic condition can exist for, e.g., at least about 6 weeks or 2 months or longer. The antibody and/or analog can be administered over a period of at least about 6 weeks, about 2 months, about 3 months, or about 6 months. In some embodiments, 1, 2, 3, 4, 5, or 6 doses of the antibody and/or analog can be administered for the entire treatment regimen. In some embodiments, 1, 2, or 3 doses of the antibody and/or analog can be administered for the entire treatment regimen.

[00411] In some aspects, an antibody and/or analog can also be administered in an irregular manner to treat a patient. For example, the antibody and/or analog can be administered 1, 2, 3, 4, 5, or more times in a period of 1 week, 2 weeks, 3 weeks, 1 month, 2 months, or 3 months in an irregular manner. Furthermore, an antibody and/or analog can be taken *pro re nata* (as needed) for treatment of a patient. For instance, the antibody and/or analog can be administered 1, 2, 3, 4, 5, or more times, whether in a regular or irregular manner, for treatment of a patient. The appropriate dosage of, frequency of dosing of and length of treatment with the antibody and/or analog can be determined by the treating physician.

[00412] For a more rapid establishment of a therapeutic level of an antibody or analog at least one loading dose of the antibody and/or analog can be administered prior to the maintenance dose. A loading dose can be administered, followed by (i) one or more additional loading doses and then one or more therapeutically effective maintenance doses, or (ii) one or more therapeutically effective maintenance doses without an additional loading dose, as deemed appropriate by the treating physician. A loading dose of an antibody and/or analog can be larger (e.g., about 1.5, 2, 3, 4, or 5 times larger) than a subsequent maintenance dose and is designed to establish a therapeutic level of the drug more quickly. The one or more therapeutically effective maintenance doses can be any therapeutically effective amount described herein. The loading dose can be about 2 or 3 times larger than the maintenance dose. A loading dose can be administered on day 1, and a maintenance dose can be administered, e.g., once weekly or once every 2 weeks thereafter for the duration of treatment. The antibody and/or analog can be administered in a loading dose of about 2-10 mg, about 10-20 mg, or about 20-100 mg, or about

3-15 mg, about 15-30 mg, or about 30-150 mg, on day 1, followed by a maintenance dose of about 1-5 mg, about 5-10 mg, or about 10-50 mg once weekly or once every 2 weeks for the duration of treatment (e.g., for at least about 2, 3, or 6 months), where the loading dose is about 2 or 3 times larger than the maintenance dose and the antibody or analog is administered parenterally (e.g., intravenously, subcutaneously or intramuscularly).

[00413] In some embodiments, two (or more) loading doses of the antibody and/or analog can be administered prior to the maintenance dose. A first loading dose of the antibody and/or analog can be administered on day 1, a second loading dose can be administered, e.g., about 1 or 2 weeks later, and a maintenance dose can be administered, e.g., once weekly or once every 2 weeks thereafter for the duration of treatment. The first loading dose can be about 3 or 4 times larger than the maintenance dose, and the second loading dose can be about 2 times larger than the maintenance dose. The antibody and/or analog can be administered in a first loading dose of about 3-15 mg, about 15-30 mg, or about 30-150 mg, or about 4-20 mg, about 20-40 mg, or about 40-200 mg, on day 1, in a second loading dose of about 2-10 mg, about 10-20 mg, or about 20-100 mg about 1 or 2 weeks later, followed by a maintenance dose of about 1-5 mg, about 5-10 mg, or about 10-50 mg once weekly or once every 2 weeks for the duration of treatment (e.g., for at least about 2, 3 or 6 months), where the first loading dose can be about 3 or 4 times larger than the maintenance dose, the second loading dose can be about 2 times larger than the maintenance dose, and the antibody or analog can be administered parenterally (e.g., intravenously, subcutaneously or intramuscularly).

Combination Therapies with Additional Therapeutic Agents

[00414] The disclosure provides a method of treating a patient, comprising administering to a subject in need of treatment a therapeutically effective amount of an antibody and/or analog described herein, optionally in combination with an additional therapeutic agent. The disclosure further provides an antibody and/or analog described herein, or a composition comprising an antibody and/or analog described herein, for use as a medicament, optionally in combination with an additional therapeutic agent. In addition, the disclosure provides for the use of an antibody and/or analog described herein in the preparation of a medicament, optionally in combination with an additional therapeutic agent.

[00415] One or more additional therapeutic agents can optionally be used in combination with an antibody or analog to treat a patient. The optional additional therapeutic agent(s) can be administered to a subject concurrently with (e.g., in the same composition as the antibody and/or analog or in separate compositions) or sequentially to (before or after) administration of the antibody and/or analog. The optional additional therapeutic agent(s) can be selected from anti-cancer agents, immunotherapy agents, immunosuppressive agents, anti-inflammatory agents,

allergy drugs, and combinations thereof. One or more immunosuppressive agents can be used in combination with an antibody and/or analog to treat a patient.

[00416] Anti-cancer agents can include, for example, a chemotherapeutic, an antibody, an antibody-drug conjugate, an immunotherapy, a chimeric antigen receptor cell therapy, a radiotherapy, an alkylating agent, a plant alkaloid, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, and/or an anti-neoplastic.

[00417] Antibodies and antibody-drug conjugates (ADC) can bind to a tumor associated antigen. The drug component of the ADC can be, for example, a chemotherapeutic, a radionucleotide, an alkylating agent, a plant alkaloid, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, and/or an anti-neoplastic. The drug component of the ADC can be attached to the antibody through a linker which can be cleavable or non-cleavable in nature.

[00418] Alkylating agents can include, for example, mustard gas derivatives (e.g., mechlorethamine, cyclophosphamide, chlorambucil, melphalan, or ifosfamide), ethylenimines (e.g., thiotepa or hexamethylmelamine), alkylsulfonates (e.g., busulfan), hydrazines and triazines (e.g., altretamine, procarbazine, dacarbazine, or temozolomide), nitrosoureas (e.g., carmustine, lomustine or streptozocin), and metal salts (e.g., carboplatin, cisplatin, or oxaliplatin). Plant alkaloids can include, for example, Vinca alkaloids (e.g., vincristine, vinblastine, or vinorelbine), taxanes (e.g., paclitaxel or docetaxel), podophyllotoxins (e.g., etoposide or tenisopide), and camptothecan analogs (e.g., irinotecan or topotecan). Antitumor antibiotics can include, for example, anthracyclines (e.g., doxorubicin, daunorubicin, epirubicin, mixoantrone, or idarubicin), and chromomycins (e.g., dactinomycin or plicamycin). Antimetabolites can include, for example, folic acid antagonists (e.g., methotrexate), pyrimidine antagonists (e.g., 5-flurouracil, foxuridine, cytarabine, capecitabine, or gemcitabine), purine antagonists (e.g., 6-mercaptopurine or 6-thioguanine), and adenosine deaminase inhibitors (e.g., cladribine, fludarabine, nelarabine, or pentostatin). Topoisomerase inhibitors can include, for example, topoisomerase I inhibitors (e.g., irinotecan or topotecan) and topoisomerase II inhibitors (e.g., amsacrine, etoposide, etoposide phosphate, or teniposide). Anti-neoplastics can include, for example, ribonucleotide reductase inhibitors (e.g., hydroxyurea), adrenocortical steroid inhibitors (e.g., mitotane), enzymes (e.g., asparaginase or pegaspargase), antimicrotubule agents (e.g., estramustine), and retinoids (e.g., bexarotene, isotretinoin, or tretinoin).

[00419] Other chemotherapeutic drugs can include, for example, an anthracycline, a camptothecin, a tubulin inhibitor, a maytansinoid, a calicheamycin, a pyrrolobenzodiazepine dimer (PBD), an auristatin, a nitrogen mustard, an ethylenimine derivative, an alkyl sulfonate, a nitrosourea, a triazene, a folic acid analog, a taxane, a COX-2 inhibitor, a pyrimidine analog, a purine analog, an antibiotic, an enzyme inhibitor, an epipodophyllotoxin, a platinum coordination

complex, a vinca alkaloid, a substituted urea, a methyl hydrazine derivative, an adrenocortical suppressant, a hormone antagonist, an antimetabolite, an alkylating agent, an antimitotic, an anti-angiogenic agent, a tyrosine kinase inhibitor, an mTOR inhibitor, a heat shock protein (HSP90) inhibitor, a proteosome inhibitor, an HDAC inhibitor, a pro-apoptotic agent, and a combination thereof.

[00420] Other chemotherapeutic agents can include, for example, 5-fluorouracil, afatinib, aplidin, azaribine, anastrozole, anthracyclines, axitinib, AVL-101, AVL-291, bendamustine, bleomycin, bortezomib, bosutinib, bryostatin-1, busulfan, calicheamycin, camptothecin, carboplatin, 10-hydroxycamptothecin, carmustine, celecoxib, chlorambucil, cisplatinum, COX-2 inhibitors, irinotecan (CPT-11), SN-38, carboplatin, cladribine, camptothecans, crizotinib, cyclophosphamide, cytarabine, dacarbazine, dasatinib, dinaciclib, docetaxel, dactinomycin, daunorubicin, DM1, DM3, DM4, doxorubicin, 2-pyrrolinodoxorubicine (2-PDox), a pro-drug form of 2-PDox (pro-2-PDox), cyano-morpholino doxorubicin, doxorubicin glucuronide, endostatin, epirubicin glucuronide, erlotinib, estramustine, epidophyllotoxin, erlotinib, entinostat, estrogen receptor binding agents, etoposide (VP16), etoposide glucuronide, etoposide phosphate, exemestane, fingolimod, floxuridine (FUdR), 3',5'-O-dioleoyl-FudR (FUdR-dO), fludarabine, flutamide, farnesyl-protein transferase inhibitors, flavopiridol, fostamatinib, ganetespib, GDC-0834, GS-1101, gefitinib, gemcitabine, hydroxyurea, ibrutinib, idarubicin, idelalisib, ifosfamide, imatinib, lapatinib, lenolidamide, leucovorin, LFM-A13, lomustine, mechlorethamine, melphalan, mercaptopurine, 6-mercaptopurine, methotrexate, mitoxantrone, mithramycin, mitomycin, mitotane, monomethylauristatin F (MMAF), monomethylauristatin D (MMAD), monomethylauristatin E (MMAE), navelbine, neratinib, nilotinib, nitrosurea, olaparib, plicomycin, procarbazine, paclitaxel, PCI-32765, pentostatin, PSI-341, raloxifene, semustine, SN-38, sorafenib, streptozocin, SU11248, sunitinib, tamoxifen, temazolomide, transplatinum, thalidomide, thioguanine, thiotepa, teniposide, topotecan, uracil mustard, vatalanib, vinorelbine, vinblastine, vincristine, vinca alkaloids and ZD1839. In some embodiments, the chemotherapeutic agents can be SN-38.

[00421] Immunotherapy is directed at boosting the body's natural defenses in order to fight a disease, a cancer or tumor. It capitalizes on the substances made by the body, or artificially in a laboratory, to improve or restore immune system function. Immunotherapies can include checkpoint inhibitors that target immune checkpoints such as CTLA-4 and PD-1/PD-L1, key regulators of the immune system that dampen the immune response. Immunotherapies can comprise anti-CTLA-4 antibody, an anti-PD-1 antibody, an anti-PD-L1 antibody, or any combinations thereof. Examples of checkpoint inhibitors that may be used as payloads can include, for example, Nivolumab (Opdivo®), Pembrolizumab (Keytruda®), Cemiplimab

(Libtayo®), Atezolizumab (Tecentriq®), Avelumab (Bavencio®), Durvalumab (Imfinzi®), Ipilimumab (Yervoy®), Lirilumab, and BMS-986016. Nivolumab, Atezolizumab and Pembrolizumab can act at the checkpoint protein PD-1 and can inhibit apoptosis of anti-tumor immune cells. Some checkpoint inhibitors can prevent the interaction between PD-1 and its ligand PD-L1. Ipilimumab can act at CTLA4 and can prevent CTLA4 from downregulating activated T-cells in the tumor. Lirilumab can act at KIR and can facilitate activation of Natural Killer cells. BMS-986016 can act at LAG3 and can activate antigen-specific T-lymphocytes and can enhance cytotoxic T cell-mediated lysis of tumor cells. Other types of immunotherapies can include, for example, monoclonal antibodies, tumor-agnostic therapies, non-specific immunotherapies, oncolytic virus therapy, adoptive cell transfer, e.g., CAR T-cell therapy and cancer vaccines. Non-specific immunotherapies can include treatment with interferons or interleukins, molecules which can help the immune system fight cancer and either slow the growth of cancer cells or, in some instance, destroy the cancer. Immunotherapies may be given instead of traditional cancer treatments, such as chemotherapy or radiation therapy, or in combination with such treatments.

[00422] Adoptive cell therapy may use cells that have originated from the subject (autologous) or from another subject (allogeneic). Examples of such adoptive cell therapies can include, but are not limited to, engineered or non-engineered macrophages, engineered or non-engineered T-cells, and/or engineered or non-engineered natural killer cells. Accordingly, adoptive cell therapies can include tumor-Infiltrating Lymphocyte (TIL) therapy, Engineered T Cell Receptor (TCR) therapy, and/or natural killer (NK) cell therapy, the details of which will be well known to those skilled in the art (Adoptive cellular therapies: the current landscape, Rohaan et al. 2019, Virchows Arch. 474(4): 449-461, which is incorporated by reference in its entirety for all purposes).

[00423] Immunosuppressive agents can include, for example, anti-CD20 antibodies (e.g., rituximab), calcineurin inhibitors (e.g., tacrolimus, cyclosporine, etc.), antiproliferative agents or IDMH inhibitors (e.g., mycophenolate mofetil, mycophenolate sodium, azathioprine, leflunomide, etc.), mTOR inhibitors (e.g., Sirolimus, everolimus, etc.), steroids (e.g., corticosteroids such as prednisone, budesonide, prednisolone, etc.), and biologics (e.g., abatacept, adalimumab, anakinra, certolizumab, etanercept, infliximab, ixekizumab, natalizumab, rituximab, secukinumab, tocilizumab, uestekinumab, vedolizumab, basiliximab, daclizumab, muromonab). Biologics can also include, for example, CTLA 4 fusion proteins, anti-TNFα antibodies, IL-1 receptor antagonist protein, TNF receptor fusion proteins, anti-IL17A antibodies, anti-α4 integrin antibodies, anti-IL6 receptor antibodies, anti-p40 subunit of IL12/IL23 antibodies, anti-$\alpha_4\beta_7$ integrin antibodies, anti-CD25 antibodies, and anti-CD3 antibodies.

[00424] One or more anti-inflammatory agents can be used in combination with an antibody or analog to treat a patient. The one or more anti-inflammatory agents can include, for example, an inhibitor of a pro-inflammatory cytokine or a receptor therefor or the production thereof (e.g., TNF-α or/and IL-6 or IL-6R). Other anti-inflammatory agents can include, for example: non-steroidal anti-inflammatory drugs (NSAIDs), immunomodulators, immunosuppressants, anti-inflammatory cytokines and compounds that increase their production, inhibitors of pro-inflammatory cytokines or receptors therefor, inhibitors of the production of pro-inflammatory cytokines or receptors therefor, inhibitors of pro-inflammatory transcription factors or their activation or expression, inhibitors of pro-inflammatory prostaglandins (e.g., prostaglandin E_2 [PGE_2]) or receptors therefor (e.g., EP_3) or the production thereof, inhibitors of leukotrienes or receptors therefor or the production thereof, inhibitors of phospholipase A2 (e.g., secreted and cytosolic PLA2), suppressors of C-reactive protein (CRP) activity or level, mast cell stabilizers, phosphodiesterase inhibitors, specialized pro-resolving mediators (SPMs), other kinds of anti-inflammatory agents, and analogs, derivatives, fragments and salts thereof.

[00425] Non-steroidal anti-inflammatory drugs (NSAIDs) can include, but are not limited to, acetic acid derivatives, anthranilic acid derivatives (fenamates), enolic acid derivatives (oxicams), propionic acid derivatives, salicylates, COX-2-selective inhibitors, other kinds of NSAIDs, such as monoterpenoids (e.g., eucalyptol and phenols [e.g., carvacrol]), anilinopyridinecarboxylic acids (e.g., clonixin), sulfonanilides (e.g., nimesulide), and dual inhibitors of lipooxygenase (e.g., 5-LOX) and cyclooxygenase (e.g., COX-2) (e.g., chebulagic acid, licofelone, 2-(3,4,5-trimethoxyphenyl)-4-(N-methylindol-3-yl)thiophene, and di-*tert*-butylphenol-based compounds [e.g., DTPBHZ, DTPINH, DTPNHZ and DTPSAL]); and analogs, derivatives and salts thereof.

[00426] The glucocorticoid class of corticosteroids can have anti-inflammatory and immunosuppressive properties. Glucocorticoids can include, but are not limited to, hydrocortisone types, halogenated steroids, carbonates, and analogs, derivatives and salts thereof.

[00427] The optional additional therapeutic agent(s) independently can be administered in any suitable mode. Potential modes of administration can include, but are not limited to, oral, parenteral (including intradermal, subcutaneous, intramuscular, intravascular, intravenous, intraarterial, intraperitoneal, intramedullary, intrathecal and topical), intracavitary, and topical (including dermal/epicutaneous, transdermal, mucosal, transmucosal, intranasal [e.g., by nasal spray or drop], intraocular [e.g., by eye drop], pulmonary [e.g., by oral or nasal inhalation], buccal, sublingual, rectal [e.g., by suppository] and vaginal [e.g., by suppository]). In some embodiments, the optional additional therapeutic agent(s) independently can be administered orally or parenterally (e.g., intravenously, subcutaneously or intramuscularly).

[00428] One or more anti-allergy agents can be used in combination with an antibody or analog to treat a patient. Such anti-allergy agents can include, for example, antihistamines (e.g., cetirizine, fexofenadine, levocetirizine, loratidine, bormpheniramine, chlorpheniramine, celmastine, diphenhydramine, ketotifen, naphazoline, pheniramine, desloratadine, azelastine, epinastine, olopatadine), decongestants (e.g., pseudoephedrine, phenylephrine, oxymetazoline), steroids (e.g., beclomethasone, ciclesonide, fluticasone furoate, mometasone, budesonide, triamcinolone, dexamethasone, loteprednol, prednisone epocrates), mast cell stabilizers (e.g., cromolyn sodium, lodoxamide-tromethamine, nedocromil, pemirolast), and leukotriene modifiers (e.g., monteleukast).

[00429] One or more anti-rejection drugs for a transplant can be used in combination with an agonist anti-hetero-EPOR antibody and/or EPO analogs/engineered EPOs that are agonists for the hetero-EPOR to treat a subject following a transplant procedure. Such anti-rejection drugs can include, for example, calcineurin inhibitors, antiproliferative agents or IDMH inhibitors, mTOR inhibitors, and steroids.

[00430] The optional additional therapeutic agent(s) independently can be administered in any suitable frequency, including, but not limited to, daily (1, 2 or more times per day), every two or three days, twice weekly, once weekly, every two weeks, every three weeks, monthly, every two months or every three months, or in an irregular manner or on an as-needed basis. The dosing frequency can depend on, e.g., the mode of administration chosen. The length of treatment with the optional additional therapeutic agent(s) can be determined by the treating physician and can independently be, e.g., at least about 1 day, 2 days, 3 days, 4 days, 1 week, 2 weeks, 3 weeks, 4 weeks (1 month), 6 weeks, 2 months, 3 months, 6 months, 1 year, 2 years, 3 years or longer.

Production of EPO Related Antibodies and EPO Analogs

[00431] The disclosure provides polynucleotides comprising nucleic acid sequences that encode EPO related antibodies (e.g., anti-EPO antibodies, anti-EPOR antibodies, or anti-CD131 antibodies), and/or EPO analogs/engineered EPOs described herein. A polynucleotide can comprise a nucleic acid sequence that encodes an EPO analog, an engineered EPO, or the V_H domain or/and the V_L domain of an anti-EPOR, an anti-CD131, or an anti-EPO mAb. A polynucleotide can comprise a nucleic acid sequence that encodes the EPO analog, the engineered EPO, or heavy chain or/and the light chain of an EPO related mAb (e.g., anti-EPO antibodies, anti-EPOR antibodies, or anti-CD131 antibodies).

[00432] The disclosure further provides constructs (which may also be called expression or cloning constructs) comprising nucleic acid sequences that encode EPO related antibodies or EPO analogs described herein. Suitable constructs include, but are not limited to, plasmids, cosmids, bacterial artificial chromosomes, yeast artificial chromosomes, lambda phages (e.g.,

those with lysogeny genes deleted), and viruses. A construct can be present in a cell episomally or integrated into a chromosome (either way the construct remains and is still a construct, a plasmid and/or a vector).

[00433] Various construct systems can be employed. One class of constructs utilize DNA elements derived from animal viruses such as adenovirus, baculovirus, bovine papilloma virus, polyoma virus, SV40 virus, vaccinia virus, and retroviruses (e.g., MMTV, MOMLV and rous sarcoma virus). Another class of constructs utilize RNA elements derived from RNA viruses such as eastern equine encephalitis virus, flaviviruses, and Semliki Forest virus.

[00434] A construct can comprise various other elements for optimal expression of mRNA in addition to a nucleic acid sequence that encodes, e.g., the V_H domain or/and the V_L domain, or the heavy chain or/and the light chain, of an EPO related mAb, or EPO analog/engineered EPO. For example, a construct can contain a transcriptional promoter, a promoter plus an operator, an enhancer, an open reading frame with or without intron(s) or/and exon(s), a termination signal, a splice signal, a secretion signal sequence or a selectable marker (e.g., a gene conferring resistance to an antibiotic or cytotoxic agent), or any combination or all thereof.

[00435] The disclosure also provides host cells comprising or expressing constructs that encode EPO related antibodies or EPO analog/engineered EPO described herein. Suitable host cells include, but are not limited to, eukaryotic cells, mammalian cells (e.g., BHK, CHO, COS, HEK293, HeLa, MDCKII and Vero cells), insect cells (e.g., Sf9 cells), yeast cells and bacterial cells (e.g., *E. coli* cells). The host cell can be a mammalian cell (e.g., a CHO cell or a HEK293 cell).

[00436] A host cell can comprise or express a construct that encodes the V_H domain or the V_L domain, or the heavy chain or the light chain, of an EPO related mAb or EPO analog. A host cell can comprise or express a single construct that encodes the EPO analog, or the V_H domain and the V_L domain, or the heavy chain and the light chain, of an EPO related mAb. The same host cell or separate host cells can comprise or express a construct that encodes the V_H domain or the heavy chain of an EPO related mAb, and a separate construct that encodes the V_L domain or the light chain of the mAb.

[00437] A construct can be transfected or introduced into a host cell by any method known in the art. Transfection agents and methods include without limitation calcium phosphate, cationic polymers (e.g., DEAE-dextran and polyethylenimine), dendrimers, fugene, cationic liposomes, electroporation, sonoporation, cell squeezing, gene gun, viral transfection and retroviral transduction.

[00438] Methods and conditions for culturing transfected host cells and recovering the recombinantly produced EPO related antibody or EPO analog/engineered EPO are known in the

art, and may be varied or optimized depending on, e.g., the particular expression vector or/and host cell employed. EPO analogs/engineered EPOs, or the V_H domain or/and the V_L domain, or the heavy chain or/and the light chain, of an EPO related mAb can be recombinantly produced. The heavy chain and the light chain of an EPO related antibody whole IgG1, IgG2 or IgG4, or the heavy chain and the light chain of an EPO related Fab fragment optionally fused with a protracting moiety, are recombinantly produced.

Numbered Embodiments

1. A method, comprising the steps of: administering an EPO analog to a patient, wherein the patient has a cancer, wherein the EPO analog is an antagonist for a hetero-EPOR; and binding the EPO analog to the hetero-EPOR thereby inhibiting the hetero-EPOR.
2. The method of embodiment 1, wherein the hetero-EPOR is on an immune cell.
3. The method of embodiment 2, wherein the immune cell is a macrophage.
4. The method of embodiment 2, wherein the immune cell is a dendritic cell.
5. The method of embodiment 2, wherein the immune cell is a T-cell.
6. The method of embodiment 5, wherein the T-cell is a cytotoxic T-cell.
7. The method of embodiment 2, wherein the immune cell is a natural killer cell.
8. The method of embodiment 2, wherein the immune cell is a B cell.
9. The method of embodiment 1, wherein the hetero-EPOR is on an endothelial cell.
10. The method of embodiment 1, wherein the binding of the EPO analog to the hetero-EPOR overcomes an immune tolerogenic state.
11. The method of embodiment 1, wherein the binding of the EPO analog to the hetero-EPOR overcomes an immune suppressive state.
12. The method of embodiment 1, wherein the cancer is a colon cancer, a breast cancer, a lung cancer, a brain cancer, or a melanoma.
13. The method of embodiment 1, further comprising the step of administering an anticancer agent.
14. The method of embodiment 13, wherein the anticancer agent is a chemotherapeutic, an anticancer antibody, an antibody-drug conjugate, an immunotherapy, a chimeric antigen receptor cell therapy, a radiotherapy, an alkylating agent, a plant alkaloid, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, or an anti-neoplastic.
15. A method, comprising the steps of: administering an anti-hetero-EPOR antibody to a patient, wherein the patient has a cancer, wherein the anti-hetero-EPOR antibody is an antagonist for a hetero-EPOR; and binding the anti-hetero-EPOR antibody to the hetero-EPOR thereby inhibiting the hetero-EPOR.

16. The method of embodiment 15, wherein the hetero-EPOR is on an immune cell.

17. The method of embodiment 16, wherein the immune cell is a macrophage.

18. The method of embodiment 16, wherein the immune cell is a dendritic cell.

19. The method of embodiment 16, wherein the immune cell is a T-cell.

20. The method of embodiment 19, wherein the T-cell is a cytotoxic T-cell.

21. The method of embodiment 16, wherein the immune cell is a natural killer cell.

22. The method of embodiment 16, wherein the immune cell is a B cell.

23. The method of embodiment 15, wherein the hetero-EPOR is on an endothelial cell.

24. The method of embodiment 15, wherein the binding of the anti-hetero-EPOR antibody to the hetero-EPOR overcomes an immune tolerogenic state.

25. The method of embodiment 15, wherein the binding of the anti-hetero-EPOR antibody to the hetero-EPOR overcomes an immune suppressive state.

26. The method of embodiment 15, wherein the cancer is a colon cancer, a breast cancer, a lung cancer, a brain cancer, or a melanoma.

27. The method of embodiment 15, further comprising the step of administering an anticancer agent.

28. The method of embodiment 27, wherein the anticancer agent is a chemotherapeutic, an anticancer antibody, an antibody-drug conjugate, an immunotherapy, a chimeric antigen receptor cell therapy, a radiotherapy, an alkylating agent, a plant alkaloid, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, or an anti-neoplastic.

29. A method, comprising the steps of: administering an anti- EPO antibody to a patient, wherein the patient has a cancer, wherein the anti- EPO antibody inhibits binding of an EPO to a hetero-EPOR; and binding the anti- EPO antibody to the EPO thereby inhibiting the hetero-EPOR.

30. The method of embodiment 29, wherein the hetero-EPOR is on an immune cell.

31. The method of embodiment 30, wherein the immune cell is a macrophage.

32. The method of embodiment 30, wherein the immune cell is a dendritic cell.

33. The method of embodiment 30, wherein the immune cell is a T-cell.

34. The method of embodiment 33, wherein the T-cell is a cytotoxic T-cell.

35. The method of embodiment 30, wherein the immune cell is a natural killer cell.

36. The method of embodiment 30, wherein the immune cell is a B cell.

37. The method of embodiment 29, wherein the hetero-EPOR is on an endothelial cell.

38. The method of embodiment 29, wherein the binding of the anti-EPO antibody to the EPO overcomes an immune tolerogenic state.

39. The method of embodiment 29, wherein the binding of the anti- EPO antibody to the EPO overcomes an immune suppressive state.

40. The method of embodiment 29, wherein the cancer is a colon cancer, a breast cancer, a lung cancer, or a melanoma.

41. The method of embodiment 29, further comprising the step of administering an anticancer agent.

42. The method of embodiment 41, wherein the anticancer agent is a chemotherapeutic, an anticancer antibody, an antibody-drug conjugate, an immunotherapy, a chimeric antigen receptor cell therapy, a radiotherapy, an alkylating agent, a plant alkaloid, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, or an anti-neoplastic.

43. A method, comprising the steps of: administering an EPO analog to a patient, wherein the EPO analog is an agonist for a hetero-EPOR; and binding the EPO analog to the hetero-EPOR thereby promoting a negative immune modulation in the patient.

44. The method of embodiment 43, wherein the negative immune modulation is an immunosuppressed state.

45. The method of embodiment 44, further the step of transplanting an organ, a bone marrow, or a plurality of stem cells for a plurality of circulating cells.

46. The method of embodiment 43, further comprising the step of administering a specific antigen, and wherein the negative immune modulation is an immunotolerogenic state to the antigen.

47. The method of embodiment 46, wherein the specific antigen is a recombinant protein, an antigen associated with an autoimmune disease, or an allergen.

48. The method of embodiment 43, wherein the patient has an autoimmune disease.

49. The method of embodiment 48, wherein the autoimmune disease is a rheumatoid arthritis, a systemic lupus erythematosus, or a multiple sclerosis.

50. The method of embodiment 43, wherein the patient has a systemic chronic inflammation.

51. A method, comprising the steps of: administering an anti-hetero-EPOR antibody to a patient, wherein the anti-hetero-EPOR antibody is an agonist for a hetero-EPOR; and binding the anti-hetero-EPOR antibody to the hetero-EPOR thereby promoting a negative immune modulation in the patient.

52. The method of embodiment 51, wherein the negative immune modulation is an immunosuppressed state.

53. The method of embodiment 51, further comprising the administration of an antigen, and wherein the negative immune modulation is an immunotolerogenic state to the antigen.

54. The method of embodiment 51, further the step of transplanting an organ, a bone marrow, or a plurality of stem cells for a plurality of circulating cells.

55. The method of embodiment 51, further comprising the step of administering a specific antigen so that the patient becomes immune tolerant to the antigen.

56. The method of embodiment 55, wherein the specific antigen is a recombinant protein, an antigen associated with an autoimmune disease, or an allergen.

57. The method of embodiment 51, wherein the patient has an autoimmune disease.

58. The method of embodiment 58, wherein the autoimmune disease is a rheumatoid arthritis, a systemic lupus erythematosus, or a multiple sclerosis.

59. The method of embodiment 51, wherein the patient has a systemic chronic inflammation.

60. A method, comprising the steps of: administering an EPO analog to a patient, wherein the patient has a cancer, wherein the EPO analog is an agonist for a homo-EPOR and does not activate the hetero-EPOR; and binding the EPO analog to the homo-EPOR thereby promoting erythropoiesis in the patient.

61. The method of embodiment 60, wherein the cancer is a colon cancer, a breast cancer, a lung cancer, a brain cancer, or a melanoma.

62. The method of embodiment 60, further comprising the step of administering an anticancer agent.

63. The method of embodiment 62, wherein the anticancer agent is a chemotherapeutic, an anticancer antibody, an antibody-drug conjugate, an immunotherapy, a chimeric antigen receptor cell therapy, a radiotherapy, an alkylating agent, a plant alkaloid, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, or an anti-neoplastic.

64. The method of embodiment 60, wherein the EPO analog is an antagonist for the hetero-EPOR.

65. The method of embodiment 60, wherein the EPO analog does not bind the hetero-EPOR.

66. A method, comprising the steps of: administering an anti-homo-EPOR antibody to a patient, wherein the patient has a cancer, wherein the anti-homo-EPOR antibody is an agonist for a homo-EPOR and does not activate the hetero-EPOR; and binding the anti-homo-EPOR antibody to the homo-EPOR thereby promoting erythropoiesis in the patient.

67. The method of embodiment 66, wherein the cancer is a colon cancer, a breast cancer, a lung cancer, a brain cancer, or a melanoma.

68. The method of embodiment 66, further comprising the step of administering an anticancer agent.

69. The method of embodiment 68, wherein the anticancer agent is a chemotherapeutic, an anticancer antibody, an antibody-drug conjugate, an immunotherapy, a chimeric antigen receptor

cell therapy, a radiotherapy, an alkylating agent, a plant alkaloid, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, or an anti-neoplastic.

70. The method of embodiment 66, wherein the anti-homo-EPOR antibody is an antagonist for the hetero-EPOR.

71. The method of embodiment 66, wherein the anti-homo-EPOR antibody does not bind the hetero-EPOR.

72. A method, comprising the steps of: administering an anti-EPO antibody to a patient, wherein the patient has a cancer, wherein the anti-EPO antibody inhibits an EPO from binding a hetero-EPOR, wherein the EPO bound to the anti-EPO antibody can bind to a homo-EPOR; binding the anti-EPO antibody to the EPO; and binding the EPO or a complex of the EPO and the anti-EPO antibody to the homo-EPOR, thereby promoting erythropoiesis in the patient.

73. The method of embodiment 72, wherein the cancer is a colon cancer, a breast cancer, a lung cancer, a brain cancer, or a melanoma.

74. The method of embodiment 72, further comprising the step of administering an anticancer agent.

75. The method of embodiment 74, wherein the anticancer agent is a chemotherapeutic, an anticancer antibody, an antibody-drug conjugate, an immunotherapy, a chimeric antigen receptor cell therapy, a radiotherapy, an alkylating agent, a plant alkaloid, an antitumor antibiotic, an antimetabolite, a topoisomerase inhibitor, or an anti-neoplastic.

76. The method of embodiment 72, further comprising the step of administering an EPO to the patient.

77. A method, comprising the steps of: administering a nucleic acid encoding an EPO analog to a patient, wherein the EPO analog is an agonist for a hetero-EPOR; expressing nucleic acid encoding the EPO analog in a cell in a patient after the cell has taken up the nucleic acid; secreting the EPO analog from the cell; and binding the EPO analog to the hetero-EPOR thereby promoting a negative immune modulation in the patient.

78. The method of embodiment 77, wherein the negative immune modulation is an immunosuppressed state.

79. The method of embodiment 77, further comprising the administration of an antigen, and wherein the negative immune modulation is an immunotolerogenic stated to the antigen.

80. The method of embodiment 79, wherein the antigen is administered as a nucleic acid encoding the antigen.

81. The method of embodiment 80, wherein the nucleic acid is an RNA.

82. The method of embodiment 77, further the step of transplanting an organ, a bone marrow, or a plurality of stem cells for a plurality of circulating cells.

83. The method of embodiment 77, further comprising the step of administering a specific antigen so that the patient becomes immune tolerant to the antigen.

84. The method of embodiment 83, wherein the specific antigen is a recombinant protein, an antigen associated with an autoimmune disease, or an allergen.

85. The method of embodiment 77, wherein the patient has an autoimmune disease.

86. The method of embodiment 85, wherein the autoimmune disease is a rheumatoid arthritis, a systemic lupus erythematosus, or a multiple sclerosis.

87. The method of embodiment 77, wherein the patient has a systemic chronic inflammation.

88. The method of embodiment 77, wherein the nucleic acid is part of a composition with a lipid nanoparticle.

89. A method, comprising the steps of: administering an siRNA to a patient, wherein the siRNA binds to mRNA encoding an EPOR, a CD131 or an EPO, wherein the patient has a cancer; and decreasing expression of the EPOR, the CD131, or the EPO, thereby inhibiting activation of a hetero-EPOR.

90. A method, comprising the steps of: administering an siRNA to a patient, wherein the siRNA binds to mRNA encoding an EPOR, a CD131 or an EPO; and decreasing expression of the EPOR, the CD131, or the EPO, thereby reducing a negative immune modulation in the patient.

91. The method of claim 90, wherein the negative immune modulation is an immunosuppressed state.

92. The method of embodiment 90, wherein an antigen is administered with the siRNA, and wherein the negative immune modulation is an immunotolerogenic state for the antigen.

93. The method of embodiment 92, wherein the antigen is administered as a nucleic acid encoding the antigen.

94. The method of embodiment 93, wherein the nucleic acid is an RNA.

95. A method, comprising the steps of: administering a HIF inhibitor to a patient; and reducing expression of a hetero-EPOR thereby reducing a negative immune modulation in the patient.

96. The method of embodiment 95, wherein the negative immune modulation is an immunosuppressed state.

97. The method of embodiment 95, wherein an antigen is administered with the PHD inhibitor, and wherein the negative immune modulation is an immunotolerogenic state for the antigen.

98. A method, comprising the steps of: administering a PHD inhibitor to a patient; and increasing expression of a hetero-EPOR, thereby promoting a negative immune modulation in the patient.

99. The method of embodiment 98, wherein the negative immune modulation is an immunosuppressed state.

100. The method of embodiment 98, wherein an antigen is administered with the PHD inhibitor, and wherein the negative immune modulation is an immunotolerogenic state for the antigen.

Other Embodiments

[00439] In some aspects, provided herein is a composition comprising an antibody or a functional fragment thereof, wherein: (i) said antibody or said functional fragment thereof selectively binds to a target comprising an erythropoietin (EPO) protein, an EPO receptor subunit, a CD131 subunit, or a combination thereof; (ii) binding of said antibody or said functional fragment thereof to said target prevents (a) formation of an EPO protein-hetero-EPO receptor complex, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit, (b) formation of a hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or (c) activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit; and (iii) said antibody or said functional fragment thereof comprises an antigen binding domain.

[00440] In some embodiments, said antigen binding domain comprises a heavy chain variable region (VH) comprising a VH complementarity determining region 1 (VH-CDR1) sequence, a VH-CDR2 sequence, and a VH-CDR3 sequence; and a light chain variable region (VL) comprising a VL-CDR1 sequence, a VL-CDR2 sequence, and a VL-CDR3 sequence; a VH and a kappa chain variable regions (VK); or a VH and a lamda chain variable regions.

[00441] In some embodiments, said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit subunit inhibits immune tolerance.

[00442] In some embodiments, said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit promotes differentiation of a plurality of naïve T cells into a plurality of effector T cells. In some embodiments, said plurality of effector T cells expresses Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin,

Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα). In some embodiments, said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit inhibits differentiation of a plurality of naïve T cells into a plurality of regulatory T cells. In some embodiments, said plurality of regulatory T cells expresses Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4). In some embodiments, said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit increases a plurality of progenitor exhausted T cells. In some embodiments, said plurality of progenitor exhausted T cells expresses Cluster of Differentiation 44 (CD44), Signaling lymphocyte activation molecule family member 6 (SLAMF6) or T cell factor 1 (TCF1).

[00443] In some embodiments, said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit stimulates immune response in cancer. In some embodiments, said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit renders cancer cells sensitive to an immune checkpoint inhibitor. In some embodiments, said immune checkpoint inhibitor comprises a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) inhibitor, a Programmed Death 1 (PD-1) inhibitor, or a Programmed Death Ligand 1 (PD-L1) inhibitor. In some embodiments, said CTLA-4 inhibitor comprises an anti-CTLA-4 antibody. In some embodiments, said PD-1 inhibitor comprises an anti-PD-1 antibody. In some embodiments, said PD-L1 inhibitor comprises an anti-PD-L1 antibody. In some embodiments, said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit attenuates tumor growth.

[00444] In some embodiments, said antibody or said functional fragment thereof is an IgG, an IgM, an IgE, an IgA, an IgD, is derived therefrom, or a combination thereof. In some embodiments, said antibody or said functional fragment thereof comprises a monoclonal antibody, a grafted antibody, a chimeric antibody, a human antibody, a humanized antibody, or a combination thereof.

[00445] In some embodiments, said antigen binding domain comprises a Fab, a Fab', a (Fab')2, a variable fragment (Fv), a single chain variable fragment (scFv), a scFv-Fc, a Fab-Fc, a VHH, a non-antibody scaffold, or a combination thereof. In some embodiments, said antigen binding domain is isolated, recombinant, synthetic, or a combination thereof.

[00446] In some embodiments, said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 63-250. In some embodiments, said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 815-943. In some embodiments, said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1331-1466.

[00447] In some embodiments, said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 251-438. In some embodiments, said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to a sequence of SEQ ID NOs: 944-1072. In some embodiments, said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1467-1602.

[00448] In some embodiments, said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 439-626. In some embodiments, said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1073-1201. In some embodiments, said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1603-1738. In some embodiments, said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 627-814. In some embodiments, said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1202-1330. In some embodiments, said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1739-1874.

[00449] In some aspects, provided herein is a composition comprising a nucleic acid sequence encoding said antibody or said functional fragment thereof of any of the compositions described herein. In some aspects, provided herein is a cell comprising any of the compositions described herein.

[00450] In some aspects, provided herein is a method of treating a disease or a condition in a subject in need thereof, said method comprising administering to said subject any of the

compositions described herein. In some embodiments, said method further comprises inhibiting immune tolerance in said subject. In some embodiments, said inhibiting immune tolerance comprises increasing immune response to a vaccine, when said vaccine is administered to said subject. In some embodiments, said inhibiting immune tolerance comprises increasing immune response to a viral or bacterial infection in said subject. In some embodiments, wherein said inhibiting immune tolerance comprises increasing immune response to an antigen produced by cancer. In some embodiments, said disease or said condition comprises a cancer or an infection. In some embodiments, said cancer comprises a lung cancer, a breast cancer, a colon cancer, a brain cancer, a melanoma, hepatocarcinoma, or a liver cancer. In some embodiments, said cancer is a melanoma. In some embodiments, said cancer is a liver cancer. In some embodiments, said cancer is a colon cancer. In some embodiments, said cancer is a breast cancer.

[00451] In some aspects, provided herein is a method treating cancer, wherein said method comprises administering a composition or a derivative thereof to a subject having cancer or at risk of having cancer, wherein said composition or said derivative thereof inhibits a hetero-erythropoietin (EPO) receptor activity in said subject. In some embodiments, said hetero-EPO receptor is expressed on a myeloid cell.

[00452] In some aspects, provided herein, is a composition comprising an antibody or a functional fragment thereof, wherein: (i) said antibody or said functional fragment thereof selectively binds to a target comprising an erythropoietin (EPO) protein, an EPO receptor subunit, a CD131 subunit, or a combination thereof; (ii) binding of said antibody or said functional fragment thereof to said target promotes (a) formation of an EPO protein-hetero-EPO receptor complex, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit, (b) formation of a hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or (c) activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit; and (iii) said antibody or said functional fragment thereof comprises an antigen binding domain.

[00453] In some embodiments, said antigen binding domain comprises a heavy chain variable region (VH) comprising a VH complementarity determining region 1 (VH-CDR1) sequence, a VH-CDR2 sequence, and a VH-CDR3 sequence; and a light chain variable region (VL) comprising a VL-CDR1 sequence, a VL-CDR2 sequence, and a VL-CDR3 sequence; a VH and a kappa chain variable regions (VK); or a VH and a lamda chain variable regions.

[00454] In some embodiments, said promoting formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit induces antigen-specific immune tolerance. In some

embodiments, said promoting formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit inhibits differentiation of a plurality of naïve T cells into a plurality of effector T cells. In some embodiments, said plurality of effector T cells expresses Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα). In some embodiments, said promoting formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit promotes differentiation of a plurality of naïve T cells into a plurality of regulatory T cells. In some embodiments, said plurality of regulatory T cells expresses Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4).

[00455] In some embodiments, said antibody or said functional fragment thereof does not affect a homo-EPO receptor activity. In some embodiments, said antibody or said functional fragment thereof does not bind a homo-EPO receptor comprising at least two EPO receptor subunits.

[00456] In some embodiments, said promoting formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit reduces immune reaction when administered to a subject having an autoimmune disease or a subject with a transplanted organ. In some embodiments, said transplanted organ comprises bone marrow, kidney, liver, lung, or heart. In some embodiments, said autoimmune disease comprises a rheumatoid arthritis, a systemic lupus erythematosus, or a multiple sclerosis.

[00457] In some embodiments, said promoting formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit reduces systemic chronic inflammation when administered to a subject suffering from a systemic chronic inflammation.

[00458] In some embodiments, said antibody or said functional fragment thereof is an IgG, an IgM, an IgE, an IgA, an IgD, is derived therefrom, or a combination thereof. In some embodiments, said antibody or said functional fragment thereof comprises a monoclonal antibody, a grafted antibody, a chimeric antibody, a human antibody, a humanized antibody, or a combination thereof. In some embodiments, said antigen binding domain comprises a Fab, a

Fab', a (Fab')2, a variable fragment (Fv), a single chain variable fragment (scFv), a scFv-Fc, a Fab-Fc, a VHH, a non-antibody scaffold, or a combination thereof. In some embodiments, said antigen binding domain is isolated, recombinant, synthetic, or a combination thereof.

[00459] In some embodiments, said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 63-250. In some embodiments, said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 815-943. In some embodiments, said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1331-1466.

[00460] In some embodiments, said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 251-438. In some embodiments, said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 944-1072. In some embodiments, said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1467-1602.

[00461] In some embodiments, said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 439-626. In some embodiments, said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1073-1201. In some embodiments, said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1603-1738. In some embodiments, said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 627-814. In some embodiments, said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1202-1330. In some embodiments, said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1739-1874.

[00462] In some embodiments, said antibody further comprises a binding domain that selectively binds to an antigen associated with tumor, a cell surface marker associated with immune cells, or a signaling molecule associated with immune cells. In some embodiments, said antigen associated with tumor is selected from the group consisting of PD1, HER2, EpCAM, CEA, CEACAM5, EGFR, CD33, CD19, CD20, CD22, and any combinations thereof. In some embodiments, said cell surface marker is DEC205, XCR1, or XCL1. In some embodiments, said signaling molecule is PD-L1, Tim3, or TREM2.

[00463] In some aspects, provided herein, is a composition comprising a nucleic acid sequence encoding said antibody or said functional fragment thereof of any of the compositions described herein. In some aspects, provided herein, is a cell comprising any of the compositions described herein.

[00464] In some aspects, provided herein, is a method of treating a disease or a condition in a subject in need thereof, said method comprising administering to said subject any of the compositions described herein. In some embodiments, said disease or said condition comprises an autoimmune disease. In some embodiments, said subject has received or is to receive an organ transplant or a foreign therapeutics protein.

[00465] In some aspects, provided herein, is composition for administering to a subject having cancer or chronic infection condition, wherein said composition or derivative thereof inhibits erythropoietin (EPO) receptor activity in a myeloid cell in said subject.

[00466] In some embodiments, said composition is an antibody or a functional fragment thereof. In some embodiments, said myeloid cell is selected from the group consisting of a macrophage, a monocyte, a dendritic cell, a basophil, a neutrophil, and an eosinophil. In some embodiments, said EPO receptor comprises a homo-EPO receptor comprising at least two EPO receptor subunits or a hetero-EPO receptor comprising an EPO receptor subunit and a CD131 subunit. In some embodiments, said EPO receptor is a hetero-EPO receptor comprising a EPO receptor subunit and a CD131 subunit. In some embodiments, said composition is an antibody or a functional fragment thereof. In some embodiments, said composition is a soluble fragment of a EPO receptor. In some embodiments, said soluble fragment is capable of binding to EPO to form a complex. In some embodiments, said complex is capable of preventing a EPO receptor activity. In some embodiments, said composition or derivative thereof comprises an engineered erythropoietin (EPO) protein, wherein said engineered EPO protein inhibits a hetero-erythropoietin (EPO) receptor activity in a myeloid cell.

[00467] In some aspects, provided herein, is a composition comprising an engineered erythropoietin (EPO) protein, wherein said engineered EPO protein inhibits a hetero-erythropoietin (EPO) receptor activity in a myeloid cell. In some embodiments, wherein said engineered EPO protein comprises at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A, R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A.

[00468] In some aspects, provided herein is a composition comprising an engineered erythropoietin (EPO) protein, wherein: said engineered EPO protein comprises at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A , R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A; and said engineered EPO protein inhibits a hetero-erythropoietin (EPO) receptor activity in a myeloid cell.

[00469] In some embodiments, said composition or derivative thereof inhibits immune tolerance. In some embodiments, said composition or derivative thereof promotes immune response. In some embodiments, said composition or derivative thereof promotes differentiation of a plurality of naïve T cells into a plurality of effector T cells. In some embodiments, said plurality of effector T cells expresses Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα). In some embodiments, said composition or derivative thereof inhibits differentiation of a plurality of naïve T cells into a plurality of regulatory T cells. In some embodiments, said plurality of regulatory T cells expresses Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4).

[00470] In some embodiments, said composition or derivative thereof increases a plurality of progenitor exhausted T cells. In some embodiments, said plurality of progenitor exhausted T cells expresses Cluster of Differentiation 44 (CD44), Signaling lymphocyte activation molecule family member 6 (SLAMF6) or T cell factor 1 (TCF1).

[00471] In some embodiments, said composition or derivative thereof stimulates immune response in cancer. In some embodiments, said composition or derivative thereof renders cancer cells sensitive to an immune checkpoint inhibitor. In some embodiments, said immune checkpoint inhibitor comprises a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) inhibitor, a Programmed Death 1 (PD-1) inhibitor, or a Programmed Death Ligand 1 (PD-L1) inhibitor. In some embodiments, said CTLA-4 inhibitor comprises an anti-CTLA-4 antibody. In some embodiments, said PD-1 inhibitor comprises an anti-PD-1 antibody. In some embodiments, said PD-L1 inhibitor comprises an anti-PD-L1 antibody. In some embodiments, said composition or derivative thereof reduces a size of said cancer or attenuates the growth of said cancer.

[00472] In some embodiments, said at least one amino acid substitution comprises R103A. In some embodiments, said at least one amino acid substitution comprises E72A. In some embodiments, said at least one amino acid substitution comprises Q58A. In some embodiments, said at least one amino acid substitution comprises L69A. In some embodiments, said at least one amino acid substitution comprises L80A. In some embodiments, said at least one amino acid substitution comprises N147K or R103A. In some embodiments, said at least one amino acid substitution comprises R150E or R103A. In some embodiments, said at least one amino acid substitution comprises Q65A or E72R. In some embodiments, said at least one amino acid substitution comprises Q65A, E72R, or N83A. In some embodiments, said at least one amino acid substitution comprises K20A, K45A, or K52A. In some embodiments, said at least one

amino acid substitution comprises K140A or K152A. In some embodiments, said at least one amino acid substitution comprises K140A, K152A, or K154A. In some embodiments, said at least one amino acid substitution comprises K20A, K45A, K52A, K140A, K152A, or K154A. In some embodiments, the position is determined by alignment with SEQ ID NO: 1.

[00473] In some embodiments, said engineered EPO further comprises an amino acid modification comprising carbamylation or PEGylation. In some embodiments, said amino acid modification comprises carbamylation of one or more lysine residues.

[00474] In some embodiments, said engineered EPO protein has a lower binding affinity to a hetero-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution. In some embodiments, said hetero-EPO receptor activity comprises phosphorylation of an intracellular domain of said hetero-EPO receptor, or activation of Janus tyrosine kinase 2 (Jak2), Signal transducer and activator of transcription 5 (Stat5), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), or Mammalian target of rapamycin (mTOR). In some embodiments, said hetero-EPO receptor activity is measured by a western blotting, an enzyme-linked immunosorbant assay (ELISA), a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or a combination thereof.

[00475] In some embodiments, said engineered EPO protein has a higher binding affinity to a homo-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution. In some embodiments, said engineered EPO protein has the same level of binding affinity to a homo-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution. In some embodiments, said engineered EPO protein binds to a homo-EPO receptor with a binding affinity that is lower than a binding affinity to a hetero-EPO receptor. In some embodiments, said engineered EPO protein does not affect or inhibit a homo-EPO receptor activity.

[00476] In some embodiments, said engineered EPO has a half-life of at least 5 hours. In some embodiments, said engineered EPO protein comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1973-2019. In some embodiments, said myeloid cell comprises a granulocyte, a monocyte, a macrophage, or a dendritic cell.

[00477] In some aspects, provided herein is a composition comprising a nucleic acid sequence encoding said EPO protein of any of the compositions described herein. In some aspects, provided herein is a cell comprising any of the compositions described herein.

[00478] In some aspects, provided herein is a method of treating a disease or a condition in a subject in need thereof, said method comprising administering to said subject any of the compositions described herein or any of the cell described herein.

[00479] In some aspects, provided herein is a method of treating anemia in a subject in need thereof, said method comprising administering to said subject any of the compositions described herein or any of the cells described herein, wherein said subject has a cancer. In some embodiments, said cancer comprises a lung cancer, a breast cancer, a colon cancer, a brain cancer, a melanoma, hepatocarcinoma, or a liver cancer. In some embodiments, said cancer is a melanoma. In some embodiments, said cancer is a liver cancer. In some embodiments, said cancer is a colon cancer. In some embodiments, said cancer is a breast cancer.

[00480] In some aspects, provided herein, is a composition comprising an engineered erythropoietin (EPO) protein, wherein said engineered EPO protein promotes a hetero-erythropoietin (EPO) receptor activity to reduce immune response, wherein said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit. In some embodiments, said engineered EPO protein comprises at least one amino acid modification and/or at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A , R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A.

[00481] In some aspects, provided herein is a composition comprising an engineered erythropoietin (EPO) protein, wherein: said engineered EPO protein comprises at least one amino acid modification and/or at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A , R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A; and said engineered EPO protein promotes a hetero-erythropoietin (EPO) receptor activity, wherein said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit.

[00482] In some embodiments, said promoting said hetero-EPO receptor activity reduces immune reaction when administered to a subject having an autoimmune disease or a subject with a transplanted organ. In some embodiments, said transplanted organ comprises bone marrow, kidney, liver, lung, or heart. In some embodiments, said autoimmune disease comprises a rheumatoid arthritis, a systemic lupus erythematosus, or a multiple sclerosis. In some embodiments, said promoting said hetero-EPO receptor activity reduces systemic chronic inflammation when administered to a subject suffering from a systemic chronic inflammation.

[00483] In some embodiments, said promoting said hetero-EPO receptor activity induces antigen-specific immune tolerance. In some embodiments, said promoting said hetero-EPO receptor activity inhibits differentiation of a plurality of naïve T cells into a plurality of effector T cells. In some embodiments, said plurality of effector T cells expresses Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα). In some embodiments, said promoting said hetero-EPO receptor activity promotes differentiation of a plurality of naïve T cells into a plurality of regulatory T cells. In some embodiments, said plurality of regulatory T cells expresses Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4).

[00484] In some embodiments, said at least one amino acid substitution comprises Q65A. In some embodiments, said at least one amino acid substitution comprises N83A. In some embodiments, the amino acid residue position is determined by alignment with SEQ ID NO: 1.

[00485] In some embodiments, said at least one amino acid modification comprises a chemical modification comprising carbamylation or PEGylation. In some embodiments, said at least one amino acid modification comprises carbamylation of one or more lysine residues. In some embodiments, said at least one amino acid modification comprises carbamylation of all lysine residues.

[00486] In some embodiments, said engineered EPO protein has higher binding affinity to said hetero-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

[00487] In some embodiments, said hetero-EPO receptor activity comprises phosphorylation of an intracellular domain of said hetero-EPO receptor, or activation of Janus tyrosine kinase 2 (Jak2), Signal transducer and activator of transcription 5 (Stat5), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), or Mammalian target of rapamycin (mTOR). In some embodiments, said hetero-EPO receptor activity is measured by a western blotting, an enzyme-linked immunosorbant assay (ELISA), a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or a combination thereof.

[00488] In some embodiments, said engineered EPO protein has a lower binding affinity to a homo-EPO receptor comprising at least two EPO receptor subunits, compared to a corresponding wild type EPO protein without said at least one amino acid substitution. In some embodiments, said engineered EPO protein has the same level of binding affinity to a homo-EPO receptor

compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

[00489] In some embodiments, said engineered EPO protein does not affect or inhibits said homo-EPO receptor activity. In some embodiments, said homo-EPO receptor activity comprises phosphorylation of an intracellular domain of said homo-EPO receptor, or activation of Janus tyrosine kinase 2 (Jak2), Signal transducer and activator of transcription 5 (Stat5), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), or Mammalian target of rapamycin (mTOR). In some embodiments, said homo-EPO receptor activity is measured by a western blotting, an enzyme-linked immunosorbant assay (ELISA), a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or a combination thereof.

[00490] In some embodiments, said engineered EPO has a half-life of at least 5 hours. In some embodiments, said engineered EPO protein comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1973-2019.

[00491] In some embodiments, said hetero-EPOR is on an immune cell. In some embodiments, said immune cell comprises a macrophage, a dendritic cell, a T-cell, a natural killer cell, or a B cell. In some embodiments, said T-cell comprises a cytotoxic T-cell. In some embodiments, said hetero-EPOR is on an endothelial cell.

[00492] In some aspects provided herein, is a composition comprising a nucleic acid sequence encoding said EPO protein of any of the compositions described herein. In some aspects provided herein, is a cell comprising any of the compositions described herein.

[00493] In some aspects provided herein, is a method of treating a disease or a condition in a subject in need thereof, said method comprising administering to said subject any of the compositions described herein or any of the cells described herein. In some embodiments, said disease or said condition comprises an autoimmune disease. In some embodiments, said subject has received or is to receive an organ transplant or a foreign therapeutics protein.

[00494] In some aspects, provided herein is a composition comprising an engineered erythropoietin (EPO) protein, said engineered EPO protein promotes a homo-erythropoietin (EPO) receptor activity and has reduced effect on a hetero-EPO receptor activity, wherein said homo-EPO receptor comprises at least two EPO receptor subunits and said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit. In some embodiments, said engineered EPO protein comprises at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A,

E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A , R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A.

[00495] In some aspects, provide herein is a composition comprising an engineered erythropoietin (EPO) protein, wherein: said engineered EPO protein comprises at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A , R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A; and said engineered EPO protein promotes a homo-erythropoietin (EPO) receptor activity and has reduced effect on a hetero-EPOR receptor activity or decreases a hetero-EPO receptor activity, wherein said homo-EPO receptor comprises at least two EPO receptor subunits and said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit.

[00496] In some embodiments, said engineered EPO has no substantial effect on said hetero-EPO receptor activity. In some embodiments, said engineered EPO inhibits said hetero-EPO receptor activity. In some embodiments, said engineered EPO protein comprises at least one amino acid substitution comprising E72A, Q 58A, L69A, or L80A. In some embodiments, said engineered EPO protein comprises Q65A, E72R, and N83A amino acid substitutions. In some embodiments, said engineered EPO protein comprises K20A, K45A, and K52A amino acid substitutions. In some embodiments, the position is determined by alignment with SEQ ID NO: 1.

[00497] In some embodiments, said engineered EPO further comprises an amino acid modification comprising carbamylation or PEGylation. In some embodiments, said amino acid modification comprises carbamylation of one or more lysine residue.

[00498] In some embodiments, said engineered EPO protein has higher binding affinity to said homo-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

[00499] In some embodiments, said homo-EPO receptor activity comprises phosphorylation of an intracellular domain of said homo-EPO receptor, or activation of Janus tyrosine kinase 2 (Jak2), signal transducer and activator of transcription 5 (Stat5), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), or Mammalian target of rapamycin (mTOR). In some embodiments, said homo-EPO receptor activity is measured by a western blotting, an enzyme-linked immunosorbant assay (ELISA), a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or a combination thereof.

[00500] In some embodiments, said engineered EPO protein has the same level of binding affinity to said hetero-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

[00501] In some embodiments, said hetero-EPOR activity comprises phosphorylation of an intracellular domain of said homo-EPO receptor, or activation of Janus tyrosine kinase 2 (Jak2), signal transducer and activator of transcription 5 (Stat5), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), or Mammalian target of rapamycin (mTOR). In some embodiments, said hetero-EPO receptor activity is measured by a western blotting, an enzyme-linked immunosorbant assay (ELISA), a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or a combination thereof.

[00502] In some embodiments, said engineered EPO protein does not affect immune tolerance. In some embodiments, said engineered EPO protein does not affect differentiation of a plurality of naïve T cells into a plurality of effector T cells. In some embodiments, said plurality of effector T cells expresses Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα). In some embodiments, said engineered EPO protein does not affect differentiation of a plurality of naïve T cells into a plurality of regulatory T cells. In some embodiments, said plurality of regulatory T cells expresses Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4). In some embodiments, said engineered EPO protein does not affect immune response.

[00503] In some embodiments, said engineered EPO has a half-life of at least 5 hours. In some embodiments, said engineered EPO protein comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1973-2019. In some embodiments, said homo-EPOR is on an erythroid progenitor cell.

[00504] In some aspects, provided herein is a composition comprising a nucleic acid sequence encoding said EPO protein of any of the compositions described herein. In some aspects, provided herein is a cell comprising any of the compositions described herein.

[00505] In some aspects, provided herein is a method of treating a disease or a condition in a subject in need thereof, said method comprising administering to said subject any of the compositions described herein or any of the cells described herein. In some embodiments, the disease or the condition comprises a cancer.

[00506] In some aspects, provided herein is a method of treating anemia in a subject in need thereof, said method comprising administering to said subject any of the compositions described

herein or any of the cells described herein. In some embodiments, said cancer comprises a lung cancer, a breast cancer, a colon cancer, a brain cancer, a melanoma, or a liver cancer. In some embodiments, said cancer is a melanoma. In some embodiments, said cancer is a liver cancer. In some embodiments, said cancer is a colon cancer. In some embodiments, said cancer is a breast cancer.

[00507] In some aspects, provided herein, is a composition for administering to a subject having cancer or chronic infection condition, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound inhibits an erythropoietin (EPO) receptor activity in a myeloid cell in said subject.

[00508] In some embodiments, the EPO receptor is a hetero-EPO receptor. In some embodiments, the hetero-EPO receptor comprises an EPO subunit and a CD131 subunit. In some embodiments, the hetero-EPO receptor is on a macrophage, monocyte, dendritic cell, basophil, neutrophil, or eosinophil. In some embodiments, the compound is an inhibitor of hypoxia-inducible factor (HIF), IL-1α, IL-1β, TNF-α, IL-6, estrogen receptors, phospholipase C-γ1, or promotion of the Cbl/p85/Episin-1 pathway. In some embodiments, the compound is an inhibitor of hypoxia-inducible factor (HIF), IL-1α, IL-1β, TNF-α, IL-6, or estrogen receptors. In some embodiments, the compound is an inhibitor of hypoxia-inducible factor (HIF).

[00509] In some embodiments, the compound is CAY10585 (LW6), Chetomin, Chrysin, Dimethyl-bisphenol A, Echinomycin, 2-Methoxyestradiol (2ME2), SYP-5, PX-478 2HCl, KC7F2, GN44028, Verucopeptin, FM19G11, PT2399, PT2385, Belzutifan, HIF-2a-IN-1, HIF-2a-IN-2, HIF-2a-IN-3, HIF-2a-IN-4, TC-S 700, IDF-11774, Paeoniflorin, Emetine hydrochloride, Glucosamine, PX12, Vitexin, BAY 87-2243, Lificiguat (YC-1), Vorinostat, Tanespimycin, Silibinin, diallyl trisulfide (DATS), Herboxidiene (GEX1A), Celastrol, Phenethyl isothiocyanate (PEITC), Gliotoxin, Sulforaphane, Acriflavin, Emodin, Cardenolide, 3,3'-Diindolylmethane (DIM), Pseudolaric acid-B (PAB), Bavachinin, Andrographolide, Isoliquiritigenin, Wondonin, Thymoquinone, or Curcumin.

[00510] The composition of nay one of claims 224 to 231, wherein the compound is CAY10585 (LW6), Chetomin, Chrysin, Dimethyl-bisphenol A, Echinomycin, 2-Methoxyestradiol (2ME2), SYP-5, PX-478 2HCl, KC7F2, GN44028, Verucopeptin, FM19G11, PT2399, PT2385, Belzutifan, HIF-2a-IN-1, HIF-2a-IN-2, HIF-2a-IN-3, HIF-2a-IN-4, TC-S 700, IDF-11774, Paeoniflorin, Emetine hydrochloride, Glucosamine, PX12, Vitexin, BAY 87-2243, Lificiguat (YC-1), Vorinostat, or Tanespimycin. In some embodiments, the compound is Chetomin, Echinomycin, PT2399, Belzutifan, Vorinostat, or Tanespimycin. In some embodiments, the compound is Silibinin, diallyl trisulfide (DATS), Herboxidiene (GEX1A), Celastrol, Phenethyl isothiocyanate (PEITC), Gliotoxin, Sulforaphane, Acriflavin, Emodin, Cardenolide, 3,3'-

Diindolylmethane (DIM), Pseudolaric acid-B (PAB), Bavachinin, Andrographolide, Isoliquiritigenin, Wondonin, Thymoquinone, or Curcumin.

[00511] In some aspects, provided herein is a composition for administering to a subject having cancer or chronic infection condition, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound inhibits an erythropoietin (EPO) receptor activity so that an immune-checkpoint blockade resistance is reversed in said subject.

[00512] In some embodiments, the EPO receptor is a hetero-EPO receptor. In some embodiments, the hetero-EPO receptor comprises an EPO subunit and a CD131 subunit. In some embodiments, the immune-checkpoint blockade is an inhibitor of CTLA-4, PD-1, or PD-L1. In some embodiments, the inhibitor of CTLA-4, PD-1, or PD-L1 is Nivolumab, Pembrolizumab, Cemiplimab, Atezolizumab, Avelumab, Durvalumab, Ipilimumab, Lirilumab, and BMS-986016. In some embodiments, the hetero-EPO receptor is on a macrophage, monocyte, dendritic cell, basophil, neutrophil, or eosinophil. In some embodiments, the compound is an inhibitor of hypoxia-inducible factor (HIF), IL-1α, IL-1β, TNF-α, IL-6, estrogen receptors, phospholipase C-γ1, or Cbl/p85/Episin-1 pathway. In some embodiments, the compound is an inhibitor of hypoxia-inducible factor (HIF), IL-1α, IL-1β, TNF-α, or IL-6. In some embodiments, the compound is an inhibitor of hypoxia-inducible factor (HIF).

[00513] In some embodiments, the compound is CAY10585 (LW6), Chetomin, Chrysin, Dimethyl-bisphenol A, Echinomycin, 2-Methoxyestradiol (2ME2), SYP-5, PX-478 2HCl, KC7F2, GN44028, Verucopeptin, FM19G11, PT2399, PT2385, Belzutifan, HIF-2a-IN-1, HIF-2a-IN-2, HIF-2a-IN-3, HIF-2a-IN-4, TC-S 700, IDF-11774, Paeoniflorin, Emetine hydrochloride, Glucosamine, PX12, Vitexin, BAY 87-2243, Lificiguat (YC-1), Vorinostat, Tanespimycin, Silibinin, diallyl trisulfide (DATS), Herboxidiene (GEX1A), Celastrol, Phenethyl isothiocyanate (PEITC), Gliotoxin, Sulforaphane, Acriflavin, Emodin, Cardenolide, 3,3'-Diindolylmethane (DIM), Pseudolaric acid-B (PAB), Bavachinin, Andrographolide, Isoliquiritigenin, Wondonin, Thymoquinone, or Curcumin.

[00514] In some embodiments, the compound is CAY10585 (LW6), Chetomin, Chrysin, Dimethyl-bisphenol A, Echinomycin, 2-Methoxyestradiol (2ME2), SYP-5, PX-478 2HCl, KC7F2, GN44028, Verucopeptin, FM19G11, PT2399, PT2385, Belzutifan, HIF-2a-IN-1, HIF-2a-IN-2, HIF-2a-IN-3, HIF-2a-IN-4, TC-S 700, IDF-11774, Paeoniflorin, Emetine hydrochloride, Glucosamine, PX12, Vitexin, BAY 87-2243, Lificiguat (YC-1), Vorinostat, or Tanespimycin. In some embodiments, the compound is Chetomin, Echinomycin, PT2399, Belzutifan, Vorinostat, or Tanespimycin. In some embodiments, the compound is Silibinin, diallyl trisulfide (DATS), Herboxidiene (GEX1A), Celastrol, Phenethyl isothiocyanate (PEITC), Gliotoxin, Sulforaphane, Acriflavin, Emodin, Cardenolide, 3,3'-Diindolylmethane (DIM),

Pseudolaric acid-B (PAB), Bavachinin, Andrographolide, Isoliquiritigenin, Wondonin, Thymoquinone, or Curcumin.

[00515] In some aspects, provided herein is a composition for administering to a subject, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound promotes a hetero-erythropoietin (EPO) receptor activity, wherein said hetero-EPO receptor comprises a EpoR subunit and CD131 subunit, so that immune tolerance to an antigen is increased in said subject; and wherein said compound has no substantial effect on a homo-EPO receptor activity wherein said homo-EPO receptor comprises at least two EPO receptor subunits.

[00516] In some embodiments, the hetero-EPO receptor is on a macrophage, monocyte, dendritic cell, basophil, neutrophil, or eosinophil. In some embodiments, the compound is an inhibitor of HIF-Prolyl Hydroxylase (PHD), NHF-4, GATA factor, IL-17, AKT/NFkB/HIF1 pathway, estrogen receptor, Epithelial membrane protein 1 (EMP-1). In some embodiments, the compound is an inhibitor of HIF-Prolyl Hydroxylase (PHD), NHF-4, GATA factor, or IL-17. In some embodiments, the compound is an inhibitor of HIF-Prolyl Hydroxylase (PHD). In some embodiments, the compound is Roxadustat, Vadadustat, Enarodustat, Desidustat, Molidustat, Dimethyloxaloylglycine, Daprodustat, Prolyl Hydroxylase inhibitor 1, TM6089, TRC160334, PHD-1-IN-1, MK-8617, JNJ-42041935, TP0463518, IOX (JICL38), IOX4, IOX3 (FG-2216), Dencichin, HIF-PHD-IN-1, AKB-6899, VH298, M1001, ML228, Dimethyloxalylglycine (DMOG), Mitoxantrone, Angiotensin II (Ang II), or 17β-estradiol.

[00517] In some embodiments, the compound is Roxadustat, Vadadustat, Enarodustat, Desidustat, Molidustat, Dimethyloxaloylglycine, Daprodustat, Prolyl Hydroxylase inhibitor 1, TM6089, TRC160334, PHD-1-IN-1, MK-8617, JNJ-42041935, TP0463518, IOX (JICL38), IOX4, IOX3 (FG-2216), Dencichin, HIF-PHD-IN-1, AKB-6899, VH298, M1001, ML228, or Dimethyloxalylglycine (DMOG).

[00518] In some embodiments, the compound is Mitoxantrone, Angiotensin II (Ang II), or 17β-estradiol. In some embodiments, the compound is an EPOR agonist. In some embodiments, the compound is LG5640. In some embodiments, the immune tolerance is to a transplant organ or self-antigen. In some embodiments, the immune tolerance is to a transplant organ. In some embodiments, the immune tolerance is to an immunosuppressed state. In some embodiments, the immune tolerance is to a self-antigen. In some embodiments, the immune tolerance is to a self-antigen.

[00519] In some aspects, provided herein is a composition for administering to a subject having cancer, comprising an RNA interference (RNAi) molecule, wherein said RNAi binds to an RNA molecule that is selected from the group consisting of an mRNA molecule that encodes a

erythropoietin (EPO) protein, an mRNA molecule that encodes a EPO receptor subunit, an mRNA molecule that encodes a CD131 subunit, and any combination thereof; wherein upon administering said RNAi to said subject, said subject's tumor mass is reduced.

[00520] In some embodiments, the tumor mass is reduced to less than 0.5 cm^3. In some embodiments, the tumor mass is reduced to less than 0.2 cm^3. In some embodiments, the tumor mass is reduced to about 0.2 cm^3.

[00521] In some aspects, provided herein is a composition for administering to a subject having cancer, comprising a RNA interference (RNAi) molecule, wherein said RNAi binds to an RNA molecule that is selected from the group consisting of an mRNA molecule that encodes a erythropoietin (EPO) protein, an mRNA molecule that encodes a EPO receptor subunit, an mRNA molecule that encodes a CD131 subunit, and any combination thereof; wherein upon administering said RNAi to said subject, said subject's immune response is increased by inducing more effector T (Teff) cells.

[00522] In some embodiments, the cancer is hepatocarcinoma. In some embodiments, the RNAi reduces EPO half-life in a subject. In some embodiments, the RNAi reduces EPO levels in a subject.

[00523] In some embodiments, the reduced EPO half-life increases survival rate. In some embodiments, the survival rate is increased two-fold. In some embodiments, the RNAi is in a nanoparticle. In some embodiments, the nanoparticle is a lipid nanoparticle. In some embodiments, the RNAi molecule is a siRNA molecule, a miRNA molecule, an antisense RNA molecule, or a lncRNA molecule.

[00524] In some embodiments, the RNAi is an siRNA molecule. In some embodiments, the siRNA molecule has a sequence length of about 15 to about 30 nucleotides. In some embodiments, the siRNA molecule has a sequence length of about 21 to about 30 nucleotides. In some embodiments, the siRNA molecule is double-stranded or single stranded.

[00525] In some embodiments, the single stranded siRNA molecule comprises a nucleic acid sequence that is at least 80%, 85%, 90%, or 95% identical to at least one of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51,

SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62.

[00526] In some embodiments, the single stranded siRNA molecule comprises a nucleic acid sequence that is 100% identical to at least one of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62.

In some aspects, provided herein is a method for treating cancer in a subject, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising any one of single stranded siRNAs described herein to said subject in a dose and schedule sufficient to reduce an expression level of a erythropoietin (EPO) protein, a EPO receptor subunit, or a CD131 subunit.

[00527] All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference and are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited.

[00528] The following examples are intended only to illustrate the disclosure. Other assays, studies, processes, protocols, procedures, methodologies, reagents and conditions may alternatively be used as appropriate.

EXAMPLES

Example 1. EPO Analogs/engineered EPOs

[00529] Eight types of EPO analogs can be engineered. EPO analogs can bind the hetero-EPOR and not the homo-EPOR, and can be either agonists or antagonists of the hetero-EPOR. Other EPO analogs can bind the homo-EPOR and not the hetero-EPOR, and can be either agonists or antagonists of the homo-EPOR. EPO analogs can bind both the homo-EPOR and the hetero-EPOR and be agonists of both, antagonists of both, or agonist of one and antagonist of the other.

[00530] Human EPO analogs that bind the hetero-EPOR (as an agonist) and do not bind the homo-EPOR are engineered. These EPO analogs can be expressed as Fc fusion proteins. EPO mutations of K20E, T44I, K45I, V46A, F48G, R143A, R150A, R150Q, L155A, and L155N in the site 1 have been shown to lose the *in vitro* bioactivity against the homo-EPOR >5 times, whereas mutations of K45I, N147K, R150E, and G151A in the stie 1 have been shown to lose the activity >50 times. These mutations lead to much reduced affinity to homo-EPOR. These mutations do not affect helix B and may still bind to the hetero-EPOR.

[00531] EPO analogs that bind the hetero-EPOR (as an agonist) and bind the homo-EPOR (as an antagonist) are engineered. The EPO analogs with mutations that reduce activation of the homo-EPOR may allow binding. For example, EPO mutations of V11S, R14A, R14E, Y15I, K97A, K97E, S104A, L108A, and R110E in the site 2 have been shown to lose *the in vitro* bioactivity of the homo-EPOR >5 times, whereas mutations of R14Q, S100E, S100T, R103A, R103E, R103H, R103N, R103Q, S104I, and L108K in the site 2 have been shown to lose the activity >50 times. These mutations do not affect helix B and so these mutants should bind to the hetero-EPOR, and act as an antagonist of the homo-EPOR.

[00532] The mutations in the site 1 and 2 may be combined to make human EPO analogs that bind the hetero-EPOR (as an agonist) with or without binding to the homo-EPOR (as an antagonist). Other examples of EPO analogs that bind the hetero-EPOR (as an agonist) and have reduced binding or do not bind the homo-EPOR are the helix B peptides described above.

[00533] Human EPO analogs that bind the hetero-EPOR (as an antagonist) and do not bind the homo-EPOR are engineered. These EPO analogs can be expressed as Fc fusion proteins. The surface residues (Q58, E62, Q65, L69, E72, R76, A79, L80, N83, S84, and S85) in the helix B are expected to play important roles in interaction with the hetero-EPOR, and will be mutated. For example, the nucleic acid encoding helix B can be mutagenized using alanine scanning and/or saturation mutagenesis. The mutations that bind the hetero-EPOR and are reduced for activation of the hetero-EPOR (but still bind the hetero-EPOR) can be combined with mutations described above that reduce EPO analog binding to the homo-EPOR. The resulting EPO analog antagonizes the hetero-EPOR and has reduced binding or does not bind to the homo-EPOR.

[00534] EPO analogs that bind the homo-EPOR (as an agonist) and do not bind the hetero-EPOR are engineered. The helix B mutations described above are screened for mutations that reduce binding to the hetero-EPOR. These EPO analogs are agonists for the homo-EPOR and have reduced or no binding to the hetero-EPOR.

[00535] EPO analogs that bind the homo-EPOR (as an antagonist) and do not bind the hetero-EPOR are engineered. These EPO analogs can be expressed as Fc fusion proteins. The helix B mutations described above are screened for mutations that reduce binding to the hetero-EPOR.

These helix B mutations are combined with EPO mutations that reduce activation of the homo-EPOR but allow binding. For example, EPO mutations of V11S, R14A, R14E, Y15I, K97A, K97E, S104A, L108A, and R110E in the site 2 have been shown to lose the *in vitro* bioactivity >5 times, whereas mutations of R14Q, S100E, S100T, R103A, R103E, R103H, R103N, R103Q, S104I, and L108K in the site 2 have been shown to lose the activity >50 times. These EPO analogs retain affinity binding to homo-EPOR but lose the signaling activity, and so, can be antagonists of the homo-EPOR and the helix B mutations reduce binding to the hetero-EPOR.

[00536] Human EPO analogs that bind the homo-EPOR (as an agonist) and the hetero-EPOR (as an antagonist) are engineered. These EPO analogs can be expressed as Fc fusion proteins. The EPO analogs with mutations in helix B that reduce activity but allow binding can be antagonists of the hetero-EPOR. EPO helixes A, C and D are not changed and so can act as an agonist at the homo-EPOR.

[00537] Human EPO analogs that bind the homo-EPOR (as an antagonist) and the hetero-EPOR (as an antagonist) are engineered. The EPO analogs with mutations in helix B that reduce activity but allow binding can be antagonists of the hetero-EPOR. These mutations are combined with EPO mutations that result in antagonists for homo-EPOR. For example, EPO mutations of V11S, R14A, R14E, Y15I, K97A, K97E, S104A, L108A, and R110E in the site 2 have been shown to lose the *in vitro* bioactivity >5 times, whereas mutations of R14Q, S100E, S100T, R103A, R103E, R103H, R103N, R103Q, S104I, and L108K in the site 2 have been shown to lose the activity >50 times. These mutations are combined with the helix B mutations that make hetero-EPOR antagonists, and so, these EPO analogs should antagonize both the hetero-EPOR and the homo-EPOR.

Example 2. Expression of human EPO Analogs/Engineered EPOs

[00538] cDNAs for each human EPO analog are synthesized and fused with the human immunoglobulin Fc domain or albumin. The fusion proteins are cloned into a mammalian expression vector under the control of a hEF1α promoter. A linker maybe inserted between the domains. The vector contains a Puromycin resistant gene for mammalian cell selection and an Ampicillin resistant gene for *E. coli* propagation. All fusion proteins contained a signal peptide at the N-terminal for secretion out of the cells. Expression vector plasmids are used to transfect 100 ml of 293 cells transiently. The culture media is harvested after 72 hours and the fusion protein is purified.

Example 3. *In Vitro* Binding by EPO Analogs/Engineered EPOs

[00539] The ability of the EPO analogs to bind to the extracellular domains of the homo-EPOR, hetero-EPOR, or CD131/CD131 is determined in a functional ELISA. Soluble homo-EPOR, CD131/CD131, and hetero-EPOR (Sino Biological) are coated on a standard ELISA. The wells

are blocked with 2% BSA. Dilutions of the EPO analogs are added to the plates and incubated. After washing, the bound EPO analogs are detected using biotinylated polyclonal anti-EPO (R&D Systems) followed by streptavidin HRP conjugate or other appropriate secondary antibodies. After washing, TMB reagent (Sigma) is added and OD absorption at 450 nm is measured in a plate reader.

Example 4. Cell Binding by EPO Analogs/Engineered EPOs

[00540] The EPO analogs are used to stain cells expressing one (or more) of the homo-EPOR, hetero-EPOR, and/or CD131/CD131. 293 cells expressing EPOR, CD131, or EPOR and CD131 are generated by lentiviral transduction. Expression of the homo-EPOR or CD131/CD131, and/or the hetero-EPOR are confirmed by staining with commercial anti-EPOR and anti-CD131 antibodies. Human leukemic UT-7 cells, erythroleukemia TF-1cells, monocytic THP-1 cells are known to express EPOR and CD131 and will be used to confirm binding of the EPO analogs. Murine erythroid progenitor cells expressing the homo-EPOR and myeloid cells expressing the hetero-EPOR can also be used to confirm the binding of the EPO analogs. For the staining experiments, the cells are incubated with the EPO analogs. After washing, the bound EPO variants are detected using biotinylated polyclonal anti-EPO (R&D Systems) followed by streptavidin PE conjugate or other appropriate secondary antibodies. Staining of the EPO analogs is quantified.

Example 5. Activation of Homo-EPOR and Hetero-EPOR

[00541] The receptor expressing cells (homo-EPOR, hetero-EPOR, or CD131/CD131) are serum-starved for 24 hours, and then incubated in the culture medium containing the EPO analogs. Cell lysates are made from these cells, and the lysates are then subjected to Western blotting analysis with antibodies against phosphorylated EPOR, CD131, JAK2, and STAT5. Alternatively, activation of the receptors can be assessed with a STAT5-luciferase reporter. Activation of homo-EPOR, hetero-EPOR, or CD131/CD131 by ligand binding leads to phosphorylation of the intracellular domains of the receptor and downstream JAK2 and STAT5.

Example 6. Erythropoiesis Stimulating Activity and/or Antigen Specific Tolerance Activity of EPO Analogs

[00542] Proliferation of human erythroleukemia TF-1 cells depends on activation of the homo-EPOR. TF-1 cells are treated with different concentrations of EPO analogs, and TF-1 cell proliferation is characterized.

[00543] Induction of FoxP3$^+$ T_{reg} is mediated by activation of the hetero-EPOR on antigen presenting cells. Human peripheral blood CD4$^+$ T-cells are co-cultured with CD14$^+$ monocytes under anti-CD3 stimulation. In the presence of both IL-2 and EPO analogs, induction of Fox3$^+$ Tregs is characterized.

[00544] Separately, murine bone marrow derived EpoR+ and EpoR- cDC1 cells are loaded with OVA *in vitro* and co-cultured with naïve OTII cells in the presence of EPO analogs. *De novo* induction of FoxP3 T-cells are used to indicate antigen-specific tolerance promoting activities of EPO analogs.

Example 7. Pharmacokinetic Assessment of EPO Analogs

[00545] EPO analogs are injected subcutaneously (s.c.) or intraperitoneally (i.p.) into mice. Serum samples are taken at different time points for up to 10 days after the injection. Concentrations of the fusion protein in the serum samples are determined using a sandwiched ELISA assay.

Example 8. Erythropoietic Activity of EPO Analogs

[00546] Normocythemic mice are injected s.c. or i.p. with EPO analogs. The mice can be engineered to express human homo-EPOR in progenitor red blood cells. Blood samples are taken at various times. The hemoglobulin levels, hematocrit and reticulocyte counts are determined. The frequencies of the erythroid progenitors in bone marrow and spleen are measured, and the effects of different EPO analogs on the medullary and extramedullary erythropoiesis are determined, respectively. Expansion of the splenic EPOR+ cDC1s and red pulp MΦs is used to assess activation of the hetero-EPOR.

Example 9. Induction of Immune Tolerance by EPO Analogs in Transplantation

[00547] BALB/c recipients of C57BL/6J heart transplants are treated with EPO analogs that are agonists for the hetero-EPOR/CD131 or vehicle control for the initial 3 days after transplantation, with or without a single perioperative dose of CTLA4-Ig. Vehicle-treated recipients reject the grafts in about a week, while tolerogenic EPO analogs prolong graft survival for >14 days. CTLA4-Ig prolongs graft survival to about 6 weeks and combination therapy with CTLA4-Ig plus tolerogenic EPO analogs act synergistically to prolong graft survival to over 10 weeks.

[00548] In addition, since autologous apoptotic cells preceding transplantation enhance survival in lethal murine graft-versus-host (GvHD) models, tolerogenic EPO analogs are administrated together with extracorporeal photopheresis (ECP) induced apoptotic cells to prevent GvHD and enhance survival. BALB/c mice are injected with C57BL/6J T-cell–depleted BM (TCD-BM) plus conventional T-cells only or with prior injection of ECP-treated BALB/c cells. ECP treatment 48 hours prior to bone marrow transplantation (BMT) in C57BL/6→BALB/c mice improves survival. Tolerogenic EPO analogs are given for 10 days, starting from the same day as ECP-induced apoptotic cell administration. The group treated with ECP only is expected to exhibit a significant improvement in survival (median survival of about 5 weeks versus about 1 week) with surviving mice showing no signs of GvHD. Co-administration of tolerogenic EPO analogs is expected to further improve survival.

Example 10. Enhancement of Antigen-Specific Tolerance with EPO Analogs

[00549] Specific antigens can be delivered to dendritic cells (DCs), e.g., type 1 conventional dendritic cells (cDC1) by antibody mediated antigen delivery through anti-DEC205 (Bonifaz, 2002) which specifically recognizes and binds DC. Ovalbumin (OVA) or MOG (Myelin oligodendrocyte glycoprotein) is conjugated to anti-mouse DEC205 (DEC205, Bio X Cell) for delivery to cDC1s.

[00550] C57BL/6J mice are immunized with anti-DEC205 conjugated with OVA (0.3–30 μg) s.c. in the footpad, and simultaneously injected s.c. or i.p. with EPO analogs that are agonists of the hetero-EPOR, or PBS (control). *De novo* induction of FoxP3 T-cells in the adoptively transferred naïve cells in the draining lymph node and spleen are used to indicate an antigen-specific tolerance effect on CD4+ T cells, i.e., increased induction of Foxp3+ T_{regs}. Similarly, the fate of adoptively transferred OTI cells will be monitored to check the antigen-specific tolerance promoting effect on CD8+ T cells, i.e., more potent deletion of antigen-specific CD8+ T cells.

[00551] In addition, animals are rechallenged with OVA in complete freund's adjuvant (CFA) on day 8. Serum samples are taken at day 15 and day 30, and anti-OVA IgG titers are determined by ELISA. Challenging the mice with an unrelated antigen such as Keyhole Limpet Hemocyanin (KLH) and measurement of anti-KLH specific IgG antibody titers serve as a control for the OVA-specific tolerance achieved by anti-DEC205 specific OVA delivery.

[00552] In addition, anti-DEC205 conjugated with MOG is administrated s.c. into the footpad of C57BL/6J mice together with EPO analogs that are agonists of the hetero-EPOR. Other Ag-delivery sites will also be tested, such as lung. MOG-specific 2D2 TCR transgenic naïve CD4+ T cells are adoptively transferred 1 day before antigen immunization with EPO analog co-administration. De novo FoxP3 T cell induction from the adoptively transferred congenic 2D2 cells is analyzed to indicate antigen-specific tolerance inducing activity. To evaluate the *in vivo* suppressive function of anti-DEC205-delivery antigen and EPO analogs, antigen-specific FoxP3+ 2D2 cells are sorted by flow cytometry for testing in *in vitro* antigen-specific T-cell immune suppression assays.

[00553] Moreover, experimental autoimmune encephalomyelitis (EAE) is induced in mice immunized with anti-DEC205-MOG with or without EPO analogs that are agonists for the hetero-EPOR. The severity score of EAE is determined over time. The EPO analogs promote antigen-specific tolerance and ameliorate EAE.

Example 11. Antigen Specific Tolerance Induced *In Vivo* with Lipid Nanoparticles (LNP) Encapsulating mRNAs Encoding Antigen

[00554] Nanoparticles injected into the circulatory or lymphatic systems are predominantly captured by macrophages in the reticuloendothelial system (for example, in liver, spleen), and

can also be captured by precursor DCs present in the blood and immature DCs residing in peripheral tissues (Cifuentes-Rius et al, Nat Nanotechnol. 2021:16(1):37-46). mRNAs encoding specific antigens, e.g., ovalbumin or MOG, are encapsulated in LNP. EPO analogs that are agonists of the hetero-EPOR are administered as recombinant proteins or co-encapsulated with the mRNA encoding the antigen. *In vivo* antigen-specific tolerance-enhancing effects are monitored as described in Example 10.

[00555] Alternatively, mRNA encoding the EPO analogs that are agonists of the hetero-EPOR are used, instead of the EPO analogs, to generate the LNP to induce antigen-specific tolerance.

Example 12. Antibodies Against the Hetero-EPOR

[00556] Antibodies against the hetero-EPOR are generated with animal immunization. The extracellular domains of EPOR, CD131, or the soluble heterodimeric EPOR/CD131 are used to immunize the animals. The antigen specific B cells or hybridoma cells are isolated and the immunoglobulin genes are sequenced. The recombinant antibodies can be subjected to the antigen binding assays with the extracellular domains of homo-EPOR, CD131/CD131, or the soluble hetero-EPOR, and the staining assays on the cells expressing EPOR only, CD131 only, or both EPOR and CD131. The cells staining with antibodies specific to the hetero-EPOR are further characterized for receptor activation by analyzing phosphorylation of the receptor, JAK2, and STAT5 after the receptor expressing cells are treated with the antibody with or without EPO.

[00557] Alternatively, the hetero-EPOR specific antibody can be isolated by screening an antibody expression library, e.g., phage display, yeast display, ribosomal display, or cell display.

[00558] Anti-hetero-EPOR antibodies can be agonists or antagonists for hetero-EPOR. Some anti-hetero-EPOR antibodies can be agonists or antagonists for the homo-EPOR or CD131/CD131 receptors.

[00559] The binding affinity of the hetero-EPOR antibodies to the extracellular domains of a hetero-EPOR, or a CD131/CD131 is determined using a functional ELISA. Soluble CD131/CD131, and hetero-EPOR (Sino Biological) are coated on a standard ELISA. The wells are blocked with 2% BSA. Dilutions of anti-hetero-EPOR antibodies are added to the plates and incubated. After washing, the bound anti-hetero-EPOR antibodies are detected using biotinylated polyclonal anti-EPO (R&D Systems) followed by streptavidin HRP conjugate or other appropriate secondary antibodies. After washing, TMB reagent (Sigma) is added and OD absorption at 450 nm is measured in a plate reader.

Example 13. Characterization of Antibodies Against the Human EPO

[00560] Antibodies against human EPO that block interaction between EPO and the hetero-EPOR are generated with animal immunization. The antigen specific B cells or hybridoma cells are isolated and sequenced. The recombinant antibodies are assayed in the antigen binding assay

and the receptor activation assay. The anti-EPO antibodies are tested for antagonist activity against the homo-EPOR and/or the hetero-EPOR. Anti-EPO antibodies can block EPO-mediated activation of the hetero-EPOR but not the homo-EPOR, or block activation of the homo-EPOR and not the hetero-EPOR, or block activation of both the homo-EPOR and the hetero-EPOR.

[00561] The binding affinity of anti-EPO antibodies to the extracellular domains of a homo-EPOR, a hetero-EPOR, or a CD131/CD131 is determined using a functional ELISA. Soluble homo-EPOR, CD131/CD131, and hetero-EPOR (Sino Biological) are coated on a standard ELISA. The wells are blocked with 2% BSA. Dilutions of anti-EPO antibodies are added to the plates and incubated. After washing, the bound anti-EPO antibodies are detected using biotinylated polyclonal anti-EPO (R&D Systems) followed by streptavidin HRP conjugate or other appropriate secondary antibodies. After washing, TMB reagent (Sigma) is added and OD absorption at 450 nm is measured in a plate reader.

Example 14. Characterization of the Immune Stimulatory Roles of the Antagonistic Anti-Hetero-EPOR and anti-EPO Antibodies in an *In Vivo* Tumor Model

[00562] Murine colon adenocarcinoma MC38 is used to test the antagonistic, anti-hetero-EPOR antibodies, and neutralizing, anti-EPO antibodies (neutralizing for activity with the hetero-EPOR). MC38 cells are engrafted (s.c.) in the right flanks of C57BL/6 mice. The mice are treated (i.p.) with the antibodies twice a week alone or in combination with anti-PD1 (Bio X Cell). Tumor volume will be measured daily.

[00563] Similarly, EO771 breast medullary adenocarcinoma cells are implanted into the mammary fat pad, and tumor size will be monitored following antagonist antibody treatment over time. A variety of other tumor cell lines, such B6-F10 melanoma, or LLC Lewis lung carcinoma can be used for the same purpose.

[00564] A spontaneous HCC tumor model based on a transposon system expressing C-Myc and a CRISPR-Cas9 system expressing a sgRNA targeting Trp53 specifically being delivered to hepatocytes via hydrodynamic tail vein (HDTV) injection is studied. 3-5 weeks after HDTV, spontaneous HCC tumors derived from C-Myc overexpression (C-MycOE) and Trp53 deletion (Trp53KO) develop in these mice. Antagonistic anti-hetero-EPOR and neutralizing, anti-EPO antibodies (neutralizing for activity with the hetero-EPOR) are administered. Luciferase co-expressing transposons are utilized to monitor spontaneous HCC growth with antibody treatment over time.

[00565] A preclinical model of liver metastasis, as established by s.c. or intrahepatic inoculation of MC38 colon tumor cells, is used to verify the liver metastasis-induced systemic tolerance inhibiting effects of antagonistic anti-hetero-EPOR antibodies, and neutralizing anti-EPO antibodies (neutralizing for activity of the hetero-EPOR). Since there is a complete abrogation of

therapeutic response to anti-PD-L1 in mice bearing both s.c. implanted MC38 and liver tumors, anti-PD-L1 responsiveness is used as a readout for the tolerance abrogating efficacy of those antibodies.

[00566] Other genetically engineered pre-clinical spontaneous tumor models, such as melanoma ($BRAF^{V600E}$ mutant mice), breast cancer (MMTV-PyMT mice), lung cancer ($Kras^{LSL\text{-}G12D/+}$;$p53^{fl/fl}$ mice) are also used to test the efficacy of therapeutic antagonist antibodies.

Example 15. Characterization of the Immunosuppressive Roles of the Agonistic Anti-Hetero-EPOR Antibody in an *In Vivo* Transplantation Model

[00567] Agonistic antibodies specific to the hetero-EPOR are tested similarly as described in Example 9.

Example 16. Induction of Antigen Specific Tolerance *In Vivo* with the Agonistic Anti-Hetero-EPOR Antibody

[00568] Agonistic antibodies specific to the hetero-EPOR are tested similarly as described in Example 10.

Example 17. Induction of Antigen Specific Tolerance *In Vivo* with PHD inhibitors

[00569] PHD inhibitors, e.g., roxadustat, vadadustat, daprodustat, and molidustat, lead to elevation of HIF levels and upregulation of EPO and EPOR, and are tested similarly as described in Example 10.

Example 18. Induction of Immune Tolerogenic Effect by EPOR

[00570] *TLI/ATS-induced tolerance to allogeneic (allo) bone marrow and heart transplants*

[00571] C57BL/6 mice were treated with 10 doses of Total lymphoid irradiation (TLI; 250 centigray (cGy) each) with 5 doses of Anti-thymocyte serum (ATS) as tolerance-inducing regimen). Radiation was targeted to the lymph nodes, spleen, and thymus, and other tissues were shielded with lead. Bone marrow (BM) cells (50×10^6) from BALB/c donors were injected intravenously (i.v.) after the last TLI dose. Hearts from BALB/c donors were transplanted on day 0. Experimental scheme is shown in **FIG. 18A**. Recipient mice were conditioned with TLI/ATS to induce sustained antigen (Ag)-specific tolerance to both allogeneic (allo) hematopoietic cell transplant (HCT) and solid organ allografts (**FIG. 18A**). Long-term tolerance in this model can be dependent upon several cell types, including regulatory T cells (Tregs), natural killer T (NKT) cells, and myeloid-derived suppressor cells. In addition, $CD8\alpha^+$ type I conventional dendritic cells (cDC1s) were found to be indispensable for TLI/ATS tolerance induction (**FIG. 18B**), as grafts were rejected in mice lacking Batf3 (Baft3 -/-), a transcription factor necessary for cDC1 development, compared to wildtype (WT) mice. For example, as shown in **FIG 18B**, less Baft3-/- mice survived post heart transplant (TX) than WT, and exhibited decreased percentage of donor type cells than WT. TLI/ATS induced profound

depletion of T cells and B cells in lymphoid organs (**FIG. 19A-19B**) through p53-dependent apoptosis, as indicated by increased TUNEL staining (**FIG. 19A**) in spleen of mice with TLI/ATS compared to untreated (UNT) mice. A high level of extramedullary erythropoiesis, as measured by percentage of CD71 and TER119 expression via flow cytometry, was observed in mice with TLI compared to UNT mice (**FIG. 19B-19C**). TLI also increased percentage of CD71+ and TER119+ **(FIG. 19D)**and increased EPO levels in blood serum (**FIG. 19E**), as detected by enzyme-linked immunoassay (ELISA) assay, in mice treated with TLI over a course of time.Since $CD8\alpha^+$ cDC1s preferentially take up apoptotic cells, and EPO levels are increased, the data suggested that EPO-EPOR signaling may be involved in $CD8\alpha^+$ cDC1-mediated tolerance following TLI/ATS. Thus, $CD8\alpha^+$ cDC1s were further analyzed from TLI/ATS conditioned mice and UNT mice. Relative to UNT mice, conditioning with TLI/ATS decreased the total number of splenic cells (**FIG. 20A**) but increased the frequency of cDCs, defined as $CD11c^{high}MHCII^{high}$cells (1.5% in UNT versus 3.01% TLI/ATS), as shown in **FIG. 20B**. Moreover, the proportion of $CD8\alpha^+$ expressing cDC1s (25.2%, $CD8\alpha^+$ $CD11b^-$) but not $CD11b^+$ expressing type II conventional dendric cells (cDC2s) (59.5%, $CD11b^+$ $CD8\alpha^-$) increased upon conditioning with TLI/ATS (**FIG. 20C**). To identify gene expression changes associated with TLI/ATS conditioning in the $CD8\alpha^+$cDC1 subset, RNAs from this subset of cells isolated from spleens of UNTor TLI/AT conditioned mice were subjected to RNA-sequencing. Transcriptomes derived from splenic $CD8\alpha^+$cDC1s in TLI/ATS conditioned versus UNT control mice clustered distinctly by principal components analysis (PCA) (**FIG. 20D**), showing difference in gene expression in TLI/ATS conditioned versus UNT control mice. In addition, a comparison of the 30 most upregulated genes in $CD8\alpha^+$ cDC1s from the TLI/ATS-conditioned vs. the UNT mice revealed that the erythropoietin receptor (EPOR) was the most differentially upregulated gene (**FIG. 20E**). Furthermore, Molecular Signatures Database (MSigDB) analysis confirmed that gene sets involved in diverse aspect of cell metabolism were positively enriched, while those involved in allograft rejection, TNFα signaling via NFκB, and inflammatory responses were negatively enriched in $CD8\alpha^+$ cDC1s upon conditioning with TLI/ATS (**FIG. 20F**). Real-time PCR was performed on selected genes, identified by RNAseq data shown in **FIG. 20E,** in splenic $CD8\alpha^+$ cDC1s and $CD11b^+$ cCD2s (**FIG. 20G**) and showed that EPOR expression was upregulated in cDC1s (**FIG. 20G, top**), confirming the RNA-sequencing data. Specifically, EPOR expression in $CD8\alpha^+$ cDC1s was increased more than 20-fold with (iii) TLI alone or (iv) with TLI/ATS compared to (i) UNT, and (ii) ATS alone had little or no effect compared to (i) UNT (**FIG. 20G**). Similar patterns were observed for MerTK, FcγR1, Axl, C1qa, and C1qb (**FIG. 20G, top**). In contrast, expression of EPOR did not increase in $CD11b^+$ cDC2s (**FIG. 20G, bottom**). EPOR expression was also assessed by using EPOR-tdT report

mice (**FIG. 20H**), treated with TLI, TLI/ATS or untreated. A selective increase in the frequency of $EPOR^+$ $CD8\alpha^+$ cDC1s following TLI (24.5%) was observed compared to UNT mice (14.1%) and this was augmented by ATS (31.9%) (**FIG. 20H**). Collectively, conditioning with TLI/ATS or TLI substantially altered the frequency of $CD8\alpha^+$ DC1s and induced the expression of EPOR and related genes within this subset.

[00572] *Immune tolerogenic phenotype in EPOR+ DCs*

[00573] To understand whether EPOR signaling plays a role in immune-modulatory function on immune cells, RNA-sequencing was performed on $EpoR^+$ and $EpoR^-$ $XCR1^+CD8\alpha^+CD11c^{high}MHCII^{high}$ cDC1s (XCR1: XC-Chemokine Receptor 1). $EpoR^+$ and $EpoR^-$ cDC1s from the spleen of EpoR-tdTomato reporter mice (n=2, each pooled from 15 mice) were first sorted by flow cytometry before subjecting $EpoR^+$ and $EpoR^-$ cDC1s to RNA-sequencing. Next, gene differential expression analysis was performed with the RNA-sequencing data using DESeq2 based on R programming. Differential expression analysis was represented as a volcano plot, and it revealed differentially expressed genes that were downregulated (left half of the graph) and upregulated (right half of the graph) in $EpoR^+$ cDC1s compared to $EpoR^-$ cDC1s (see **FIG. 3A**). A heat map was generated using DESeq2 as an alternative way to represent upregulated and downregulated genes in $EpoR^+$ and $EpoR^-$ cDC1s, as shown in **FIG. 3B.** Heat map revealed genes of interest grouped into tolerogenic functional groups, showing that genes associated with immune tolerance is upregulated in $EpoR^+$ cDC1s.

[00574] *EPOR in BM chimerism*

[00575] To investigate EPOR's immune tolerogenic phenotype, BM chimerism was analyzed in mice with hetero-EPOR deletion in CD8α+ dendritic cells ($EPOR^{\Delta CD11c}$ mice). $EPOR^{\Delta CD11c}$ ($CD11c^{cre+}$; $EPOR^{flox/flox}$) mice were generated by breeding mice bearing floxed EPOR with a CD11c-Cre strain, $EPOR^{\Delta CD11c}$ ($CD11c^{cre+}$; $EPOR^{floxed(flox/flox)}$). $EPOR^{\Delta CD11c}$($H\text{-}2b^+$) recipient mice were given BM from MHC-mismatched BALB/c ($H\text{-}2d^+$) donors. Wild-type C57BL/6 (WT), $Batf3^{-/-}$ and $EPOR^{flox/flox}$ mice on the C57BL/6 background ($H\text{-}2b^+$) were used as control recipients. Allogeneic BM cells were infused immediately after the last dose of TLI, and chimerism was assessed as early as day 14 thereafter. As shown in **FIG. 21**, $EPOR^{flox/flox}$ mice displayed similar levels of BM chimerism in B cells, T cells, and granulocytes as WT mice. In contrast, and similar to $Batf3^{-/-}$ mice, $EPOR^{\Delta CD11c}$ mice failed to achieve BM chimerism, as shown by the decreased percentage of donor B cells, T cells and granulocytes. Importantly, $CD8\alpha^+$ cDC1-specific EPOR expression was found to be indispensable for BM chimerism and tolerance induction, as reflected by the abrogation of chimerism when EPOR expression was abolished in these cells. Collectively, these data demonstrate that EPOR-expressing cDC1s are tolerogenic. They also support the use of TLI/AT-induced tolerance as an ideal model to

investigate the role of EPO-EPOR signaling-dependent tolerogenic CD8α$^+$ cDC1s in cell-associated Ag-specific tolerance.

[00576] Next, whether CD4$^+$ FoxP3$^+$ Tregs are activated and expanded by CD8α$^+$ cDC1s following TLI or TLI/ATS, and whether the extent of allo-BM "loading" from the transplant is an important factor in the establishment of mixed chimerism (engraftment) were tested. To examine the relative importance of FoxP3$^+$ Tregs in the induction and maintenance of immune tolerance to allo-BM cells, diphtheria toxin (DT) and the FoxP3-DTR system was used to deplete FoxP3$^+$ Tregs in recipient mice during different time windows following allo-BM injection, from day 0 to 14 (Group A, top) or day 29 to 41 (Group B, bottom), respectively, as shown in **FIG. 22A**. Briefly, FoxP3-DTR recipient mice were either untreated (UNT) or treated with 10 daily doses of TLI (240cGy each) and ATS (5 doses, every other day) for 14 days except weekends (TLI/ATS). On day 0, BM cells from allo-donors (MHCI-H2Kb) were injected intravenously (*i.v.)* and chimerism was monitored by blood sampling starting on day 14 (**FIG. 22A**). Group A (left 3 bars in all 4 graphs), which started DT treatment (Tx) on day 1 after BM injection, did not have any detectable chimerism detectable on day 14, day 28, or day 55, as shown in **FIG. 22B**. In contrast, similar to wild-type mice (**FIG. 21**), chimerism was detected on day 14 in Group B mice (right 3 bars in all 4 graphs) and continued to increase through day 28 in the absence of (w/o) DT. However, when DT was administered from day 15 to day 28, there was no further increase and instead, a decline of the already established chimerism was observed (**FIG. 22B).** These data validated the importance of CD4$^+$ FoxP3$^+$ Tregs in the establishment and maintenance of chimerism after allo-BM encounter.

[00577] Next, to investigate CD8α$^+$ cDC1-dependent Ag-specific FoxP3$^+$ Treg induction and expansion and to avoid the selective effect of TLI and/or ATS on the remaining T cells, OTII cells (cells expressing ovalbumin (Ova) specific αβTCRs) were adoptively transferred and allo-BM was substituted with Ova-expressing BM. Adoptive transfer of Ova-specific TCR transgenic OTII T cells allowed monitoring of the Ag-specific CD4$^+$ T cell response. As expected, CD4$^+$ FoxP3$^+$ OTII Treg frequency (**FIG. 23A**) and mean fluorescence intensities (MFIs) (**FIG. 23B**) of FoxP3 in OTII cells increased dramatically after 5 days in TLI-conditioned recipients compared to untreated mice. This effect was absent in Batf3$^{-/-}$ (**FIG. 23A-23B**) and EPOR$^{\Delta CD11c}$ recipient mice (**FIG. 23C-23D**), confirming that CD8α$^+$ cDC1s and EPOR are indispensable for Ag-specific CD4$^+$ FoxP3$^+$ Treg induction and expansion. Interestingly, in TLI-conditioned EPOR$^{\Delta CD11c}$recipient mice, both Foxp3$^+$ OTII percentage and FoxP3 MFI in OTII cells were decreased compared to UNT (**FIG. 23C-23D**). FoxP3-DTR mice were treated with TLI/ATS for 14 days. Allogeneic Balb/C bone marrow cells were infused i.v. immediately on the next day after TLI/ATS treatment (Day 0). 100ng Diphtheria toxin (DT) was given i.p. on day -1, day 0,

and day 1.As shown in **FIG. 24A**, Bone marrow chimerism was analyzed by donor derived individual immune cell subset in the host blood.with or without DT. As shown in **FIG. 24B**, host CD4+ T cells were analyzed by flow cytometry on day 5, and percentages of FoxP3+ Tregs, and FoxP3-CD73+FR4+ anergic T cells were quantified. IFNg expression was seen in host CD4+FoxP3- T cells. As shown in **FIG. 24C**, statistical analysis of the frequency of host CD4+ T cells, FoxP3+ Treg cells in host CD4+ T cells, FoxP3-CD73+FR4+ anergic cells in host CD4+ T cells, and IFNg+ cells in host CD4+FoxP3- cells were performed. As shown in **FIG. 24D**, correlation of FoxP3+ Treg cells frequency in host CD4+ T cells with FoxP3-FR4+CD73+ anergic cells in host CD4+ T cells was analyzed. Deletion of $CD4^+$ $FoxP3^+$ Tregs with DT led to the anergic reversal of $CD4^+$ $FoxP3^-$$CD44^+$ $CD73^+$ folate receptor 4+ ($FR4^+$) anergic T cells, and an uncontrolled CD4+ $FoxP3^-$ T cell immune response, as indicated by a marked expansion of interferon gamma ($IFN\gamma^+$) effector T cells, suggesting tolerance escape (**FIGs. 24A-24D).**It was further observed that TLI conditioning imprinted dynamic expansion and activation of recipient $CD4^+$ $FoxP3^+$ Tregs in response to allo-BM, which was dependent on $CD8\alpha^+$ cDC1s. Taken together, these data suggest that EPO signaling contributes to Ag-specific tolerance induction and maintenance, primarily through upregulated EPOR expression on $CD8\alpha^+$ cDC1s, which induce both regulatory and anergic Ag-specific $CD4^+$ T cells.

[00578] *Characterization of the tolerogenic phenotype, function and cellular tolerance of EPOR+ cDC1s before and after TLI/AT*

[00579] To confirm $EPOR^+$ cDCs after TLI conditioning preferentially take up i.v. injected allogeneic BM cells, live Balb/C BM cells were labeled with a fluorescent dye, 5-chloromethylfluorescein diacetate (CMFDA), and injected i.v. into wild-type C57BL/6J mice. Compared to $CD8\alpha^-$ cDC2s, $CD8\alpha^+$ cDC1s preferentially took up i.v. injected live BM cells, with TLI conditioning further increasing uptake (**FIG. 25A**). $CD8\alpha^+$ cDC1s from TLI-conditioned mice displayed greater engulfment after 12 hour compared to UNT mice (**FIGs. 25B-25C**). CD103 and DEC-205, which are markers for cDC1s, co-staining revealed that $CD8\alpha^+$ cDC1s, which preferentially took up more allogeneic BM cells, had higher expression of both markers (**FIGs. 25A-25C**). EPOR-tdT and $EPOR^{\Delta CD11c}$mice can be further utilized to assess whether the EPOR expression correlates with $CMFDA^+$ allogeneic BM uptake in $CD8\alpha^+$ cDC1s.

[00580] *Identification of cDC1-specific EPO-EPOR signaling events downstream of TLI/AT*

[00581] To verify EPO-EPOR signaling in $CD8\alpha^+$ cDC1s following TLI, phosphorylation of Akt, ERK, and STAT5 was measured by flow cytometry. In parallel with EPOR upregulation **(FIG. 20)**, phosphorylation of all of these molecules was also upregulated following TLI (**FIG. 26**). These data confirm downstream EPOR signaling pathways in $CD8\alpha^+$ cDC1s following TLI. PI3K-Akt are important for running mTOR pathway and as expected, following TLI, $CD8\alpha^+$

cDC1s displayed higher activation of mTOR, indicated by phosphorylation of downstream effector ribosomal protein S6 kinases (S6Ks) and activation of the translation inhibitor eIF4E-binding proteins (4E-BPs), as shown in **FIG. 26A**. Furthermore, adding ATS further enhanced 4EBP1 phosphorylation (**FIG. 26**). $CD8\alpha^+$ cDC1s were also more metabolically active and had greater mTORC1 activity than $CD11b^+$ cDC2s, which could be further enhanced by TLI conditioning (**FIG. 26**). This finding suggests that EPO signaling can be critical for tuning mTOR activity selectively in $CD8\alpha^+$ cDC1s following TLI or TLI/ATS. In this regard, CD11c-specific Raptor and mTOR conditional knock out mice have been generated to investigate their tolerogenic involvement in $EPOR^+$ cDC1s, as shown by the measurement of donor cells of the different mouse strains in **FIG. 26B**. The metabolic activity of $EPOR^+$ and $EPOR^-$ cDC1s using a Seahorse instrument that measures oxygen consumption rate and extracellular acidification rate in a multi-well format can be analyzed and this will enable interrogation of key cellular functions such as mitochondrial respiration and glycolysis. In addition, the relationship of these findings to $EPOR^+$ cDC1 tolerogenic function can be analyzed.

[00582] *EPOR in BM chimerism and tolerance to organ transplant*

[00583] To investigate EPOR's immune tolerogenic phenotype and its effect in organ transplant, heart transplantation was performed with mice with hetero-EPOR knockout in myeloid cells. Host mice, such as wild-type mice (C57Bl/6J), Batf3 knockout mice ($Batf3^{-/-}$), mice with $CD11c^{Cre}$ ($CD11c^{Cre}$), mice with $EPOR^{flox/flox}$ ($EPOR^{flox/flox}$), and mice with knockout of hetero-EPOR in dendritic cells ($EPOR^{\Delta CD11c}$), were given donor BALB/c neonatal heart transplants on day 0. ATS was injected intraperitoneally (i.p.) in the mice on days 0, 2, 6, 8, and 10. Host mice were conditioned over 14 days with 10 doses of TLI of 240 cGy each. As shown in **FIG. 4A**, EpoR-tdTomato expression in EpoR-tdTomato hosts was analyzed by flow cytometry on the $XCR1^+CD8a^+$ cDC1s in the spleen on the next day of the last dose of TLI/ATS (Tolerance-inducing regimen) compared with untreated (baseline) mice. Flow cytometry revealed that with tolerance-inducing regiment, there is increased expression of EPOR in cDC1s, confirming EPOR's immune tolerogenic phenotype. On day 15, bone marrow transplantation was performed (BMT) by injecting 50×10^6 host or BALB/c donor bone marrow cells from the same strain as the heart grafts via i.v.. Chimerism and heart graft survival were monitored for 100 days after organ transplantation. As shown in **FIG. 4B**, percentages of donor type ($H2K^{d+}$) cells (e.g, marker of Balb/C MHCI) among T cells in the peripheral blood of hosts 28 days after BMT was measured. In $EPOR^{\Delta CD11c}$ mice, there was a statistically significant decrease in donor T cells compared to C57B1/6J, with no difference between positive control $Batf3^{-/-}$ mice, suggesting that EPOR is necessary for immunogenic tolerance. Furthermore, when the percentage of hosts with heart graft survival was measured at serial time points (see **FIG. 4C**), $EPOR^{\Delta CD11c}$ mice were not

able to survive post heart transplantation, similar to what was seen with positive control Batf3$^{-/-}$ mice, compared to negative control mice (e.g., C57Bl/6J, CD11c^{Cre} , EPOR$^{flox/flox}$). This showed that EPOR knockout from myeloid cells prevented tolerance to transplanted organs in mice.

[00584] *EPOR signaling in stimulation of Ag-specific Tregs in vitro and in vivo*

[00585] To investigate EPOR function in promoting antigen-specific tolerance, EpoR-tdTomato mice were given ATS i.p. on days 0, 2, 6, 8 and 10, and conditioned over 14 days with 10 doses of TLI (240 cGy) each. EPOR^{+} and EPOR^{-} XCR1^{+}CD8α^{+}CD11c^{high}MHCII^{high} cDC1s were sorted by flow cytometry on the next day of the last dose of TLI/ATS and co-cultured with naïve OT-II cells isolated from OT-II$^{CD45.1/CD45.1}$ mice in the presence of 15 gray irradiated Ova-expressing thymocytes. The ratio of DC: OT-II: Ova-thymocytes was 1: 5: 2. No or 20IU/200ul recombinant human EPO (rhEPO) was added to the co-culture every day for 6 continuous days. FoxP3 expression on OT-II cells was analyzed by flow cytometry, and OT-II cells were gated as live-dead aqua-CD45.1^{+}CD45.2^{-}CD3^{+}TCRva2^{+}CD4^{+}CD8^{-}. OT-II cells were prelabeled with CellTrace™ Violet (CTV) before being put into the co-culture. The percentage of FoxP3^{+} Tregs was higher in (i) EPOR^{+} cDC1s compared to (ii) EPOR^{-} cDC1s as shown in **FIG. 5A**.

[00586] In another experiment, C57BL/6J or EPOR$^{\Delta CD11c}$ hosts were injected with ATS via i.p. on days 0, 2, 6, 8, and 10. Hosts were conditioned over 14 days with 10 doses of 240 cGy (TLI/ATS treatment) each or were left untreated. On day 15, 50 × 10^{6} 2W1S-Balb/C donor bone marrow cells were injected i.v. 14 days after the injection, FoxP3 expression was analyzed in 2W1S tetramer^{+} H2K^{b+}CD3^{+} TCRβ^{+} CD4^{+} T cells, representing endogenous 2W1S-MHCII TCR specific host CD4+ T cells, from the spleens via flow cytometry to measure the host endogenous donor Ag(2W1S)-specific CD+T cell immune response. As shown in **FIG. 5B**, flow cytometry data revealed that TLI/ATS treatment in EpoR$^{\Delta CD11c}$ hosts lead to less expression of FoxP3 (1.17%) as compared to TLI/ATS treatment in C57BL/6J (56.8%), further verifying the need for EPOR in DCs to induce Ag-specific Treg *in vivo*.

Example 19. Effect of EPOR Deletion on Tumor Burden

[00587] In this example, how hetero-EPOR knockout affects tumor burden was investigated, as another role of EPOR can be in regulating tumor burden.

[00588] *Lewis lung carcinoma and breast adenocarcinoma*

[00589] To see how EPOR affects lung carcinoma tumor burden, 5 x 10^{5} lewis lung carcinoma cells (LLC) were subcutaneously implanted into wild type C57BL/6J (WT) and mice with knockout of EPOR in macrophages (EpoR$^{\Delta LysM}$) mice. 5 mg/kg of αPD-L1 (Programmed Death-Ligand 1) (e.g., clone 10F.9G2; BioXCell) or rat IgG isotype was given intraperitoneally (i.p.) every two days starting from day 6 after tumor implantation with visible tumors. Tumor size was measured at various time points (e.g., Day 14, 17, 19, 21). As shown in **FIG. 6A**, the size of the

tumor from (iii) $EpoR^{\Delta LysM}$ was smaller than the tumor from (i) WT mice. The tumor size of $EpoR^{\Delta LysM}$ was similar to that of (ii) wild-type mice treated with αPD-L1 (**FIG. 6A**). Similarly, 5 x 10^5 E0771-Ovalbumin expressing breast adenocarcinoma was subcutaneously implanted into wild type C57BL/6J and $EpoR^{\Delta CD11c}$ mice to observe changes in tumor size. Tumor size was measured at various time points (e.g., Day 6, 7, 9, 11). As shown in **FIG. 6B**, the size of the tumor from (ii) $EpoR^{\Delta CD11c}$ mice was smaller than the tumor from (i) wild-type mice. These results suggest that EPOR deletion from myeloid cells reduces lewis lung carcinoma and breast adenocarcinoma tumor burden in mice.

[00590] *Colon cancer*

[00591] The effect of EPOR on colon cancer was investigated. $Zbtb46^{gfp/+}EpoR^{tdTomato/+}$ mice were implanted with MC38-Ova (colon cancer) cells (5×10^5). These mice were used as Zbtb46 can be used to define conventional dendritic cells. On day 12, tumors were explanted followed by flow cytometric analysis of EpoR-tdTomato expression on tumor infiltrating immune cells (n = 3-4). For flow cytometric analysis, classical dendritic cells (cDCs) were gated as live-dead blue$^-$ $CD45^+$ $CD11c^+$ $Zbtb46^+$. cDC1s were gated as live-dead blue-$CD45^+$ $CD11c^+$ $Zbtb46^+$ $XCR1^+$ $CD103^+$ $SIRPa^-$. Non cDC1s were gated as live-dead blue$^-$$CD45^+$$CD11c^+$$Zbtb46^+$$XCR1^-$. Macrophages were gated as live-dead blue$^-$$CD45^+$$CD3^-$$CD19^-$$NK1.1^-$ $MHCII^{low}Ly6C^{low}CD64^+F480^+CX3CR1^+$. Monocytes were gated as live-dead blue$^-$$CD45^+$$CD3^-$ CD19-NK1.1-$Ly6C^{high}CD64^{low}Ly6G^-$. Neutrophils were gated as live-dead blue$^-$$CD45^+$$CD3^-$ CD19-NK1.1-$CD11b^+Ly6G^-$. T cells were gated as live-dead blue$^-$$CD45^+$$CD3^+$$CD19^-$$NK1.1^-$ $CD11b^-$. B cells were gated as live-dead blue$^-$$CD45^+$$CD3^-$$CD19^+$$NK1.1^-$$CD11b^-$. NK cells were gated as live-dead blue$^-$$CD45^+$$CD3^-$$CD19^-$$NK1.1^-$$CD11b^-$. As shown in **FIG. 7A**, flow cytometric analysis showed that EPOR is expressed in various infiltrating immune cells, with the most expression in cDCs of $Zbtb46^{gfp/+}EpoR^{tdTomato/+}$ mice implanted with MC38-Ova. Thus, EPOR was knocked out in cDCs of mice ($EpoR^{\Delta XCR1}$) to determine whether deletion of EPOR in cDCs would affect colon cancer tumor growth. $5x10^5$ $MC38\text{-}Ova^{dim}$ cells were subcutaneously implanted into $EpoR^{flox/flox}$ and $EpoR^{\Delta XCR1}$ mice. $mTOR^{flox/flox}$ and $mTOR^{\Delta XCR1}$ mice were also subcutaneously implanted with $5x10^5$ $MC38\text{-}Ova^{dim}$ cells as controls. As shown in **FIG. 7B (right graph)-7C**, (i) $EpoR^{\Delta XCR1}$ mice had a statistically significant decrease in tumor size than (ii) $EpoR^{flox/flox}$ mice. Similar effect was observed in (ii) $mTOR^{flox/flox}$ and (i) $mTOR^{\Delta XCR1}$ mice, where $mTOR^{\Delta XCR1}$ mice had a statistically significant decrease in tumor size than $mTOR^{flox/flox}$ mice (left graph of FIG. 7B). These results confirmed that EPOR deletion from cDCs reduces colon cancer tumor burden.

[00592] *Hepatocellular carcinoma (HCC)*

[00593] To see whether EPOR deletion affects resistance of tumors to immune checkpoint blockade (cold tumors), a spontaneous model of cold HCC was generated by delivering plasmids pCMV-SB13, pT3-EF1a-C-Myc-IRES-Luciferase, and pX330-sgRNA targeting Trp53 to the liver of C57BL/6J (WT) or $EpoR^{\Delta LysM}$ mice using hydrodynamic tail vein injection (HDTV) *in vivo* ($Trp53^{KO}$/C-myc^{OE}-Luc+) as shown in **FIG. 8A**. After two weeks, WT and $EpoR^{\Delta LysM}$ mice were treated with either 2 mg/kg of αPD1 (e.g., Clone 29F.1A12, BioXCell) or IgG isotype via intraperitoneal injection (i.p.) as indicated in the experimental scheme shown in **FIG. 8A**. Next, bioluminescence assay was performed to monitor tumor burden by measuring the luciferin-based bioluminescence. As shown in **FIG. 8B**, $EpoR^{\Delta LysM}$ mice with IgG Isotype had lower bioluminescence than wild-type mice with IgG Isotype, signifying that knockout of EpoR in macrophages lowers tumor burden. With additional treatment with αPD1 in $EpoR^{\Delta LysM}$ mice, tumor burden was further reduced. In addition to monitoring tumor burden, percent survival was also calculated. As shown in **FIG. 8C**, $EpoR^{\Delta LysM}$ mice with IgG Isotype and $EpoR^{\Delta LysM}$ mice with αPD1 had greater percent survival than wild-type mice with or without αPD1.

[00594] *Melanoma*

[00595] To see how EPOR affects melanoma tumor burden, $1x10^6$ of B16F10-Ova cells were subcutaneously implanted into $EpoR^{flox/flox}$ and $EpoR^{\Delta XCR1}$ mice to induce melanoma. 2mg/kg of αPD1 (e.g., Clone 29F.1A12, BioXCell) was given i.p. as indicated in the experimental scheme shown in **FIG. 9A**. Melanoma tumor size was measured across various timepoints (e.g., day 0, 7, 8, 11, 13, 15). As shown in **FIG. 9B**, (iii) $EpoR^{\Delta XCR1}$ mice had a statistically significant decrease in tumor growth than (i) control mice. Furthermore, (iv) $EpoR^{\Delta XCR1}$ mice treated with αPD1 had a statistically significant decrease in tumor growth than (ii) control mice with αPD1 and $EpoR^{\Delta XCR1}$ mice without αPD1, suggesting that the knockout of EpoR in cDCs combined with αPD1 can further reduce tumor growth compared to without combining with αPD1. On day 12 after tumor implantation, tumor infiltrating CD8+ T cells were analyzed for effector T cell markers. T cells were gated as live-dead $blue^-CD45^+CD3^+CD8^+CD11b^-MHCII^-$, and expression of $Perforin^+$, Granzyme B^+, interferon gamma ($IFN\gamma^+$) and tumor necrosis factor alpha (TNFα+) were analyzed by flow cytometry as shown in **FIG. 9C**. Flow cytometry data revealed that $EpoR^{\Delta XCR1}$ mice have elevated inflammatory cytokines (Perforin: 56%, IFNγ: 33.4%, GranzymeB+: 45.6%, TNFα: 43.4%) and effector CD+ T cells than $EpoR^{flox/flox}$ mice (Perforin: 14%, IFNγ: 11.1%, GranzymeB+: 7.26%, TNFα: 2.78%), suggesting that when EPOR is absent in cDC1s, immune checkpoint blockade (ICB)-resistant cold tumor (e.g., melanoma) can be converted into ICB-sensitive tumors.

[00596] *Colon cancer in presence of liver metastasis*

[00597] Liver metastasis can promote tumor growth and can diminish immunotherapy efficacy. Thus, whether deletion of hetero-EPOR can abrogate the acceleration of tumor growth by liver metastasis was investigated. First, wild-type mice were implanted with MC38 tumor cells (e.g., 5×10^5) subcutaneously, or subcutaneously and at the liver to model liver metastasis. Next, colon tumor growth was monitored. As shown in **FIG. 12A**, with liver metastasis there was greater colon tumor growth than without liver metastasis, confirming that liver metastasis promote tumor growth. To see how knockout of hetero-EPOR in macrophage can affect tumor growth with or without liver metastasis, $EpoR^{\Delta LysM}$ mice were implanted with MC38 tumor cells (e.g., 5×10^5) subcutaneously, or subcutaneously and at the liver to model liver metastasis. As shown in **FIG. 12B**, $EpoR^{\Delta LysM}$ mice with or without liver metastasis had decreased tumor growth as compared to with wildtype mice with liver metastasis. These results suggest that liver metastasis can accelerate the growth of primary colon tumor; however, this effect can be prevented in the absence of EPOR in macrophages.

Example 20. Effect of EPO Overexpression on Tumor Burden

[00598] Data from Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC) shows that patients with high EPO levels had lower percentage of survival compared to patients with low EPO levels (**FIG. 10**). Thus, the effect of EPO on advancement of tumors in mice with regressing HCC was explored. Regressive HCC model was established by orthotopically implanting allogeneic 3 x 10^6 Hepa1-6 cells to C57BL/6 mice, as shown in the experimental scheme in **FIG. 11A**. While tumors grew continuously in the first two weeks following injection, spontaneous tumor regression (complete or partial) was observed on Day 21. In addition, two Hepa1-6 stable cell lines were generated by using lentiviruses, with either empty vehicle (Hepa1-6_EV) or with overexpression of EPO ($Hepa1\text{-}6_Epo^{OE}$), as shown in the experimental scheme in **FIG. 11A**. At day 14 after the progression phase, and at day 21 after the regression phase, tumors were harvested (**FIG. 11B**) and the size of tumors was measured. Quantification of tumor volume and complete response (CR) rate showed that mice with EPO overexpression had greater tumor volume than mice without EPO overexpression at day 21 (**FIG. 11C**), suggesting that overexpression of EPO enables tumor growth in regressive HCC.

Example 21. Effect of EPO and EPOR Modulation on Tumor Burden

[00599] As demonstrated in Example 19, deletion of hetero-EPOR in myeloid cells lead to a decrease in tumor growth. When there is overexpression of EPO, as demonstrated in Example 20, there is an increase in tumor growth. Thus, how tumor burden is affected by knockdown of hetero-EPOR in mice with hepatocellular carcinoma (HCC) with EPO overexpression was explored. As shown in the experimental scheme in **FIG. 13A**, C57BL/6 mice were orthotopically implanted with 3 x 10^6 of Hepa1-6 cells that overexpress EPO ($Hepa1\text{-}6_Epo^{OE}$).

After one week, mice were treated with liposomes containing 50 μg of either siRNA targeting EPOR (siEpor) or non-target control siRNA (siNTC) via intravenous injection every four days for a total of three doses. After three weeks post-injection, tumors were harvested, as shown in **FIG. 13B**, and the tumor volume was measured. In addition, a spontaneous model of cold HCC was generated by delivering plasmids pCMV-SB13, pT3-EF1a-C-Myc, and pX330-sgRNA targeting Trp53 to the liver of mice using hydrodynamic tail vein injection (HDTV) *in vivo* (**FIG. 13A**). After two weeks, mice were treated with liposomes containing 50 μg of either siEpor or siNTC via intravenous injection every four days for a total of six doses (**FIG. 13A**). After five weeks post-injection, livers were harvested, as shown in **FIG. 13C**, and liver weight was measured. The results showed that tumors from mice treated with siEpor had decreased tumor volume compared to mice treated with siNTC, suggesting that knocking down EPOR by using siEpor can reduce tumor growth in mice even when EPO is overexpressed.

[00600] In addition, macrophage-targeted liposomes loaded with siRNA targeting EPOR were tested. Physical properties of the macrophage-targeted liposomes are shown in **FIG. 14A**. To confirm the liposomes are targeted specifically to macrophages, C57BL/6 mice implanted with Hepa1-6_Epo^{OE} were administrated with liposomes loaded with 50 μg of fluorescein isothiocyanate (FITC)-conjugated siRNA. After 24 hours, tumors were harvested and dissociated into single cell suspension. Using flow cytometry analysis the percentage of FITC^{+} cells in different myeloid cell types were measured. As shown in **FIG. 14B** flow cytometry analysis indicated that macrophages are the major cell type that take up the liposomes. Next, to test the knockdown efficiency of siRNA targeting EPOR, 3 x 10^6 Epo-overexpressing Hepa1-6 cells were orthotopically implanted in C57BL/6 mice. After one week, mice were treated with liposomes containing 50 μg of either siRNA targeting EPOR (siEpor) or non-target control siRNA (siNTC) via intravenous injection every four days for a total of three doses. Tumors were harvested after 3 weeks post-injection and dissociated into single cell suspension. Macrophages were isolated with magnetic-activated cell sorting and RNA was extracted for real-time PCR quantification. The knockdown efficiency of EPOR in tumor-infiltrating macrophages is shown in **FIG. 14C**. EPOR mRNA levels in macrophages from mice injected with siEpor were lower than EPOR mRNA levels in macrophages from mice injected with siNTC (**FIG. 14C**).

Example 22. EPOR expression in patients with cancer

[00601] Human fresh tumor or tumor metastasis specimens were dissected from patients by surgery. Fresh specimens were digested with Liberase™ TL and DNase, and single cell suspension was made by lysing red cells with ACK lysis buffer. CD45+ tumor infiltrating immune cells were further analyzed with anti-CD11c, anti-HLA-DR, anti-CD123, anti-CD14, anti-CD16, anti-CD141, anti-anti-XCR1, anti-CD1c, anti-CD131 and anti-EpoR ab by flow

cytometry. Liver metastasis paired blood were analyzed by flow cytometry in the same way. Healthy donor blood, and liver cancer or liver cirrhosis patient blood were used to compare with EpoR+ cell percentage in liver metastasis patient blood CD45+ cell.

[00602] Myeloid cells from patients with breast cancer were collected and analyzed for EPOR expression with flow cytometry, as shown in **FIG. 15A**. Flow cytometry showed that myeloid cells from patients with breast cancer expressed high levels of EPOR. As shown in **FIG. 15B**, myeloid cells from breast cancer metastatic lymph node also expressed high levels of EPOR.

[00603] The amount of Epor+ peripheral blood mononuclear cells (PBMCs) of patients with metastatic liver cancer, patients with liver cancer or cirrhosis, and healthy donor were analyzed via flow cytometry and quantified as shown in **FIG. 16A** and **FIG. 16B**, respectively. PBMCs of patients with metastatic liver cancer had higher frequencies of Epor+ cells than PMBCs of healthy donor or patients with liver cancer.

Example 23. Antibodies Against the Homo-EPOR

[00604] Antibodies against the homo-EPOR are generated with animal immunization. The extracellular domains of EPOR are used to immunize the animals. The antigen specific B cells or hybridoma cells are isolated and the immunoglobulin genes are sequenced. The recombinant antibodies will be subjected to the antigen binding assays with the extracellular domains of homo-EPOR or the soluble homo-EPOR, and the staining assays on the cells expressing EPOR. The cells staining with antibodies specific to the homo-EPOR are further characterized for receptor activation by analyzing phosphorylation of the receptor, JAK2, and STAT5 after the receptor expressing cells are treated with the antibody with or without EPO.

[00605] Alternatively, the homo-EPOR specific antibody can be isolated by screening an antibody expression library, e.g., phage display, yeast display, ribosomal display, cell display.

[00606] Anti-homo-EPOR antibodies can be agonists or antagonists for homo-EPOR. Some anti-homo-EPOR antibodies can be agonists or antagonists for the hetero-EPOR.

[00607] The binding affinity of the homo-EPOR antibodies to the extracellular domains of a homo-EPOR is determined using a functional ELISA. Soluble homo-EPOR (Sino Biological) are coated on a standard ELISA. The wells are blocked with 2% BSA. Dilutions of anti-homo-EPOR antibodies are added to the plates and incubated. After washing, the bound anti-homo-EPOR antibodies are detected using biotinylated polyclonal anti-EPO (R&D Systems) followed by streptavidin HRP conjugate or other appropriate secondary antibodies. After washing, TMB reagent (Sigma) is added and OD absorption at 450 nm is measured in a plate reader.

Example 24. Erythropoiesis Stimulating Activity and/or Antigen Specific Tolerance Activity of Agonistic Anti-Homo-EPOR Antibodies

[00608] Agonistic antibodies specific to the homo-EPOR are tested similarly as described in Example 6.

Example 25. Erythropoietic Activity of Anti-Homo-EPOR Antibodies

[00609] Agonistic antibodies specific to the homo-EPOR are tested similarly as described in Example 8.

Example 26. Antibodies Against the Hetero-EPOR

[00610] Antibodies against the hetero-EPOR were generated with animal immunization. Chimeric Fc fusion proteins of the extracellular domains of human EPOR and human CD131 (SinoBiological, Cat# CT010-H02H) were immunized in the ATX-GK and ATX-GL mice from Alloy Therapeutics. The ATX-GK strain contains the human antibody heavy chains and the human antibody kappa light chains whereas the ATX-GL strain contains the human antibody heavy chains and the human antibody lamda light chains. B cells from spleen and lymph nodes were harvested after immunization.

[00611] The B cells from ATX-GL mice were stained with fluorescence labeled recombinant hEPOR-Fc Fc (SinoBiological, Cat# 10707-H02H) and hCD131-Fc (IME021, inhouse). After counter screening with an irrelevant human Fc fusion protein, the positive B cells that bind hEPOR-Fc, hCD131-Fc, or both were sorted into 3 populations and subjected to single cells sequencing. 188, 136, and 129 unique human antibody sequences were obtained from the EPOR-Fc binders, the CD131-Fc binders, and the EPOR-Fc/CD131-Fc binders, respectively. The VH-CDR3, VL-CDR3, full length VH, and full length VL sequences are listed in **Tables 4-9**.

[00612] The B cells from ATX-GK mice were fused with mouse myeloma cells to generate hybridoma. The hybridoma cells were screened twice. In the first screening, 293 cells expressing human EPOR, human CD131, or both were used as the primary screen. 87 hybridoma antibodies have been isolated by positive staining on 293T cells expressing human EPOR (hEPOR), human CD131 (hCD131), or both, with the hybridoma supernatants (**Table 11** and **FIG. 17**). Hybridoma clones and their efficiency of blocking EPO/EPOR interaction are shown in **Table 11** and **FIG. 17**. Expression of EPOR and CD131 was confirmed by flow cytometry with Phycoerythrin (PE)-labeled anti-EPOR (R&D, Cat# FAB307P) and Alexa Fluor® 647 (AF647)-labeled anti-CD131 (BD Bioscience, Cat# 564191), respectively (**FIG. 28B**). All hybridoma clones were purified and sequenced. 17 clones with unique antibody sequences are shown in **Table 10** and **FIG. 28A**. Binding kinetics with soluble hetero-EPOR (EPOR-CD131-Fc), soluble EPO receptor subunit of hetero-EPOR (EPOR-Fc), and soluble CD131 subunit of hetero-EPOR (CD131-Fc) were measured in Octet BLI by capturing the hybridoma antibodies in the supernatants on biosensors coated with anti-mouse Fc first and

dipping the biosensors into the solutions containing 30 nM of the soluble receptor Fc fusion proteins. The supernatants were also used to block the interaction between EPO and EPOR. The soluble EPOR-CD131-Fc was first captured on biosensors coated with anti-human Fc and then dipped into 10 nM of EPO with or without the hybridoma supernatants. Clones M1 and M2 exhibited potent binding to EPOR-CD131-Fc and EPOR-Fc. Clone M82 exhibited potent binding to CD131-Fc. Clone M26 bound all three soluble receptors with high affinity (**FIG. 28A**). Clone M2 exhibited nearly complete blocking on the EPO/EPOR interaction while clones M1, M3, M9, M19, M24, M26, M41, M52, M54, M82, and M87 exhibited partial blocking activities. Clones M37, M38, M43, M71, and M80 did not block the EPO/EPOR interaction under this condition (**FIG. 28A**).

[00613] The purified antibodies were used to stain the human leukemia UT-7 cells, 293T/EPOR, 293T/CD131, and 293T/EPOR/CD131 cells to confirm antigen binding. The UT-7 cells were maintained in Roswell Park Memorial Institute (RPMI) with 10% Fetal Bovine Serum (FBS) and 5 ng/ml of recombinant human GM-CSF (Peprotech, Cat# 300-03). The 293T cells expressing hEPOR, hCD131, or both were maintained in Dulbecco's Modified Eagle Medium (DMEM) with 10% FBS. $1x10^6$ cells/ml were incubated with purified hybridoma clones M2 and M41 at a 3-fold dilution series starting from 20 μg/ml for 30 minutes at 4°C. After washing, the cells were incubated with PE labeled secondary antibody and subjected to flowcytometric analysis. Both M2 and M41 exhibited robust binding activities at 20 μg/ml. However, M2 showed ~100% mean or median fluorescence intensity (MFI) at 27 ng/ml whereas M41 lost most of the binding at 0.74 μg/ml, suggesting M2 has a higher affinity for anti-EPOR binding than M41 (**FIG. 29A**). The binding profiles of the 293T/EPOR/CD131 cells are similar except the peak MFIs around 1500, half of that of the 293T/EPOR cells (**FIG. 29B**). M2 and M41 did not stain the 293T/CD131 cells indicating they are specific to EPOR (**FIG. 29C**). M2 exhibited a much more stronger staining signal on the UT-7 cells with MFI ~18,000 suggesting a higher expression level of EPOR in the UT-7 cells (**FIG. 29D**). However, the peak staining signal of M41 on the UT-7 cells was similar to that of 293T/EPOR cells suggesting the epitopes these two clones bind on EPOR may be different (**FIG. 29D**).

[00614] EPOR activation leads to phosphorylation of Stat5. A flow-based assay on phosphorylated Stat5 was set up to test the blocking activities of anti-EPOR antibodies. The UT-7 cells were cultured without GM-CSF for overnight before the EPO stimulation. $3x10^6$ cells/ml were incubated with 20 μg/ml of anti-EPOR for 15 minutes before stimulation with 0.1 μg/ml of recombinant human EPO (Peprotech, Cat# 100-64) for 10 minutes at 37°C. The cells were fixed immediately with Cytofix buffer (BD Bioscience, Cat# 554655) and permeabilized with methanol. After washing, cells were stained with PE labeled anti-Stat5 (BD Biosciences, Cat#

612567) and subjected to flow cytometry analysis. M2 exhibited complete blocking on the Stat 5 phosphorylation whereas M41 showed partial blocking (**FIG. 30**).

[00615] In the second screening, Elisa binding assays of the recombinant hEPOR-Fc, mEPOR-Fc (IME066, inhouse), and a heterodimeric knobs-in-holes Fc fusion protein of hEPOR ECD and hCD131 D3-D4 domains (IME027/078, inhouse) were used as the primary screen. 205 positive clones were isolated and expanded.

Example 27. Erythropoiesis Stimulating Activity and/or Antigen Specific Tolerance Activity of Agonistic Anti-Hetero-EPOR Antibodies

[00616] Agonistic antibodies specific to the hetero-EPOR are tested similarly as described in Example 6.

Example 28. Erythropoietic Activity of Anti-Hetero-EPOR Antibodies

[00617] Agonistic antibodies specific to the hetero-EPOR are tested similarly as described in Example 8.

Example 29. Engineering EPOs and Activation of Homo-EPOR and Hetero-EPOR by Engineered EPOs

[00618] To generate EPO analogs that selectively activate homo-EPORs or hetero-EPORs, EPO analogs were engineered to have amino acid substitutions in Site 1, Site 1/2, or Helix B, as indicated in **Tables 3-1** and **3-2**. EPO analogs with amino acid substitutions of one or more Lys residues that can mimic carbamylated EPOs (CEPOs) were also generated (**Tables 3-1** and **3-2**). Recombinant human EPO (rhEPO) was cloned into mammalian expression vectors to express as human immunoglobulin Fc or albumin fusion proteins. EPO was fused at the N-terminus of human IgG4 Fc or human serum albumin (HSA) in expression vectors IME001 or IME003, respectively, and at the C-terminus of human albumin in IME004. Expression of IME001, 003, and 004 was carried out in Expi293 cells (ThermoFisher, Cat# A41249) by transient transfection. IME001 was purified by Protein A chromatography whereas IME003 and IME004 were purified by CaptureSelect Human Albumin Affinity Matrix (ThermoFisher, Cat# 191297005). The dimeric IME001 and monomeric IME003 and IME004 are shown in SDS-PAGE (**FIG. 31A**).

[00619] Receptor binding activities of IME001, IME003, and IME004 were confirmed in a cell staining assay. The 293T cells expressing EPOR were prepared with lentiviral transduction and FACS sorting. The 293T/EPOR cells were first validated by staining with an anti-EPOR Phycoerythrin (PE) conjugate (R&D Systems, Cat# FAB307P) in **FIG. 32A**. The 293T/EPOR cells were incubated with IME001 at 0.01, 0.1, or 1 μg/ml for 30 minutes at 4 °C. After washing, the cells were incubated with a secondary anti-human Fc PE conjugate (R&D systems, Cat# FAB110P) and then subjected to flow cytometry analysis. IME001 exhibited robust binding even at 0.01 μg/ml (**FIG. 32B**). Staining of IME003 and IME004 was carried out similarly. The

293T/EPOR cells were incubated with IME003 or IME004 at 0.1, 1, or 10 μg/ml for 30 minutes at 4 °C, followed by incubation with biotinylated anti-HSA (ThermoFisher, Cat# A80-129B) and streptavidin PE conjugate (R&S systems, Cat# F0040). Both IME003 and IME004 exhibited robust binding at 1 μg/ml and much reduced binding at 0.1 μg/ml (**FIG. 32C**).

[00620] Next, EPOR activation level was measured using purified engineered EPO analogs. Activation of homo-EPOR or hetero-EPOR by ligand (EPO) binding leads to phosphorylation of the intracellular domains of the receptor and downstream JAK2 and STAT5, which can be used to assay EPO activities. EPO can be modified by carbamylation to generate carbamylated EPO (CEPO) which is unable to activate the homodimeric EPOR (homo-EPOR) but retains the ability to activate the heterodimeric EPOR (hetero-EPOR). Briefly, 1 mg/ml of rhEPO was mixed with 1 M Na-borate (pH ~ 8.8) first. Recrystallized KOCN was then added to a final concentration of 1 M. The mixture was incubated at 37 °C for 24 hours before being dialyzed against milli-Q water and subsequently against 20 mM sodium citrate in 0.1 M NaCl, pH 6.0. After dialysis, CEPO was concentrated and buffer was changed to PBS. CEPO was validated by protection from Lys-C digestion. rhEPO or CEPO was incubated with 10 mM DTT, 30 mM iodoacetic acid and 5 M urea for 30 minutes in the dark before Lys-C proteinase (NEB, Cat# P8109S) was added for 20 hours at 37 °C. The digested samples were then analyzed in SDS-PAGE. rhEPO was completely degraded by Lyc-C whereas CEPO was protected (**FIG. 31B**).

[00621] IME001, IME003, IME004, and CEPO were used to stimulate the 293T/EPOR cells for 10 minutes after overnight culturing in DMEM without FBS. The cells were immediately lysed and the lysate was subjected to Western blotting with Human Phospho-STAT5a/b (Y694/Y699) Antibody (R&D systems, Cat# MAB41901). IME001, IME003, and IME004 at 1 μg/ml exhibited robust stimulation activities for Stat5 phosphorylation whereas CEPO was inactive (**FIG. 33A**). Similar results were obtained with the STAT5 alpha/beta (Phospho) [pY694/pY699] Human InstantOne™ ELISA Kit (Invitrogen, Cat# 85-86112-11). After stimulation with 1 μg/ml of IME001, IME003, and IME004, the 293T/EPOR cell lysate was prepared and subjected to the phosphor Stat5 ELISA assay. All three proteins exhibited ~10 folds higher signals than the untreated control (**FIG. 33B**).

[00622] EPO binds the homo-EPOR on two sites, a high affinity site 1 and a low affinity site 2 which is important for the receptor signaling. EPO variants with mutations on site 1 (K47D, N147K, R150E, G151A) or site 2 (R103A), or both were cloned into IME001 as Fc fusion proteins (**Table 3-1**). They were produced from Expi293 cells similarly as IME001 and were used to stimulate the 293T/EPOR cells. Phosphorylation of Stat5 was assayed by Western blotting and/or specific ELISA kit. IME005-007 with single mutations in the site 1 significantly reduced the Stat5 phosphorylation which is further reduced when combined with the site 2

mutation R103A in IME009-011 (**Table 3-1**). IME008 that carries the site 2 mutation R103A exhibited a much reduced, albeit still significant, activity. Interestingly, when R103A was introduced in the monomeric EPO-HSA fusion protein in IME043, the EPOR activation was abolished, indicating that the dimeric Fc fusion protein may have enhanced EPOR activation. The EPO variants that do not activate the homo-EPOR may still activate the heterodimeric EPOR to mediate immune response.

[00623] The helix B of EPO is not involved in the conventional sites 1 or 2 of interaction with the homo-EPOR. However, it has been suggested to be important in interaction with the heterodimeric EPOR/CD131 (hetero-EPOR). The peptide derived from the surface residues of the helix B has been demonstrated to be able to activate the hetero-EPOR but not the homo-EPOR. The helix B peptide (HBP) RMEVGQQAVEVWQGLALLSEAVLRGQALLV or the surface peptide of the helix B (HBSP) QEQLERALNSS was cloned at the C terminus of albumin to express as albumin fusion proteins in IME030 or IME031, respectively. IME030 and IME031 did not activate the homo-EPOR as expected (**Table 3-1**). The surface residues in the helix B were mutated in order to disrupt the interaction between EPO and the hetero-EPOR. Mutations of Q58A, E62A, E62R, Q65A, L69A, E72A, E72R, R76A, R76E, L80A, N83A, S84A, or S85A were introduced in the helix B of EPO as single mutations or multiple mutations as Fc fusions or albumin fusions. IME012, IME015, IME032, and IME034 lost most of the activities to stimulate the homo-EPOR, whereas IME013-014, IME033, IME037-040, IME042, and IME044-045 maintained most of the activities to stimulate the homo-EPOR (**Table 3-1**). The helix B residues can be further engineered by saturation mutagenesis to identify the EPO variants that activate the homo-EPOR but not the hetero-EPOR, which can mediate erythropoiesis without promoting cancer growth.

[00624] The Lys residues in EPO can be modified by carbamylation resulting in carbamylated EPO (CEPO), which has been demonstrated to activate the hetero-EPOR but not the homo-EPOR, suggesting some of the Lys residues are required for activation of the homo-EPOR. The eight Lys residues (K20, K45, K52, K97, K116, K140, K152, and K154) were mutated to Ala as single mutations or multiple mutations. IME046 maintained most of the activities to stimulate the homo-EPOR, whereas IME047-049 lost most of the activities to stimulate the homo-EPOR (**Table 3-1**). The Lys residues can be further engineered by saturation mutagenesis to differentiate activation of the hetero-EPOR and the homo-EPOR.

[00625] The 293T cells expressing both EPOR and CD131 were used to test activation of the hetero-EPOR. Wild-type EPO stimulated phosphorylation of Stat5 in the 293T/EPOR/CD131 cells as effectively as in the 293T/EPOR cells. CEPO, which was inactive for Stat5 phosphorylation in 293T/EPOR cells, was able to stimulate Stat5 phosphorylation in

293T/EPOR/CD131 cells, albeit at a lower activity than EPO (**Tables 3-1 & 3-2**), indicating presence of heterodimeric EPOR/CD131 in these cells. Consistently, the helix B-derived peptide fusion IME031 also stimulated Stat5 phosphorylation in the 293T/EPOR/CD131 cells. IME008, IME010, IME011, and IME043, which carry mutations in the site 1 and/or site 2, did not stimulate phosphorylation of Stat5 in the 293T/EPOR/CD131 cells. IME013 and IME040, which carry mutations in the helix B, exhibited potent phosphorylation of Stat5 in the 293T/EPOR/CD131 cells similar to that in the 293T/EPOR cells. However, IME033 and IME037-039 exhibited much reduced level of activities in the 293T/EPOR/CD131 cells than that in the 293T/EPOR cells, suggesting that residues Q58, L69, E72, and L80 are important for the interaction between EPO and the hetero-EPOR. IME046 containing the Lys to Ala mutations at positions of K20, K45, and K52 was fully active in Stat5 phosphorylation in the 293T/EPOR cells but lost most of the activities in the 293T/EPOR/CD131 cells (**Table 3-2**), indicating majority of the EPOR in these cells are the hetero- EPOR. Further EPO engineering by saturation mutagenesis in these positions can be carried out to identify EPO variants specific to the homo-EPOR.

[00626] The amino acid sequence and nucleic acid sequence of human EPO including the signal peptide sequence are shown in **FIG. 34**. The amino acid residue position numbers in EPO variants do not include the amino acid residue position numbers of the signal peptide. The amino acid sequence of human EPO without the signal peptide sequence is the sequence of SEQ ID NO: 1.

[00627] The extracellular domain of EPOR consists of 2 domains D1 and D2 which are both required for EPO binding. The Fc fusion protein of the EPOR extracellular domain (ECD) EPOR-Fc has been reported to bind EPO and block the EPOR activation. EPOR-Fc has been cloned in a mammalian expression vector IME020 and produced in HEK293 cells, and demonstrated its binding to EPO (**FIG. 32D**). EPOR Mutation of F93A was introduced in IME020 to produce IME083 to remove binding of EPO to either monomeric EPOR ECD or dimeric EPOR-Fc. Binding of IME003 and IME004 to IME083 was tested similarly as IME020. There was no binding between IME003 or IME004 to IME083 (**FIG. 41A**).

[00628] The extracellular domain of CD131 consists of 4 domains D1, D2, D3, and D4. The D1 and D2 domains are responsible for dimerization distal to the membrane. The D3 and D4 domains are likely the regions interacting with EPOR. Heterodimerc Fc fusion proteins were constructed with EPOR ECD and CD131 ECD via knobs-in-holes technology. The designs are shown in **Table 3-3**. The sequences of the receptor ECDs are shown in **FIGs. 42A-42D**. The EPO binding of these Fc fusions were assayed similarly in an ELISA binding assay. IME061/IME062 and IME061/IME063 exhibited potent binding to IME003 or IME004 with

EC50 of ~10 ng/ml, whereas IME061/IME064 did not, suggesting both CD131 D3 and D4 domains are required for EPO binding (**FIG. 41B-41C**). Interestingly, IME063/IME084 also exhibited similar potent binding suggesting the EPO binding requires the CD131 D3 and D4 domains under this condition since the F93A mutation in IME084 abolished the binding from the EPOR arm. The heterodimeric EPOR(F93A)/CD131-Fc likely contains a specific binding site of the hetero-EPOR to EPO, and may be used to block the hetero-EPOR and not the homo-EPOR.

Table 3-1. Engineered EPOs and Stat5 Phosphorylation in 293T/EPOR cells

Plasmid	Protein	Mutations	Note	EPO-mediated Stat5 Phosphorylation in 293T/EPOR	
				Western	Elisa
	rhEPO	none	WT	+++	100%
	CEPO	Carbamylated Lys		-	0
IME001	EPO-Fc	none	WT	+++	100%
IME002	EPO-Fc	N24Q/N38Q/N83Q	No N-Glycan	ND	ND
IME003	EPO-HSA	none	WT	+++	100%
IME004	HSA-EPO	none	WT	+++	100%
IME005	EPO-Fc	K45D	Site 1	+	86%
IME006	EPO-Fc	N147K	Site 1	+	37%
IME007	EPO-Fc	R150E	Site 1	+/-	27%
IME008	EPO-Fc	R103A	Site 2	+	30%
IME009	EPO-Fc	K45D/R103A	Site 1&2	-	13%
IME010	EPO-Fc	N147K/R103A	Site 1&2	-	5%
IME011	EPO-Fc	R150E/R103A	Site 1&2	-	5%
IME012	EPO-Fc	E62R	Helix B	-	4%
IME013	EPO-Fc	Q65A	Helix B	+++	100%
IME014	EPO-Fc	E72R	Helix B	+++	82%
IME015	EPO-Fc	R76E	Helix B	-	27%
IME016	EPO-Fc	E62A/Q65A/E72A/R76A	Helix B	ND	ND
IME017	HBP-Fc		Helix B peptide	ND	ND
IME028	EPO-Fc	N24A/N38A/N83A	No N-Glycan	+++	ND
IME029	EPO-Fc	N24S/N38S/N83S	No N-Glycan	+++	ND
IME030	HSA-HBP		Helix B peptide	-	0
IME031	HSA-HBSP		Helix B surface peptide	-	0
IME032	EPO-Fc	E62A	Helix B	+	2%
IME033	EPO-Fc	E72A	Helix B	+++	75%
IME034	EPO-Fc	R76A	Helix B	+	5%
IME035	EPO-Fc	G151A	Site 1	ND	ND
IME036	EPO-Fc	R103A/G151A	Site 1&2	ND	ND
IME037	EPO-Fc	Q58A	Helix B	+++	71%
IME038	EPO-Fc	L69A	Helix B	++	57%
IME039	EPO-Fc	L80A	Helix B	+++	32%
IME040	EPO-Fc	N83A	Helix B	+++	45%
IME041	EPO-Fc	S84A	Helix B	ND	ND
IME042	EPO-Fc	S85A	Helix B	+++	ND

Plasmid	Protein	Mutations	Note	EPO-mediated Stat5 Phosphorylation in 293T/EPOR	
				Western	Elisa
IME043	EPO-HSA	R103A	Site 2	-	0
IME044	EPO-HSA	Q65A/E72R	Helix B	+++	94%
IME045	EPO-HSA	Q65A/E72R/N83A	Helix B	+++	105%
IME046	EPO-HSA	K20A/K45A/K52A	Lys	+++	90%
IME047	EPO-HSA	K140A/K152A	Lys	+	23%
IME048	EPO-HSA	K140A/K152A/K154A	Lys	+	11%
IME049	EPO-HSA	K20A/K45A/K52A/K140A/ K152A/K154A	Lys	+	15%
IME050	EPO-HSA	K97A/K116A	Lys	ND	ND
IME051	EPO-HSA	K20A/K45A/K52A/K97A/ K116A/K140A/K152A/ K154A	Lys	ND	ND
IME077	EPO-HSA	K45D/R103A	Site 1&2		
IME085	EPO-HSA	K97A	Lys	ND	ND
IME086	EPO-HSA	K116A	Lys	ND	ND
IME087	EPO-HSA	K140A	Lys	ND	ND
IME088	EPO-HSA	K152A	Lys	ND	ND
IME089	EPO-HSA	Q58A/Q65A/E72R	Helix B	ND	ND
IME090	EPO-HSA	L80A/N83A/S84A/S85A	Helix B	ND	ND
IME091	EPO-HSA	Q58A/Q65A/E72R/ L80A/N83A/S84A/S85A	Helix B	ND	ND
IME092	EPO-HSA	Q58A/L69A	Helix B	ND	ND
IME093	EPO-HSA	Q58A/L80A	Helix B	ND	ND
IME094	EPO-HSA	L69A/L80A	Helix B	ND	ND
IME095	EPO-HSA	Q58A/L69A/L80A	Helix B	ND	ND

Table 3-2. Engineered EPOs and Stat5 Phosphorylation in 293T/EPOR/CD131 cells

Plasmid	Protein	Mutations	Note	EPO-mediated Stat5 Phosphorylation in 293T/EPOR/CD131	
				Western	Elisa
rhEPO	EPO-Fc	none	WT	+++	+++
CEPO	EPO-Fc	Carbamylated Lys		+	+
IME001	EPO-Fc	none	WT	+++	ND
IME004	HSA-EPO	none	WT	+++	ND
IME008	EPO-Fc	R103A	Site 2	+	ND
IME010	EPO-Fc	N147K/R103A	Site 1&2	-	+
IME011	EPO-Fc	R150E/R103A	Site 1&2	-	ND
IME013	EPO-Fc	Q65A	Helix B	+++	ND
IME030	HSA-HBP		Helix B peptide	-	ND
IME031	HSA-HBSP		Helix B surface peptide	+	ND
IME033	EPO-Fc	E72A	Helix B	+	ND
IME037	EPO-Fc	Q58A	Helix B	+	ND
IME038	EPO-Fc	L69A	Helix B	+	+

Plasmid	Protein	Mutations	Note	EPO-mediated Stat5 Phosphorylation in 293T/EPOR/CD131	
				Western	Elisa
IME039	EPO-Fc	L80A	Helix B	+	ND
IME040	EPO-Fc	N83A	Helix B	+++	ND
IME043	EPO-HSA	R103A	Site 2	-	-
IME044	EPO-HSA	Q65A/E72R	Helix B	-	+
IME045	EPO-HSA	Q65A/E72R/N83A	Helix B	+	ND
IME046	EPO-HSA	K20A/K45A/K52A	Lys	+	+
IME047	EPO-HSA	K140A/K152A	Lys	-	ND
IME048	EPO-HSA	K140A/K152A/K154A	Lys	-	ND
IME049	EPO-HSA	K20A/K45A/K52A/K140A /K152A/K154A	Lys	-	ND

Table 3-3. Design of Heterodimeric EPOR/CD131-Fc Fusion Proteins

Plasmid	EPOR Arm (holes)	CD131 Arm (knobs)
IME061	hEPOR ECD	
IME062		hCD131 ECD
IME063		hCD131 D3D4
IME064		hCD131 D4
IME084	hEPOR ECD (F93A)	

Example 30. Treatment of Chronic Infection by EPOR Antagonists (Anti-EPO Antibodies, Anti-EPOR Antibodies, Anti-CD131 Antibodies, and/or EPO Analogs/Engineered EPOs)

Hetero-EPOR antagonists (anti-EPO antibodies, anti-EPOR antibodies, anti-CD131 antibodies, and/or EPO analogs/engineered EPOs that have antagonistic effects to hetero-EPOR) are administered to a chronic LCMV model. Mice are infected with 2×10^6 plaque-forming units (PFU) of LCMV-c13 by intravenous injection. The mice are treated with the EPOR antagonist by i.p. injection once or twice a week. At day 21, LCMV specific endogenous CD8+ T cells are detected by gp33-tetramer in CD8+TCRb+ T cells. Further detailed analysis of the gp33+ T cell fate are determined with anti-CD44, anti-PD-1, anti-Tim3, anti-SLAMF6, anti-CX3CR1, anti-KLRG1, and anti-TCF1 abs by flow cytometry in the spleen, lung and liver.

Example 31. Selectivity and Specificity of anti-EPO, anti-EPOR, and anti-CD131 antibodies

[00629] Anti-EPO, anti-EPOR, and anti-CD131 antibodies described herein are tested and analyzed for specificity and selectivity. Antibody specificity can be assessed by comparing binding signals in cells that express an endogenous level of a target, to binding signals in cells that overexpress a target, or to binding signals in cells that do not express a target. Antibodies with high specificity will have binding signal that responds proportionately with the amount of target protein present in cells and will not show any significant levels of non-specific binding signals (at the optimal dilution of the antibodies) in cells that do not express a target. 293T cells are transduced with lentiviruses encoding human EPOR or human CD131 to generate 293T cells

expressing EPOR, CD131, or both. Anti-EPOR or anti-CD131 antibodies are used to stain the wild-type 293T cells, 293T/EPOR cells, 293T/CD131 cells, or 293T/EPOR/CD131 cells to confirm the binding specificity (**Fig 28B**). The antibody specificity can also be assessed by binding to the soluble receptors. The extracellular domains of EPOR or CD131 are produced as soluble Fc fusion proteins. The heterodimeric EPOR/CD131 is also produced as soluble Fc fusion proteins by knobs-in-holes design. These soluble receptor Fc fusion proteins are used to bind the antibodies in ELISA assays or Octet BLI assays (**Fig 24A; 32D**).

[00630] Antibody selectivity can be assessed by comparing the reactivity to the intended target protein to the reactivity to other closely related proteins. Antibodies with high selectivity will have strong binding signal to a target protein without cross-reactivity to other closely related proteins (at the same time and at the same dilution), which can be tested by using antibodies to other related proteins (positive control antibodies). EPOR is a classical type-I cytokine receptor that belongs to the cytokine receptor family that also includes growth hormone receptor, prolactin receptor, and thrombopoietin receptor. CD131 is a common β chain receptor for GM-CSF, IL3, and IL5 as well. The anti-EPOR and anti-CD131 antibodies will be tested against these receptors for selectivity.

Example 32. Effect of EPOR deletion on tumor Ag-specific CD8+ T-cell

[00631] In this example, how EPOR deletion in dendritic cells affects tumor Ag-specific CD8+ T-cells was investigated. As shown in **FIG. 27A**, control mice, mice with EpoR knockout in dendritic cells ($EpoR^{\Delta XCR1}$), and mice with mTOR knockout in dendritic cells ($mTOR^{\Delta XCR1}$) were given s.c. injection of B16F10-Ova to induce melanoma tumor at day 0 (D0). At day 7 (D7), mice were given i.v. injection of OT-I (CD8+ T-cells expressing T cell antigen receptor). At day 14, OT-I were isolated from tumor-draining lymph nodes (tdLN) of the mice, and the cells were analyzed by flow cytometry. The cells were analyzed for cell proliferation, as measured by CTV (cell trace violet), and for expression of exhausted T-cell markers (e.g., CD44, SLAMF6, PD-1, and Tim3), as shown in **FIG. 27B**. Flow cytometry data showed that $EpoR^{\Delta XCR1}$ and $mTOR^{\Delta XCR1}$ mice had 80.2% and 82.2% cells expressing CD44, a marker of progenitor exhausted T-cells, compared to 55.2% cells from control mice. Number of cells expressing SLAMF6, another marker of progenitor exhausted T-cells, was also measured via flow cytometry, and showed that $EpoR^{\Delta XCR1}$ and $mTOR^{\Delta XCR1}$ mice had more SLAMF6-expressing cells than control mice. There were, however, no significant changes in number of cells expressing markers of terminally exhausted T-cells (e.g., PD-1 and Tim3), compared to control mice. These data suggested that dendritic cell specific knockout of EpoR or mTOR can regulate Ag-specific CD8+ T-cell priming toward progenitor exhausted T-cells, which can be easier to control in tumor progression than terminally exhausted T-cells. Furthermore, quantification of percent of proliferated OT-I showed

that $EpoR^{\Delta XCR1}$ and $mTOR^{\Delta XCR1}$ mice had statistically significant increased percent of proliferated OT-I compared to control (**FIG. 27C**), suggesting that changes in proliferation of OT-I cells with changes in markers for exhausted T-cell compared to control can be a possible mechanism for reduced tumor burden in mice with $EpoR^{\Delta XCR1}$ as shown in **Example 19**.

[00632] Example 33. Effect of CEPO in antigen-specific tolerance

[00633] $CD11c^{Int}MHCII^{High}XCR1^{+}$cDC1s collected from peripheral lymph nodes (pLN) of mice were loaded with irradiated Ova-thy cells, cocultured with naïve OTII cells, and were either left untreated or treated with EPO or carbamylated (CEPO). $CD11c^{Int}MHCII^{High}XCR1^{+}$cDC1s with or without EPO/CEPO treatment were analyzed for FoxP3 expressing cells and proliferation with CellTrace™ Violet (CTV), via flow cytometry. As shown in **FIG. 38A**, flow cytometry analysis revealed that treatment with EPO or CEPO led to increased FoxP3 expressing cells at 71.2% or 69.3%, respectively, compared to untreated cells at 25.5%. Furthermore, quantification of the percent FoxP3+ Tregs in live OTII showed statistically a significant increase in the percentage of FoxP3+ Tregs with EPO or CEPO treatment compared to cells with no treatment. Since CEPO activates hetero-EPOR and not homo-EPOR, the result of increased FoxP3+ Tregs in live OTII with CEPO treatment suggest that hetero-EPOR activation mediates antigen-specific tolerance.

[00634] For further *in vitro* studies on the effect of CEPO with potential dependency to EPOR or mTOR, experiments with mice with mTOR knockout in dendritic cells ($mTOR^{\Delta XCR1}$), mice with EPOR knockout in dendritic cells ($EPOR^{\Delta XCR1}$) can be performed, as shown in **FIG. 38B**. $CD11c^{Int}MHCII^{High}XCR1^{+}$cDC1s are collected from peripheral lymph nodes (pLN) of mice with mTOR knockout in dendritic cells ($mTOR^{\Delta XCR1}$), mice with EPOR knockout in dendritic cells ($EPOR^{\Delta XCR1}$), and their littermate controls. The cells are loaded with irradiated Ova-thy cells and cocultured with naïve OTII cells with or without CEPO. Downstream analysis, such as flow cytometry analysis to measure FoxP3 expression and proliferation, is performed.

[00635] Example 34. Effect of EPOR on Peripheral Lymph Node (pLN) Migratory cDC1s

[00636] Peripheral lymph nodes (pLNs) were analyzed by flow cytometry from $EpoR^{tdt/+}$, $Zbtb46^{gfp/+}EpoR^{tdT/+}$, $CCR7^{-/-}EpoR^{tdT/+}$, $Batf3^{-/-}EpoR^{tdT/+}$, and wild type (WT) C57BL/6J mice to see whether EPOR was mainly expressed on migratory cDCs or resident cDCs. As shown in **FIG. 35A**, flow cytometry analysis revealed that for each mouse strains, EpoR-tdTomato was shown to be expressed by migratory cDCs ($MHCII^{high}CD11^{inter}$) and resident cDCs ($MHC^{inter}CD11^{high}$), but mostly in migratory cDCs. Similarly, histogram representation (**FIG. 35B**) showed EPOR expression in migratory and resident cDC1s of individual mouse strains. EPOR expressing cells on individual inguinal (10.5%), axillary (19.5%), branchial (10.4%), or superficial cervical (15.5%) lymph nodes was also quantified via flow cytometry, as shown in **FIG. 35C**. Furthermore, pLN migratory cDCs were gated as $XCR1^{+}$ cDC1s and $XCR1^{-}$ cDC2s,

and further gated with EPOR and CD103 expression via flow cytometry analysis. As shown in **FIG. 35D**, compared to the expression of EpoR in $XCR1^+$ cDC1s of $EpoR^{tdt/+}$and $Zbtb46^{gfp/+}EpoR^{tdT/+}$, there were decreased expression of EPOR in $XCR1^+$ cDC1s of $CCR7^{-/-}$ $EpoR^{tdT/+}$ and $Batf3^{-/-}EpoR^{tdT/+}$, suggesting that EPOR is mainly expressed on pLN migatory cDC1s in CCR7 and Batf3 dependent manners.

[00637] A different mouse strain was also created to analyze EPOR expression. As shown in **FIG. 35E**, EpoR-tdT-cre mice were cross bred with Rosa26-lox-Stop-lox-EYFP mice. EpoR-tdT-cre expression led to EYFP expression through floxing out the stop codon. pLN migratory cDC1s ($MHCII^{high}CD11^{inter}XCR1^+$) were gated for EYFP expression, via flow cytometry analysis, showing expression of EYEP and EPOR in pLN migratory cDC1s.

[00638] Next, peripheral lymph node migratory $EpoR^+XCR1^+$ cDC1s were characterized. As shown in the flow cytometry analysis in **FIG. 36**, peripheral lymph node migratory $EpoR^+XCR1^+$ cDC1s expressed DEC205 (CD205) and CCR7. Expression of PD-L1, Tim3, Axl and CD131 on $EpoR^{high}$ migratory cDC1s versus $EpoR^{low}$ migratory cDCs was analyzed, as shown in the histogram in **FIG. 36**.

[00639] To see if peripheral lymph node migratory $EpoR^+XCR1^+$ cDC1s mediate Ag-specific Tregs, pLN migratory EpoR+ cDC1s and $EpoR^-$ cDC1s were first sorted by flow cytometry, as shown in **FIG. 37A**. $2x10^4$ $CD45.2^+$ cDC1s were cocultured with $1x10^5$ purified macrophages and CellTrace™ Violet (CTV) labeled naïve $CD45.1^+$ OT-II cells. 100 ng/200ul DEC-205-Ova were added as cDC1-specific targeting antigen or cell-associated antigen. TGFβ was also added with a concentration of 2ng/ml. Next, cells with or without TGFβ treatment were analyzed for FoxP3 expression and proliferation with CTV, via flow cytometry. As shown in **FIG. 37B**, OT-II (e.g., $CD45.1^+CD3^+TCRva2^+CD4^+CD8^-$ cells) cultured with EpoR+ cDC1s with or without TGFβ displayed greater FoxP3 expression than OT-II cultured with $EpoR^-$ cDC1s. Quantification of both percent and mean or median fluorescence intensity (MFI) of FoxP3+ Tregs in live OTII showed statistically significant increase of FoxP3+ Tregs with EpoR+ cDC1s and TGFβ treatment compared to with EpoR+ cDC1s and TGFβ treatment.

[00640] Similar experiment was conducted with Gray irradiated Act-mOVA thymocytes and EPO treatment. $2x10^4$ $CD45.2^+$ cDC1s were cocultured with $1x10^5$ purified macrophages and CellTrace™ Violet (CTV) labeled naïve $CD45.1^+$ OT-II cells. $4x10^4$ 15 Gray irradiated Act-mOVA thymocytes ($CD45.2^+$) were added as cDC1-specific targeting antigen or cell-associated antigen. TGFβ was also added with a concentration of 2 ng/ml. EPO was added every day at a concentration of 40 IU/200ul over the course of five consecutive days. At day 6, cells with or without TGFβ treatment and with or without EPO treatment were analyzed for FoxP3 expression and proliferation with CTV, via flow cytometry. As shown in FIG. 37C, OT-II (e.g.,

$CD45.1^+CD3^+TCRva2^+CD4^+CD8^-$ cells) cultured with EpoR+ cDC1s displayed greater FoxP3 expression than OT-II cultured with $EpoR^-$ cDC1s. Addition of EPO increased the percent and MFI of FoxP3+ Tregs in live OTII cultured with $EpoR^-$ cDC1s to a level that was comparable to EpoR+ cDC1s with EPO. Collectively, the results suggest that peripheral lymph node migratory $EpoR^+XCR1^+$ cDC1s induced Ag-specific Tregs towards both DEC205-Ova and Ova-expressing cells.

[00641] Example 35. *In vivo* Studies on Migratory cDCs and Effect of EPO on Peripheral Ag-specific Tolerance

[00642] Migratory cDCs were s.c. injected into the 3rd mammary fat pad into the draining lymph node of mice, as shown in the experimental scheme in **FIG. 39A**. The cDC1s of the 3rd mammary fat pad were collected and analyzed via flow cytometry. As shown in **FIG. 39B**, cDCs from 3rd mammary fat pad were gated as live-dead $aqua^-CD11c^+Zbtb46^+$. $EPOR^+$ cDC1s were gated within $XCR1^+$ cDC1s and $CD103^+$. Flow cytometry analysis showed that majority of the 3rd mammary fat pad cDC1s expressed EPOR (76.8%). To investigate the effect of migratory cDCs carrying apoptotic cells, PKH67 labeled $CD45.1^+$ dexamethasone (DEX)-induced apoptotic thymocytes were s.c. injected into the 3rd mammary fat pad. After 12 hours later, the draining lymph node (inguinal LN) was analyzed by flow cytometry. As shown in **FIG. 39C**, $CD45.2^+CD45.1^-$ host cells were gated, and PKH67 positive signal was found in migratory ($MHCII^{high}CD11c^{inter}$) and resident cDCs ($MHCII^{inter}CD11c^{high}$) versus EpoR expression. It was found that migratory cDCs carrying apoptotic cells expressed more EPOR compared to resident cDCs.

[00643] Effect of EPO was studied *in vivo*, as shown in **FIG. 40A**, by injecting i.v. $5x10^5$ purified macrophages and CellTrace™ Violet (CTV) labeled naïve $CD45.1^+$ OT-II cells at day -1. At day 0, Dexamethasone (DEX)-induced apoptotic Act-mOVA thymocytes were s.c. injected into the 3rd mammary fat pad. 50 IU EPO was given i.p. for over the course of 4 consecutive days. At day 4, $CD45.1^+$OT-II in the draining lymph node (inguinal LN) was analyzed by flow cytometry. As shown in **FIG. 40B**, OT-II from mice with or without EPO treatment were gated as $CD45.1^+CD3^+TCRva2^+CD4^+CD8^-$. OTII was further gated for FoxP3 expression was versus CTV. Flow cytometry analysis revealed that with EPO, there was statistically significant increase in FoxP3+ cells (58.3% with EPO vs. 7.23% without EPO) and FoxP3 expression in adoptively transferred OTII, as measured by percent of FoxP3+ cells and MFI, respectively. The results showed that EPO promoted the peripheral Ag-specific tolerance in the draining lymph node towards cell associated Ags (Ova). A similar experiment can be done with CEPO.

[00644] Sequences

[00645] **Table 4.** VH-CDR3 and VL-CDR3 Sequences for Anti-EPOR Antibodies

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA sequence SEQ ID NO	Full LC AA sequence SEQ ID NO
clonotype10	20	IGHV6-1	IGLV2-14	CARKGELLGAFDIW	63	CSSYTSSSTWVF	251	439	627
clonotype13	18	IGHV6-1	IGLV2-23	CARKWELRDAFDIW	64	CCSYAGRSTLGIDWVF	252	440	628
clonotype22	8	IGHV3-20	IGLV3-1	CAREDYGDPGWFDPW	65	CQAWDSSTYVF	253	441	629
clonotype31	6	IGHV4-39	IGLV3-27	CATLTGDGDYW	66	CYSAADNNLVF	254	442	630
clonotype33	6	IGHV3-21	IGLV3-19	CARDRSSSWYSFDYW	67	CNSRDSSGNHRVF	255	443	631
clonotype36	6	IGHV3-21	IGLV2-11	CARDGITGTTFYFDYW	68	CCSYAGSYTWVF	256	444	632
clonotype42	5	IGHV3-33	IGLV2-8	CASIAAAGRDYW	69	CSSYAGSNNLVF	257	445	633
clonotype43	5	IGHV3-23	IGLV2-14	CAKAPELRFDYW	70	CSSYTSSSTYVF	258	446	634
clonotype44	5	IGHV1-18	IGLV2-23	CARNHYYYMDVW	71	CCSYAGSSTYVVF	259	447	635
clonotype45	5	IGHV4-34	IGLV3-19	CARGELGIGYWYFDLW	72	CNSRDSSGNHVVF	260	448	636
clonotype47	4	IGHV3-33	IGLV3-21	CARDTGITMVRGVFDYW	73	CQVWDSSSDHPVF	261	449	637
clonotype56	4	IGHV3-73	IGLV5-45	CNGVYGGSSYFFDYW	74	CMIWHSSAVVF	262	450	638
clonotype58	3	IGHV1-2	IGLV3-19	CARDETTIFDYW	75	CNSRDSSGNWVF	263	451	639
clonotype62	3	IGHV1-18	IGLV3-10	CARLGCNGTSCYTSWYYHFYMDVW	76	CYSTDSSGNHSWVF	264	452	640
clonotype66	3	IGHV3-33	IGLV2-14	CARDEDYYGSGSYSFDYW	77	CSSYTSSSTLVF	265	453	641
clonotype69	3	IGHV4-4	IGLV5-45	CARRGAARPFDYW	78	CMIWHSSAYVVF	266	454	642
clonotype75	2	IGHV2-5	IGLV3-1	CAHSNWNYGYFDLW	79	CQAWDSSTAWVF	267	455	643
clonotype80	2	IGHV3-23	IGLV3-10	CAKKDIVATHFDYW	80	CYSTDSSGNHKVF	268	456	644
clonotype82	2	IGHV3-15	IGLV3-19	CTTADYDFWSGYYMDVW	81	CNSRDSSGNHWVF	269	457	645
clonotype95	2	IGHV3-48	IGLV2-11	CARDRYNFDYW	82	CCSYAGSSWVF	270	458	646
clonotype99	2	IGHV3-20	IGLV2-14	CARGGDTAMVTVFDYW	83	CSSYTSSSTLVF	271	459	647
clonotype102	2	IGHV5-51	IGLV2-23	CARQINWGAIDYW	84	CCSYAGSSTFVVF	272	460	648
clonotype103	2	IGHV1-18	IGLV2-23	CARQITATRGFDYW	85	CCSYAGSSTFVVF	273	461	649
clonotype109	2	IGHV6-1	IGLV2-23	CARKWELRDTFDIW	86	CCSYAGSSTLGIDWVF	274	462	650

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA sequence SEQ ID NO	Full LC AA sequence SEQ ID NO
clonotype110	2	IGHV4-34	IGLV4-3	CASYGDFFDYW	87	CGESHTIDGQVGVVF	275	463	651
clonotype111	2	IGHV3-21	IGLV4-3	CARETELTVMDVW	88	CGESHTIDGQVGWVF	276	464	652
clonotype112	2	IGHV3-15	IGLV3-19	CTTDWEYYDFWSGYYSPYFDYW	89	CNSRDSSGNHVVF	277	465	653
clonotype397	1	IGHV4-30-4	IGLV3-21	CARAFDYW	90	CQVWDSRSDHVVF	278	466	654
clonotype398	1	IGHV4-30-4	IGLV3-21	CVRAFDYW	91	CQVWDLYSAHVVF	279	467	655
clonotype399	1	IGHV3-15	IGLV3-10	CTTGANW	92	CYSTDSSGNHWVF	280	468	656
clonotype400	1	IGHV1-8	IGLV2-14	CARVAFDIW	93	CSSYTSSSTVF	281	469	657
clonotype401	1	IGHV1-18	IGLV2-8	CARQIGDYW	94	CSAYAGSNNVVF	282	470	658
clonotype402	1	IGHV3-23	IGLV1-44	CHQTGEDYW	95	CAAWDDSLNGWVF	283	471	659
clonotype407	1	IGHV3-15	IGLV3-25	CTTGGTHW	96	CQSADSSATWVF	284	472	660
clonotype408	1	IGHV1-8	IGLV3-10	CARRSFLDYW	97	CYSTDSSGNHRVF	285	473	661
clonotype409	1	IGHV3-15	IGLV3-25	CTTGGTNW	98	CQSLDSSGTYWVF	286	474	662
clonotype413	1	IGHV3-21	IGLV3-1	CARESSGFDYW	99	CQAWDSSTVVF	287	475	663
clonotype414	1	IGHV1-8	IGLV3-1	CARGSSWFDYW	100	CQAWDSSTVVF	288	476	664
clonotype415	1	IGHV3-15	IGLV3-1	CTLNWGDYW	101	CQAWDSSTVVF	289	477	665
clonotype418	1	IGHV3-21	IGLV3-19	CARAADAFDIW	102	CNSRDSSGNHWVF	290	478	666
clonotype419	1	IGHV3-13	IGLV2-23	CARGGSDAFDIW	103	CCSYAGSVVF	291	479	667
clonotype420	1	IGHV3-15	IGLV3-19	CTTDHPYYW	104	CNSRDSSGNHVVF	292	480	668
clonotype421	1	IGHV3-15	IGLV3-19	CTTDHPYYW	105	CNSRDSSGNHWVF	293	481	669
clonotype423	1	IGHV3-33	IGLV1-36	CALAVTGFDYW	106	CAAWDDRLNGPVF	294	482	670
clonotype424	1	IGHV3-11	IGLV2-23	CARDGAAFDIW	107	CCSYAGSSTLVF	295	483	671
clonotype426	1	IGHV1-18	IGLV3-1	CARDRGYSFDYW	108	CQAWDSSTF	296	484	672
clonotype427	1	IGHV1-18	IGLV3-27	CARNHYYYLDVW	109	CYSAADNNRVF	297	485	673
clonotype428	1	IGHV3-13	IGLV3-27	CARVSPTGTTDYW	110	CYSAADNNLVF	298	486	674
clonotype429	1	IGHV3-15	IGLV3-27	CTARPLGDVW	111	CYSAADNNYVF	299	487	675

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA sequence SEQ ID NO	Full LC AA sequence SEQ ID NO
clonotype430	1	IGHV3-15	IGLV3-27	CTTDNGFDYW	112	CYSAADNNLVF	300	488	676
clonotype431	1	IGHV3-21	IGLV3-19	CARDLISSFDYW	113	CNSRDSSGNHLVF	301	489	677
clonotype432	1	IGHV3-7	IGLV3-19	CARRIVGAFDYW	114	CNSRDSSGNHLVF	302	490	678
clonotype434	1	IGHV1-46	IGLV3-21	CARGGWGTMDVW	115	CQVWDSSSDHVVF	303	491	679
clonotype435	1	IGHV3-48	IGLV3-10	CAREGWELLDYW	116	CYSTDSSGNHRVF	304	492	680
clonotype436	1	IGHV3-53	IGLV7-43	CARDNWDSYFDYW	117	CLLYYGGARVF	305	493	681
clonotype437	1	IGHV3-20	IGLV2-8	CARTTVTHMDVW	118	CSSYAGSNNLVF	306	494	682
clonotype438	1	IGHV3-53	IGLV2-23	CARDWNYDAFDIW	119	CCSYAGSSTWVF	307	495	683
clonotype439	1	IGHV3-21	IGLV2-23	CARGDPGWFDPW	120	CCSYAGSSTFWVF	308	496	684
clonotype442	1	IGHV3-74	IGLV3-1	CARENWNYWFDPW	121	CQAWDSSTVVF	309	497	685
clonotype443	1	IGHV4-4	IGLV3-1	CARLRPGDSFDYW	122	CQAWDSSTALVF	310	498	686
clonotype444	1	IGHV7-4-1	IGLV3-1	CARSPNWGLFDYW	123	CQAWDSSTSGVF	311	499	687
clonotype445	1	IGHV3-21	IGLV3-19	CARDRGATGFDYW	124	CNSRDSSGNHWVF	312	500	688
clonotype446	1	IGHV1-18	IGLV3-10	CARESGELLGDYW	125	CYSTDSSGNHRVF	313	501	689
clonotype448	1	IGHV3-13	IGLV3-19	CARYSGSYYYFDYW	126	CNSRDSSGNHVVF	314	502	690
clonotype450	1	IGHV3-33	IGLV3-10	CARGIAAAGKDYW	127	CYSTDSSGNHAVF	315	503	691
clonotype451	1	IGHV5-51	IGLV3-21	CARQDSNYVFDYW	128	CQVWDSSSDHVVF	316	504	692
clonotype452	1	IGHV3-7	IGLV1-44	CARDHSAWSFDYW	129	CATWDDSLNGRVF	317	505	693
clonotype453	1	IGHV3-7	IGLV2-8	CARRRGSCSFDYW	130	CSSYAGSNNLVF	318	506	694
clonotype454	1	IGHV1-18	IGLV2-8	CARRSYANCFDYW	131	CSSYAGSNNWVF	319	507	695
clonotype455	1	IGHV3-74	IGLV2-23	CARDEQLVPFDIW	132	CCSYAGSSTLVF	320	508	696
clonotype456	1	IGHV3-53	IGLV2-23	CARDGAAAGDFQHW	133	CCSYAGSSTWVF	321	509	697
clonotype457	1	IGHV3-43	IGLV2-8	CAKDSGSYYFDYW	134	CSSYAGSNNFVVF	322	510	698
clonotype458	1	IGHV3-11	IGLV1-40	CARDGQLWSFDYW	135	CQSYDSSLSDVVF	323	511	699
clonotype459	1	IGHV3-53	IGLV1-40	CGRVVPIGNWFDPW	136	CQSYDSSLSGWVF	324	512	700
clonotype460	1	IGHV3-7	IGLV5-45	CARDSNWGVFDYW	137	CMIWHSSAWVF	325	513	701

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA sequence SEQ ID NO	Full LC AA sequence SEQ ID NO
clonotype461	1	IGHV3-7	IGLV5-45	CARDRLTGDLDYW	138	CMIWHSSAWVF	326	514	702
clonotype464	1	IGHV3-74	IGLV3-9	CAREGDRSDAFAIW	139	CQVWDSSGSWVF	327	515	703
clonotype465	1	IGHV3-21	IGLV3-10	CARQQWLGYYFDYW	140	CYSTDSSGNHRVF	328	516	704
clonotype466	1	IGHV3-7	IGLV3-19	CARDSNFLYYFDYW	141	CNSRDTSGNYLVF	329	517	705
clonotype468	1	IGHV1-18	IGLV3-19	CARQITGTRGFDYW	142	CNSRDSSGNHWVF	330	518	706
clonotype469	1	IGHV1-8	IGLV3-10	CARMGYSNYPFDYW	143	CYSTDSSGNHVVF	331	519	707
clonotype470	1	IGHV1-46	IGLV3-19	CARGIPTTVTPDYW	144	CNSRDSSGNHLVF	332	520	708
clonotype471	1	IGHV3-13	IGLV3-10	CARAGLLTGDAFDIW	145	CYSTDSSGNHRVF	333	521	709
clonotype474	1	IGHV3-15	IGLV7-43	CITGTTFPFDYW	146	CLLYYGGAWVF	334	522	710
clonotype475	1	IGHV3-64	IGLV2-14	CTKGGVGASFDYW	147	CSSYTSSSTWVF	335	523	711
clonotype476	1	IGHV3-21	IGLV1-44	CARGDYSNYYFDYW	148	CAAWDDSLNGWVF	336	524	712
clonotype477	1	IGHV4-34	IGLV2-8	CARWEQPW	149	CSSYAGSNNWVF	337	525	713
clonotype478	1	IGHV1-46	IGLV2-23	CARRTGTTHYFDYW	150	CCSYAGSSTLVF	338	526	714
clonotype479	1	IGHV3-11	IGLV2-23	CARGLWLGLYFDYW	151	CCSYAGSSTWVF	339	527	715
clonotype480	1	IGHV5-51	IGLV2-8	CARFLGSSYYFDYW	152	CSSYAGSNNFEVF	340	528	716
clonotype481	1	IGHV3-48	IGLV5-45	CARGGAAAGAFDIW	153	CMIWHSSAWVF	341	529	717
clonotype486	1	IGHV4-30-4	IGLV3-1	CARAEWELLWFDPW	154	CQAWDSSTVVF	342	530	718
clonotype487	1	IGHV2-5	IGLV3-25	CAHNYFYISGYFYW	155	CQSANSGTWVF	343	531	719
clonotype488	1	IGHV3-30	IGLV3-1	CAKDPLRVVNYMDVW	156	CQAWDSSTVVF	344	532	720
clonotype490	1	IGHV2-5	IGLV3-25	CAQTGYNSWSFDYW	157	CQSADSSGTWVF	345	533	721
clonotype492	1	IGHV1-18	IGLV3-19	CAREDAWNYGWFDPW	158	CNSRDSSGNHVVF	346	534	722
clonotype493	1	IGHV1-18	IGLV3-10	CAREILWLGGYFDYW	159	CYSTDSSGNHRVF	347	535	723
clonotype494	1	IGHV7-4-1	IGLV3-19	CAREYSSGWYYFDYW	160	CNSRDSSGNHLVF	348	536	724
clonotype495	1	IGHV1-2	IGLV3-10	CARERIAVAPPFDYW	161	CYSTDSSGNHRVF	349	537	725
clonotype496	1	IGHV1-8	IGLV3-10	CARAGWELPEYFQHW	162	CYSTDSSGNHRVF	350	538	726
clonotype497	1	IGHV1-8	IGLV3-10	CARGGDDYSNLFDYW	163	CYSTDSSGNHRVF	351	539	727

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA sequence SEQ ID NO	Full LC AA sequence SEQ ID NO
clonotype498	1	IGHV1-69D	IGLV3-21	CARTPLGIGRSFDLW	164	CQVWDSNSDHWVF	352	540	728
clonotype499	1	IGHV3-15	IGLV3-25	CTTASTVTTGDYW	165	CQSADSSGTYPVF	353	541	729
clonotype501	1	IGHV6-1	IGLV3-19	CARERTEIDYW	166	CNSRDSSGNHWVF	354	542	730
clonotype502	1	IGHV3-15	IGLV7-46	CTTGRYFDWFDYW	167	CLLSYSGARVF	355	543	731
clonotype504	1	IGHV3-15	IGLV2-8	CTTASGSYWFDPW	168	CSSYAGSNNLVF	356	544	732
clonotype505	1	IGHV3-30	IGLV2-23	CAKGNWNYGDAFDIW	169	CCSYAGSSTYVF	357	545	733
clonotype506	1	IGHV3-20	IGLV2-14	CARENYDFWSGFDPW	170	CSSYTSSSTVVF	358	546	734
clonotype507	1	IGHV6-1	IGLV2-23	CAREDRGFDYW	171	CCSYAGSSNVVF	359	547	735
clonotype508	1	IGHV3-43	IGLV2-23	CAKRAVVTDYYMDVW	172	CCSYAGSSTFWVF	360	548	736
clonotype509	1	IGHV3-48	IGLV2-8	CARTSSWSYDAFDIW	173	CSSYAGSNNFVVF	361	549	737
clonotype511	1	IGHV1-46	IGLV3-1	CARERGHTVTPYFDYW	174	CQATEVF	362	550	738
clonotype512	1	IGHV3-48	IGLV3-27	CARDGPQVGATDFDYW	175	CYSAADNKVF	363	551	739
clonotype513	1	IGHV3-15	IGLV3-1	CTTEYSSSENFDYW	176	CQAWDSSTAVF	364	552	740
clonotype514	1	IGHV3-74	IGLV3-1	CARDLGAARPRGFDYW	177	CQAWDSSTVVF	365	553	741
clonotype515	1	IGHV3-23	IGLV3-10	CAKEGDSGYDSAFDIW	178	CYSTDSSGNRVF	366	554	742
clonotype517	1	IGHV4-4	IGLV3-10	CARVLNWNYGDAFDIW	179	CYSTDSSGNHRGF	367	555	743
clonotype518	1	IGHV4-4	IGLV2-11	CARDPSIVGATAFDIW	180	CCSYAQGVVF	368	556	744
clonotype519	1	IGHV4-4	IGLV3-19	CARSHIVGVNGGFDYW	181	CNSRDSSGNHWVF	369	557	745
clonotype520	1	IGHV3-21	IGLV3-19	CARDRYNWNYRAFDIW	182	CNSRDSSGNHLVF	370	558	746
clonotype522	1	IGHV3-7	IGLV3-19	CARDLGRGTISWFDPW	183	CNSRDSSGNHWVF	371	559	747
clonotype523	1	IGHV2-5	IGLV3-21	CTQTGYDSRWSFAYW	184	CQVWDSSSDHWVF	372	560	748
clonotype524	1	IGHV1-18	IGLV3-19	CAREGQWRGRGWFALW	185	CNSRDSSGNHLVF	373	561	749
clonotype526	1	IGHV7-4-1	IGLV3-19	CARERYFEDFHYMDVW	186	CNSRDSSGNHLVF	374	562	750
clonotype527	1	IGHV1-2	IGLV3-19	CARSSWLQLTYYFDYW	187	CNSRDSSGNHLLF	375	563	751
clonotype528	1	IGHV1-46	IGLV3-19	CAREGLQLGSNWFDPW	188	CKSRDSSGNHVVF	376	564	752
clonotype529	1	IGHV3-48	IGLV3-10	CARNDILTGEDAFDIW	189	CYSTDSSGNHRVF	377	565	753

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA sequence SEQ ID NO	Full LC AA sequence SEQ ID NO
clonotype530	1	IGHV3-23	IGLV3-19	CAKESIIVGATMFDYW	190	CNSRDSSGNHWVF	378	566	754
clonotype531	1	IGHV3-30	IGLV3-19	CAKGIAALGYYYMDVW	191	CNSRDSSGNHLVF	379	567	755
clonotype532	1	IGHV5-51	IGLV3-19	CAKRRITGSHNWFDPW	192	CNSRDSSGNHLVF	380	568	756
clonotype534	1	IGHV7-4-1	IGLV7-43	CARGGTIFGVVNFDYW	193	CLLYYGGARVF	381	569	757
clonotype537	1	IGHV3-33	IGLV2-23	CLSRSGYSAHNDGDYW	194	CCSYAGSSTWVF	382	570	758
clonotype538	1	IGHV1-2	IGLV1-40	CTKEGLVVRPDWFDPW	195	CQSYDSSLSGPVF	383	571	759
clonotype539	1	IGHV6-1	IGLV2-23	CARKGRDVFDIW	196	CCSYAGSSTYWVF	384	572	760
clonotype540	1	IGHV1-18	IGLV1-40	CAREGSGSYSDAFDIW	197	CQSYDSSLSGSYVF	385	573	761
clonotype541	1	IGHV2-5	IGLV5-45	CTHTEYRNTWCVDYW	198	CMIWHSSAIVF	386	574	762
clonotype542	1	IGHV2-5	IGLV5-45	CAHSPYTSGWPFDYW	199	CMIWHSSASVF	387	575	763
clonotype543	1	IGHV1-8	IGLV5-45	CARVSYSSSWSLFDYW	200	CMIWHSSAWVF	388	576	764
clonotype548	1	IGHV2-70	IGLV3-19	CARIRGVGALDGFDFW	201	CNSRDSSGNHLVF	389	577	765
clonotype549	1	IGHV1-18	IGLV3-19	CARPLDYGDYEGWFDPW	202	CNSRDSSGNHLVF	390	578	766
clonotype550	1	IGHV1-18	IGLV3-19	CAREGRTNYFYYYMDVW	203	CNSRDSSGNHWVF	391	579	767
clonotype552	1	IGHV3-43	IGLV3-19	CAKDITASGDYYYMDVW	204	CNSRDSSGNHLVF	392	580	768
clonotype553	1	IGHV3-48	IGLV3-19	CARDRVYNWNDGAFDIW	205	CNSRDSSGNHVVF	393	581	769
clonotype554	1	IGHV3-23	IGLV3-19	CAKDQRYNWNSWYFDLW	206	CNSRDSSGNHLVF	394	582	770
clonotype555	1	IGHV3-33	IGLV3-10	CARDHGGVTTYNWFDPW	207	CYSTDSSGNHRVF	395	583	771
clonotype559	1	IGHV1-2	IGLV2-8	CARDRMVRGVLDAFDIW	208	CSSYAGSNNVVF	396	584	772
clonotype560	1	IGHV3-48	IGLV2-8	CVRGYSSGWYNWYFDLW	209	CSSYAGSNNLVF	397	585	773
clonotype561	1	IGHV3-11	IGLV7-43	CARKVPGIAAAGAFDYW	210	CLLYYGGAQLVF	398	586	774
clonotype562	1	IGHV7-4-1	IGLV1-40	CARGGYGYNFWIRFDPW	211	CQSYDNSLSGSVF	399	587	775
clonotype568	1	IGHV4-39	IGLV3-27	CASYWNFDYW	212	CYSAADNNLVF	400	588	776
clonotype569	1	IGHV4-4	IGLV3-10	CARVLGYSYGYRRWFDPW	213	CYSTDSSGNHRVF	401	589	777
clonotype573	1	IGHV3-15	IGLV3-21	CTTEGSFNFYYFMDVW	214	CQVWDSTSDHYVF	402	590	778
clonotype576	1	IGHV4-59	IGLV2-23	CARDPFYYDFSDYYYMDVW	215	CCSYAGTISWVF	403	591	779

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA sequence SEQ ID NO	Full LC AA sequence SEQ ID NO
clonotype577	1	IGHV3-23	IGLV2-23	CAKNEARDYYGSGSFDYW	216	CCSYAGSSTYVF	404	592	780
clonotype578	1	IGHV3-20	IGLV2-8	CASLVGATDYYFYYMDVW	217	CSSYAGSNNWVF	405	593	781
clonotype579	1	IGHV6-1	IGLV2-23	CARKWELLDAFDIW	218	CCSYAGSSTWVF	406	594	782
clonotype581	1	IGHV3-48	IGLV1-40	CAREERDDYSNYGYFQHW	219	CQSYDSSLSGWVF	407	595	783
clonotype582	1	IGHV6-1	IGLV2-18	CARGDWNYGVLDSW	220	CSSYTSSSTYVVF	408	596	784
clonotype583	1	IGHV1-18	IGLV1-40	CARSGYNWNYDYYFMDVW	221	CQSYDISLSGSVVF	409	597	785
clonotype586	1	IGHV3-20	IGLV3-1	CARDGCSSTSCYGNWFDPW	222	CQAWDSSTAVF	410	598	786
clonotype587	1	IGHV6-1	IGLV3-10	CARVDFGIVGAIDYW	223	CYSTDSSGKIF	411	599	787
clonotype588	1	IGHV3-21	IGLV3-19	CARDRDDFWSGYSPYFDYW	224	CNSRDSSGNHWVF	412	600	788
clonotype589	1	IGHV3-21	IGLV3-19	CAREKYDILTGYSPYFDYW	225	CNSRDSSGNHWVF	413	601	789
clonotype596	1	IGHV3-15	IGLV3-10	CTTDQVSGSYGDAFDIW	226	CYSTDSSGNHRVF	414	602	790
clonotype598	1	IGHV3-23	IGLV3-19	CAKRAGSGTYYRGYYFDYW	227	CNSRDSSGNHWVF	415	603	791
clonotype599	1	IGHV3-33	IGLV3-19	CAGTYYYDSSGYLNYMDVW	228	CNSRDSSGNHLVF	416	604	792
clonotype600	1	IGHV4-39	IGLV3-19	CASEGPYFDYW	229	CNSRDSSGNHWVF	417	605	793
clonotype601	1	IGHV1-18	IGLV2-14	CARAYCGGDCYYSNAFDAW	230	CSSYTSSSTVVF	418	606	794
clonotype602	1	IGHV3-15	IGLV2-23	CTTDRVTIFGLARMDVW	231	CCSYAGSSTWVF	419	607	795
clonotype607	1	IGHV3-48	IGLV3-19	CARDPTTIFGVVPYYYMDVW	232	CYSRDSSGNHLVF	420	608	796
clonotype608	1	IGHV3-15	IGLV3-21	CTTDRDYYGSGSYYFDYW	233	CQVWDSSSDHRVF	421	609	797
clonotype610	1	IGHV4-39	IGLV3-19	CAREDLIGNDYW	234	CNSRDSSGNHLVF	422	610	798
clonotype611	1	IGHV6-1	IGLV3-19	CSRDRLIVGASYFDLW	235	CNSRDSNGNHWVF	423	611	799
clonotype612	1	IGHV3-20	IGLV2-23	CAREKAPAHRSSWSWYFDLW	236	CCSYAGSSWVF	424	612	800
clonotype613	1	IGHV1-2	IGLV1-40	CTREGIAAANPGYFYYMDVW	237	CQSYDGTLGGWIF	425	613	801
clonotype616	1	IGHV1-2	IGLV3-19	CARCDMVRGVIDHYYNYMDVW	238	CNSRDSSGNHWVF	426	614	802
clonotype617	1	IGHV4-61	IGLV2-23	CVRQTYDSWTGYSFFYFDYW	239	CCSYAGSSWVF	427	615	803

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA sequence SEQ ID NO	Full LC AA sequence SEQ ID NO
clonotype622	1	IGHV3-73	IGLV3-1	CTRPMITFGGVIVYDAFDIW	240	CQAWDSSTVIF	428	616	804
clonotype625	1	IGHV4-34	IGLV3-10	CARGWGSSSWYYFDYW	241	CYSTDSSGNHRVF	429	617	805
clonotype626	1	IGHV4-34	IGLV3-19	CARGIFGVGGNWFDPW	242	CNSRDSSGNHLVF	430	618	806
clonotype629	1	IGHV4-39	IGLV2-8	CARYSSSWSGFDYW	243	CSSYAGSNNF	431	619	807
clonotype630	1	IGHV4-39	IGLV3-19	CARGGSYYVYFDYW	244	CNSRDSSGNHWVF	432	620	808
clonotype634	1	IGHV3-7	IGLV3-21	CSRDTDCSSTSCYFNWNPFFDYW	245	CQVWDSSSDHVVF	433	621	809
clonotype638	1	IGHV4-39	IGLV3-1	CARGGYSYGLNWFDPW	246	CQAWDSSTVVF	434	622	810
clonotype641	1	IGHV4-39	IGLV3-19	CARTYYDFWSGYLNWFDPW	247	CNSRDSSGNHVVF	435	623	811
clonotype644	1	IGHV4-34	IGLV2-8	CARWRNYYDSSGSPYWYFDLW	248	CSSYAGSNNWVF	436	624	812
clonotype646	1	IGHV4-39	IGLV2-14	CARQGRITMVRGVIPFDYW	249	CSSYTSSSTLVF	437	625	813
clonotype647	1	IGHV4-34	IGLV7-46	CAGGYCSSTSCRYNWNYGGWFDPW	250	CLLSYSGARVF	438	626	814

[00646] **Table 5.** Full Heavy Chain (HC) and Light Chain (LC) Sequences for Anti-EPOR Antibodies

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
439	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAVSVKSRITINPDTSKNQFSLQLNSVTPEDTAVYYCARKGELLGAFDIWGQGTMVTVSS	627	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTWVFGGGTKLTVL
440	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSNSAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYAGSVKSRIIIIPDTSKNQLSLQLKSVTPEDTAVYYCARKWELRDAFDIWGQGTMVTVSS	628	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGRSTLGIDWVFGGGTKVTVL
441	EVQLVESGGSVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAREDYGDPGWFDPWGQGTLVTVSS	629	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTYVFGTGTKVTVL
442	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCATLTGDGDYWGQGTLVTVSS	630	SYELTQPSSVSVSPGQTARITCSGDVLAKKYARWFQQKPGQAPVLVIYKDSERPSGIPERFSGSSSGTTVTLTISGAQVEDEADYYCYSAADNNLVFGGGTKLTVL
443	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDRSSSWYSFDYWGQGTLVTVSS	631	SSELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYGKNNRPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNHRVFGGGTKLTVL
444	EVQLVESGGGLVTPGGSLRLSCAASGFTFNNYSMNWVRQAPGKGLEWVSSISSSSSYIYYADSVKGRFTISRDNAKNSLYLPMISLRAEDTAVYYCARDGITGTTFYFDYWGQGTLVTVSS	632	QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSYTWVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
445	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCASIAAAGRDYWGQGTLVTVSS	633	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNLVFGGGTKLTVL
446	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKAPELRFDYWGQGTLVTVSS	634	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTYVFGTGTKVTVL
447	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISPYNGNTNYAQ NLQDRVTMITDTSTTTAYMELRSLRSDDTAV YYCARNHYYYMDVWGKGTTVTVSS	635	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTYVVFGGGTKLTVL
448	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSG YYWSWIRQPPGKGLEWIGEINHSGSTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARGELGIGYWYFDLWGRGTLVTVSS	636	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL
449	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARDTGITMVRGVFDYWGQGTLVTVSS	637	SYVLTQPPSVSVAPGKTARITCGGNNIGSKS VHWYQQKPGQAPVLVIYYDSDRPSGIPERFS GSNSGNTATLTISRVEAGDEADYYCQVWDSS SDHPVFGGGTKLTVL
450	EVQLVESGGDLVQPGGSLKLSCAASGFSFSG STLHWVRQASGKGLEWIGHIRSKPNNYATLY GASVKGRFTISRDDSKNTAYLQMNSLKIEDT AVYYCNGVYGGSSYFFDYWGQGTLVTVSS	638	QAVLTQPASLSASPGASASLTCTLRSGINVG TYRIYWYQQKPGSPPQYLLRYKSDSDKQQGS GVPSRFSGSKDASANAGILLISGLQSEDEAD YYCMIWHSSAVVFGGGTKLTVL
451	QVQLVQSGAEVKKPGASVKVSCKASGYTFTG YYMHWVRQAPGQGLEWMGWINPNSGGTNYAQ KFQGRVTMTRDTSISTAYMELSRLRSDDTAV YYCARDETTIFDYWGQGTLVTVSS	639	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNWVFGGGTKLTVL
452	QVQLVQSGAEVTKPGASVKVSCKASGYTFIN YGISWVRQAPGQGLEWMGWISAYSGNRNYAQ KFQDRVIMTTDTFTNTAYMELRSLRSDDTAV YYCARLGCNGTSCYTSWYYHFYMDVWGKGTT VTVSS	640	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHSWVFGGGTKLTVL
453	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARDEDYYGSGSYSFDYWGQGTLVTVSS	641	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTLVFGGGTKLTVL
454	QVQLQESGPGLVKPSGTLSLTCAVSGGSISS SNWWSWVRQPPGKGLEWIGEIYHSGSTNYNP SLKSRVTISVDKSKNQFSLKLSSVTAADTAV YYCARRGAARPFDYWGQGTLVTVSS	642	QAVLTQPASLSASPGASASLTCTLRSGINVG TYRIYWYQQKPGSPPQYLLRYKSDSDKQQGS GVPSRFSGSKDASANAGILLISGLQSEDEAD YYCMIWHSSAYVVFGGGTKLTVL
455	QITLKESGPTLVKPTQTLTLTCTFSGFSLST SGVGVGWIRQPPGKALEWLALIYWNDDKRYS PSLKSRLTITKDTSKNQVVLTMTNMDPVDTA TYYCAHSNWNYGYFDLWGRGTLVTVSS	643	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TAWVFGGGTKLTVL
456	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKKDIVATHFDYWGQGTLVTVSS	644	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHKVFGGGTKLTVL
457	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTADYDFWSGYYMDVWGKGTTVTVSS	645	SSEMTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
458	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCARDRYNFDYWGQGTLVTVSS	646	QSALTQPRSVSGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVPD RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSWVFGGGTKLTVL
459	EVQLVESGGGVVRPGGSLRLSCAASGFTFDD YGMSWVRQAPGKGLEWVSGINWNGGSTGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCARGGDTAMVTVFDYWGQGTLVTVSS	647	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTLVFGTGTKVTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
460	EVQLVQSGAEVKKPGESLKISCKGSGYSFTS YWIGWVRQMSGKGLEWMGIIYPSDSDTRYSP SFQGQVTISADKSISTAYLQWSSLKASDTAM YYCARQINWGAIDYWGQGTLVTVSS	648	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTFVVFGGGTKLTVL
461	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISVYNGNTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARQITATRGFDYWGQGTLVTVSS	649	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTFVVFGGGTKLTVL
462	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSS NSAAWSWIRQSPSRGLEWLGRTYYRSKWYND YAVSVKSRITINPDTSKNQFSLQLNSVTPED TAVYYCARKWELRDTFDIWGQGTMVTVSS	650	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTLGIDWVFGGGTKLTVL
463	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSG YYWSWIRQPPGKGLEWIGEINHSGSTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCASYGDFFDYWGQGTLVTVSS	651	LPVLTQPPSASALLGASIKLTCTLSSEHSTY TIEWYQQRPGRSPQYIMKVKSDGSHSKGDGI PDRFMGSSSGADRYLTFSNLQSDDEAEYHCG ESHTIDGQVGVVFGGGTKLTVL
464	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARETELTVMDVWGKGTTVTVSS	652	LPVLTQPPSASALLGASIKLTCTLSSEHSTY TIEWYQQRPGRSPQYIMKVKSDGSHSKGDGI PDRFMGSSSGADRYLTFSNLQSDDEAEYHCG ESHTIDGQVGWVFGGGTKLTVL
465	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTDWEYYDFWSGYYSPYFDYWGQGTL VTVSS	653	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL
466	QVQLQESGPGLVKPSQTLSLTCTVSGGSISS GGYYWSWIRQHPGKGLEWIGYIYYIGITYYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTA VYYCARAFDYWGQGTLVTVSS	654	SYVLTQPPSVSVPPGKTARITCGGNNVGSKS VHWYQQKPGQAPVLVIYYDTDRPSGIPERFS GSNSGNTATLSISRVEAGDEADYYCQVWDSR SDHVVFGGGTKLTVL
467	QVQLQESGPGLVKPSQTLSLTCTVSGGSISS GGYYWSWIRQHPGKGLEWIGYFYYSGSTYYN PSLKSRVSISVDTSKNQFSLRLSSVTVADTA VYYCVRAFDYWGQGTLVTASS	655	SYVLTQPPSVSVAPGKTARITCGGNTFGSKT VHWYQQKPGQAPVLVIYYDSDRPSGIPERFS GSNSGNTATLTISRVEAGDEADYYCQVWDLY SAHVVFGGGTNLTVL
468	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTGANWGQGTLVTVSS	656	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHWVFGGGTKLTVL
469	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARVAFDIWGQGTMVTVSS	657	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTVFGGGTKLTVL
470	QVQLVQSGAEAKKPGASVKVSCMASGYTFTT YGISWVRQAPGQGLEWMGWISAYNGNTKYAQ KLQGRVTMTTDTSTRTAYMELRSLRSDDTAV YYCARQIGDYWGQGTLVTVSS	658	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVIKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSAY AGSNNVVFGGGTQLTVL
471	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCHQTGEDYWGQGTLVTVSS	659	QSVLTQPPSASGTPGQRVTISCSGSSSNIGS NTVNWYQQLPGTAPKLLIYSNNQRPSGVPDR FSGSKSGTSASLAISGLQSEDEADYYCAAWD DSLNGWVFGGGTKLTVL
472	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKSDGGTRDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AMFYCTTGGTHWGQGTLVTVSS	660	SYELTQPPSVSVSPGQTARITCSADALPKQY AYWYQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGVQAEDEADYYCQSADSS ATWVFGGGTKLTVL
473	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARRSFLDYWGQGTLVTVSS	661	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
474	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY ATPVKGRFTISRADSKNTLFLQMSSLKTEDT AVYFCTTGGTNWGQGTLVTVSS	662	SYELTQPPSVSVSPGQTARITCSADALPKQY AYWYQQKPGQAPVVVIYKDSERPSGIPERFS GSSSGTTVTLTISGVQAEDEADYYCQSLDSS GTYWVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
475	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARESSGFDYWGQGTLVTVSS	663	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
476	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARGSSWFDYWGQGTLVTVSS	664	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
477	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTLNWGDYWGQGTLVTVSS	665	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
478	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARAADAFDIWGQGTMVTVSS	666	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
479	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCARGGSDAFDIWGQGTMVTVSS	667	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSVVFGGGTKLTVL
480	EVQLVESGGGLVKPGGSLRLSCTASEFTFRN AWMIWVRQAPGKGLEWVGRIRSEIDGGTTDY AAPVKGRFTISRDDSKDTLYLYMNSLKVEDT AVYYCTTDHPYYWGHGTLVTVSS	668	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL
481	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDF TAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTDHPYYWGQGTLVTVSS	669	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
482	QVQLVESGGGVVQPGRSLRLSCAASGFTFSN YGIHWVRQAPGKGLEWVAVIWYDGSNEYYVD SVKGRFIISRDNSKNTLYLQMNSLRAEDTAL YYCALAVTGFDYWGQGTLVTVSS	670	QSVLTQPPSVSEAPRQRVTISCSGSSSNIGN NAVNWYQQLPGKAPKLLIYYDDLLPSGVSDR FSGSKSGTSASLAISGLQSEDEADYYCAAWD DRLNGPVFGGGTKLTVL
483	QVQLVESGGGLVKPGGSLRLSCAASGFTFSD YYMSWIRQAPGKGLEWVSYISSSGSTIYYPD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDGAAFDIWGQGTMVTVSS	671	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDETDYYCCSY AGSSTLVFGGGTKLTVL
484	QIQLVQSGAEMKKPGASVKVSCKASGYTFTN YGISWVRQAPGQGLEWMGWINTYNDKTNFAL KVQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARDRGYSFDYWGQGTLVTVSS	672	SYELTQPPSVSVSPGQTASITCSGDKLGDKH ACWYQQKPGQSPMLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQPMDEADYYCQAWDSS TFGGGTKLTVL
485	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ RLQGRVTMTTDTSTSTAYMELRSLISDDTAV YYCARNHYYYLDVWGKGTTVTVSS	673	SYELTQPSSVSVSPGQTARITCSGDVLAKKY ARWFQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGAQVEDEADYYCYSAADN NRVFGGGTKLTVL
486	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCARVSPTGTTDYWGQGTLVTVSS	674	SYELTQPSSVSVSPGQTARITCSGDVLAKKY ARWFQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGAQVEDEADYYCYSAADN NLVFGGGTKLTVL
487	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTARPLGDVWGKGTTVTVSS	675	SYELTQPSSVSVSPGQTARITCSGDVLAKKY ARWFQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGAQVEDEADYYCYSAADN NYVFGTGTKVTVL
488	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTDNGFDYWGQGTLVTVSS	676	SYELTQPSSVSVSPGQTARITCSGDVLAKKY ARWFQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGAQVEDEADYYCYSAADN NLVFGGGTKLTVL
489	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDLISSFDYWGQGTLVTVSS	677	SSELTQDPAVSVALGQTVRITCQGDRLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYHCNSRDSS GNHLVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
490	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARRIVGAFDYWGQGTLVTVSS	678	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
491	QVQLIQSGTEVKKPGASVKVSCMASRYTFTS YYIHWVRQAPGQGLEWMGIINPSGGTTGYAQ KFQGRVTMTRDTSTSTVYMELYSLRSEDTAV YYCARGGWGTMDVWGKGTTVTVSS	679	SYVLTQPPSVSVAPGKTARITCGGNNIGSKS VHWYQQKPGQAPVLVIYYDSDRPSGIPERFS GSNSGNTATLTISRVEAGDEADYYCQVWDSS SDHVVFGGGTKLTVL
492	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCAREGWELLDYWGQGTLVTVSS	680	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
493	EVQLVESGGGLIQPGGSLRLSCAASGLTVST NYMSWVRQAPGKGLEWVSVLYSGGGTYYADS VKGRFTISRDNSKNTLCLQMNSLRAEDTAMY YCARDNWDSYFDYWGQGTLVTVSS	681	QTVVTQEPSLTVSPGGTVTLTCASSTGAVTS GYYPNWFQQKPGQAPRALIYSTSNKHSWTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCLLY YGGARVFGGGTKLTVL
494	EVQLVESGGGVVRPGGSLRLSCAASGFTFDD YGMSWVRQAPGKGLEWVSGINWNGGSTGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCARTTVTHMDVWGKGTTVTVSS	682	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNLVFGGGTKLTVL
495	EVQLVESGGGLIQPGGSLRLSCAASGFTVSS NYMSWVRQAPGKGLEWVSVIYSGGSTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARDWNYDAFDIWGQGTMVTVSS	683	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTWVFGGGTKLTVL
496	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGDPGWFDPWGQGTLVTVSS	684	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTFWVFGGGTKLTVL
497	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMHWVRQAPGKGLVWVSRINSDGSSTSYAD SVKGRFTISRDNAKNTLYLQMNSLRAEDTAV YYCARENWNYWFDPWGQGTLVTVSS	685	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
498	QVQLQESGPGLVKPSGTLSLTCAVSGGSISS NNWWSWVRQPPGKGLEWIGEIYHSGSTNYNP SLKSRVTISVDKSKNQFSLKVNSVTAADTAI FYCARLRPGDSFDYWGLGTLVTVSS	686	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQRPGQSPVLVIYQDNKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TALVFGGGTKLTVL
499	QVHLVQSGSELKKPGASVKVSCKASGYTFTR NGLNWVRQAPGQGLEWMGWINTNIGNPTYAQ GFTGRFVFSLDTSVSTAYLQISRLQAEDTAV YYCARSPNWGLFDYWGQGTLVTVSS	687	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TSGVFGGGTKLTVL
500	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDRGATGFDYWGQGTLVTVSS	688	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
501	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARESGELLGDYWGQGTLVTVSS	689	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
502	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCARYSGSYYYFDYWGQGTLVTVSS	690	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL
503	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARGIAAAGKDYWGQGTLVTVSS	691	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHAVFGGGTQLTVL
504	EVQLVQSGAEVKKPGESLKISCKGSGYSFTS YWIGWVRQMPGKGLEWMGIIYPGDSDTRYSP SFQGQVTISADKSISTAYLQWSSLKASDTAM YYCARQDSNYVFDYWGQGTLVTVSS	692	SYVLTQPPSVSVAPGKTARITCGGNNIGSKS VHWYQQKPGQAPVLVIYYDSDRPSGIPERFS GSNSGNTATLTISRVEAGDEADYYCQVWDSS SDHVVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
505	EVQLVESGGGLVQPGGSLRLSCAASGFTFSN YWMSWVRQAPGKGLEWVANIKYDGREQYYVD SVKGRFAISRDNAKNSLSLQMNSLRAEDTAI YYCARDHSAWSFDYWGQGTLVTVSS	693	QSVLTQSPSAFGTPGQRVTISCSGSISNLGS NTVNWYQQLPGTAPKLLIYSNNQRPSGVPDR FSGSKSGTSASLAISGLQFEDEADYHCATWD DSLNGRVFGGGTKLTVL
506	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARRRGSCSFDYWGQGTLVTVSS	694	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNLVFGGGTKLTVL
507	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARRSYANCFDYWGQGTLVTVSS	695	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNWVFGGGTKLTVL
508	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMHWVRQAPGKGLVWVSRINSDGSSTSYAD SVKGRFTISRDNAKNTLYLQMNSLRAEDTAV YYCARDEQLVPFDIWGQGTMVTVSS	696	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTLVFGGGTKLTVL
509	EVQLVESGGGLIQPGGSLRLSCAASGFTVSS NYMSWVRQAPGKGLEWVSVIYSGGSTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARDGAAAGDFQHWGQGTLVTVSS	697	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTWVFGGGTKLTVL
510	EVQLVESGGGLVQPGRSLRLSCAASGFTFDD YAMHWVRQAPGKGLEWVSGISWNSGSIGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDSGSYYFDYWGQGTLVTVSS	698	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNFVVFGGGTKLTVL
511	QVQLVESGGGLVKPGGSLRLSCAASGFTFSD YYMSWIRQAPGKGLEWVSYISSSGSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDGQLWSFDYWGQGTLVTVSS	699	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIYGNSNRPSGVPD RFSGSKSGTSASLAITGLQAEDEADYYCQSY DSSLSDVVFGGGTKLTVL
512	EVQLVESGGGLIQPGGSLRLSCAASGFTVSR NYMSWVRQAPGKGLEWVSIIYAGGNTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTGVY YCGRVVPIGNWFDPWGQGTLVTVSS	700	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIYGNNNRPSGVPD RFSGSKSGTSASLAITGLQAEDEADYYCQSY DSSLSGWVFGGGTKLTVL
513	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDSNWGVFDYWGQGTLVTVSS	701	QAVLTQPASLSASPGASASLTCTLRSGINVG TYRIYWYQQKPGSPPQYLLRYKSDSDKQQGS GVPSRFSGSKDASANAGILLISGLQSEDEAD YYCMIWHSSAWVFGGGTKLTVL
514	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDRLTGDLDYWGQGTLVTVSS	702	QAVLTQPASLSASPGASASLTCTLRSGINVG TYRIYWYQQKPGSPPQYLLRYKSDSDKQQGS GVPSRFSGSKDASANAGILLISGLQSEDEAD YYCMIWHSSAWVFGGGTKLTVL
515	EVYLVESGGGLVQPGGSLRLSCEASGFTFSR YWMHWVRQVPGKGLVWVSRINIVGSTIDYAD SVKGRFTISRDNAKNTLYLQMDSLTAEDTAV YYCAREGDRSDAFAIWGQGTMVTVSS	703	SHELTQPLSVSVALGQSAMITCRGNNIGSQN VHWYHQKPGQAPVLVIYRNINRPSGIPERFS GSTSGTTATLTISRAQAGDEADYYCQVWDSS GSWVFGGGAKLTVL
516	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARQQWLGYYFDYWGQGTLVTVSS	704	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
517	EVQLVESGGGLVQPGGSLRLSCAASGFTFSI YWMSWVRQAPGKGLEWVATIKEDGSEKYYVD SVKGRFTISRDNAKNSLFLQMNSLRADDTAV YYCARDSNFLYYFDYWGQGDLVTVSS	705	SSELTQDPALSVALGQTVRITCQGDSLRSFY ASWYQQKPGQAPVLVIYGKSNRPSGIPDRFS GSGSGNTASLTITGAQAEDEADFYCNSRDTS GNYLVFGGGTKLTVL
518	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ KLQGRVTMTTDTSTNTAYMELRSLRSDDTAV YYCARQITGTRGFDYWGQGTLVTVSS	706	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
519	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARMGYSNYPFDYWGQGTLVTVSS	707	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHVVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
520	QVQLVQSGSEVKKPGASVKVSCKASGYTFTS YYMHWVRQAPGQGLEWMGIINPSGGSTSYAQ KFQGRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARGIPTTVTPDYWGQGTLVTVSS	708	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
521	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCARAGLLTGDAFDIWGQGTMVTVSS	709	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
522	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCITGTTFPFDYWGQGTLVTVSS	710	QTVVTQEPSLTVSPGGTVTLTCASSTGAVTS GYYPNWFQQKPGQTPRALIYSTSNKHSWTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCLLY YGGAWVFGGGTKLTVL
523	EVQLVESGEGLVQPGGSLRLSCAASGFTFSS HAMHWVRQAPGKGLEYVSAISSNGGNTYYAD SVKGRFTISRDNSKNTLYLQVGSLRPEDMAI YYCTKGGVGASFDYWGQGTLVTVSS	711	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQHHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTWVFGGGTKLTVL
524	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGDYSNYYFDYWGQGTLVTVSS	712	QSVLTQPPSASGTPGQRVTISCSGSSSNIGS NTVNWYQQLPGTAPKLLIYSNNQRPSGVPDR FSGSKSGTSASLAISGLQSEDEADYYCAAWD DSLNGWVFGGGTKLTVL
525	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSG YYWSWIRQPPGKGLEWIGEINHSGSTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARWEQPWGQGTLVTVSS	713	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNWVFGGGTKLTVL
526	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YYMHWVRQAPGQGLEWMGIINPSGGSTSYAQ KFQGRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARRTGTTHYFDYWGQGTLVTVSS	714	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTLVFGGGTKLTVL
527	QVQLVESGGGLVKPGGSLRLSCAASGFTFSD YYMSWIRQAPGKGLEWVSYISSSGSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGLWLGLYFDYWGQGTLVTVSS	715	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTWVFGGGTKLTVL
528	EVQLVQSGAEVKKPGESLKISCKGSGYSFTS YWIGWVRQMPGKGLEWMGIIYPGDSDTRYSP SFQGQVTISADKSISTAYLQWSSLKASDTAM YYCARFLGSSYYFDYWGQGTLVTVSS	716	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNFEVFGGGTKLTVL
529	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCARGGAAAGAFDIWGQGTMVTVSS	717	QAVLTQPASLSASPGASASLTCTLRSGINVG TYRIYWYQQKPGSPPQYLLRYKSDSDKQQGS GVPSRFSGSKDASANAGILLISGLQSEDEAD YYCMIWHSSAWVFGGGTKLTVL
530	QVQLQESGPGLVKPSQTLSLTCTVSGGSISS GGYYWSWIRQHPGKGLEWIGYIFYSGSTYYN PSLKSRVTISVDTSKKQYSLKLRSVTAADTA VYYCARAEWELLWFDPWGQGTLVTVSS	718	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVVVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
531	QITLKESGPTLVKPTQTLTLTCTFSGFSLST SGVGVGWIRQPPGKALEWLALIYWNDDKRYS PSLKSRLTITKDTSKNQVVLTMTNMDPVDTA TYFCAHNYFYISGYFYWGQGTLVTVSS	719	SYELTHPPSVSVSPGQTARITCSADALPKQY AYWYQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTSVTLTISGVQAEDEADYYCQSANSG TWVFGGGTKLTVL
532	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVISYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKDPLRVVNYMDVWGKGTTVTVSS	720	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDTKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
533	QITLKESGPTLVKPTQTLTLTCTFSGFSLST SGVGVGWIRQPPGKALEWLALIYWSDDKRYS PSLKNRLTITKDTSKNQVVLTMTNMDPLATA TYYCAQTGYNSWSFDYWGQGTLVTVSS	721	SYELTQPPSVSVSPGQTARITCSADALPNQY AYWYQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGVQAEDEADYYCQSADSS GTWVFGGGTKLTVL
534	QVQLVQSGAEVKKPGASVKVSCKASGYPFTS YGINWVRQAPGQGLEWMGWISAYNSNTNYAE KFQGRVTMTTDTSTTTAYMDLRSLRSDDTAV YYCAREDAWNYGWFDPWGQGTLVTVSS	722	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
535	QVQLVQSGAEVKKPGASVKVSCKASGYSFTG YDISWVRQAPRQGLEWMGWISAYNGNTNYAQ KFQARVTMTTDTSTSTAYMELRSLRSDDTAV YYCAREILWLGGYFDYWGQGTLVTVSS	723	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
536	QVHLVQSGSELKKPGASVKVSCKASGYTFSS YDMNWIRQAPGQGLEWMGWINTNTGNPTYAQ GFTGRFVFSLDTSVSTAYLQISSLKAEDTAV YYCAREYSSGWYYFDYWGQGALVTVSS	724	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
537	QVQLVQSGAEVKKPGASVKVSCKASGYTFTG YYMHWVRQAPGQGLEWMGWINPNSGGTNYAQ KFQGRVTMTRDTSISTAYMELSRLRSDDTAV YYCARERIAVAPPFDYWGQGTLVTVSS	725	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
538	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARAGWELPEYFQHWGQGTLVTVSS	726	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
539	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARGGDDYSNLFDYWGQGTLVTVSS	727	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
540	QVQLVQSGAEVKKPGSSVKVPCKASGDTFSN FAINWVRQAPGQGLEWMGGIIPIFATANYAQ NFQGRVTITADESTSAAYMEVSSLRFEDTAV YYCARTPLGIGRSFDLWGQGTMVTVSS	728	SYVLTQPPSVSVAPGKTARITCGGNNIGSKS VHWYQQTPGQAPVLVIYYDSDRPSGIPDRFS GSNSGNTATLTISRVEAGDEADYYCQVWDSN SDHWVFGGGTKLTVL
541	EVHLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKRKTDGGTTDF ASPVKGRFTISRDDSNNTLYLQMNSLKTEDT AVYYCTTASTVTTGDYWGQGTLVTVSS	729	SYELTQPPSVSVSPGQTARITCSADALPKQY AYWYQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGVQAEDEADYYCQSADSS GTYPVFGGGTKLTVL
542	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYND YAVSVKSRITINPDTSKNQFSLQLNSVTPED TAVYYCARERTEIDYWGQGTLVTVSS	730	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
543	EVQLVESGGGLVKPGGSLRLSCAASGFTFNN AWMIWVRQAPGKGLEWVGRIKSKTDGGTTDY GAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTGRYFDWFDYWGQGTLVIVSS	731	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTS GHYPYWFQQKPGQAPRTLIYDTSNKHSWTPA RFSGSLLGGKAALTLSGAQPEDEAEYYCLLS YSGARVFGGGTKLTVL
544	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTASGSYWFDPWGQGTLVTVSS	732	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNLVFGGGTKLTVL
545	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVISYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKGNWNYGDAFDIWGQGTMVTVSS	733	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTYVFGTGTKVTVL
546	QVQLVESGGGVVRPGGSLRLSCAASGFTFDD YGMSWVRQAPGKGLEWVSGINWNGGSTGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCARENYDFWSGFDPWGQGTLVTVSS	734	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTVVFGGGTKLTVL
547	QVHLQQSGPGLVKPSQTLSLTCAISGDSVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYNG YAESVKSRITINPDTSKNQFSLQLNSVTPED TAVYYCAREDRGFDYWGQGTLVTVSS	735	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSNVVFGGGTNLTVL
548	EVQLVESGGGLVQPGRSLRLSCAASGFTFDD YAMHWVRQAPGKGLEWVSGISWNSGSIGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKRAVVTDYYMDVWGKGTTVTVSS	736	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTFWVFGGGTKLTVL
549	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSNTIYYAD SVKGRFTISRDNAKNSLYLQMSSLRDEDTAV YYCARTSSWSYDAFDIWGQGTMVTVSS	737	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNFVVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
550	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YYMHWVRQAPGQGLEWMGIINPSGGSTSYAQ KFQGRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARERGHTVTPYFDYWGQGTLVTVSS	738	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQATEVF GGGTKLTVL
551	EVQLVESGGGLVQPGGSLRLSCAASGFNFSS YNMNWVRQTPGKGLEWVSYISNTGNTIYYVD SVKGRFTISRDNAKNSLYLQLNSLRDEDTAV YFCARDGPQVGATDFDYWGQGTLVTVSS	739	SYELTQPSSVSVSPGQTAKITCSGDVLAKKY ARWFQQKPGQVPVLVIYKDSERPSGIPERFS GSSSGATVTLTISGAQVEDEADYYCYSAADN KVFGGGTKLTVL
552	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKRKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTEYSSSENFDYWGQGTLVTVSS	740	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVVVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TAVFGGGTKLTVL
553	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMHWVRQAPGKGLVWVSRINSDGSSTSYAD SVKGRFTISRDNAKNTLYLQMNSLRAEDTAV YYCARDLGAARPRGFDYWGQGTLVTVSS	741	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
554	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKEGDSGYDSAFDIWGQGTMVTVSS	742	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNRVFGGGTKLTVL
555	QVQLQESGPGLVKPSGTLSLTCAVSGGSISS NNWWSWVRQPPGKGLEWIGEIYHSGSTNYNP SLKSRVTISVDKSKNQFSLKLSSVTAADTAV YYCARVLNWNYGDAFDIWGQGTMVTVSS	743	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRGFGGGTKLTVL
556	QVQLQESGPGLVKPSGTLSLTCAVSGGSISS SNWWSWVRQPPGKGLEWIGEIYHSGSTNYNP SLKSRVTISVDKSKNQFSLKLSSVTAADTAV YYCARDPSIVGATAFDIWGQGTMVTVSS	744	QSALTQPRSVSGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVPD RFSGSKSGNTASLTISGLQAEDEADYYCCSY AQGVVFGGGTKLTVL
557	QVQLQESGPGLVKPSGTLSLTCAVSGGSIIS SNWWSWVRQSPGKGLGWIGEIYHSGSTTYNP SLKSRVTISVDKSKNQFSLKLSSVTAADTAL YYCARSHIVGVNGGFDYWGQGTLVTVSS	745	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLLIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
558	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDRYNWNYRAFDIWGQGTMVTVSS	746	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGTGTKVTVL
559	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDLGRGTISWFDPWGQGTLVTVSS	747	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
560	QITLKESGPTLVKATQTLTLTCTFSGFSLNS SGVGVVWIRQPPGKALEWLALIYWNGDKRYS QSLKNRLTITEDTSKNQVVLAMTNMDPVDTA TYYCTQTGYDSRWSFAYWGQGTLVTVSS	748	SYVLTQPPSVSVAPGKTARITCGGNNIGSKS VHWYQQKPGQAPVLVIYYDSDRPSGIPERFS GSNSGNTATLTISRVEAGDEADYYCQVWDSS SDHWVFGGGTKLTVL
561	QGQLVQSGAEVKKPGASVKVSCKTSGYIFMN YGITWVRHAPGQGLEWMGWISAYNGNTNYAQ KVQGRVTMTTDTSTSTANMELRSLRSDDTAV YYCAREGQWRGRGWFALWGQGTQVTVSS	749	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
562	QVQLVQSGSELKKPGASVKVSCKASGYTFTN YAMNWVRQAPGQGLEWMGWINTNTGKPTYAQ GFTGRFVFSLDTSVSTAHLQISGLKAEDTAV YYCARERYFEDFHYMDVWGKGTTVTVSS	750	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
563	QVQLVQSGAEVKKPGASVKVSCKASGYTFTD NYIHWVRRAPGQGLEWMGWLNPNSGGTNFAQ KFQGRVTMTRDTSISSVYMILSSLRSDDTAV YYCARSSWLQLTYYFDYWGQGTLVTVSS	751	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSNSGNTASLTITGAQAEDEADYYCNSRDSS GNHLLFGGGTKLTVL
564	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YYIHWVRQAPGQGLEWMGIINPSGGSTSYAQ KFQGRVTMTRDTSTSTVYMEVSSLRSEDTAV YYCAREGLQLGSNWFDPWGQGTLVTVFS	752	SSELTQDPGVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVMYGKKNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCKSRDSS GNHVVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
565	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCARNDILTGEDAFDIWGQGTMVTVSS	753	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
566	EVQMVESGGGLVQPGGSLRLSCAASGFTFSN YAMSWVRQAPGKGLGWVSGISGSGGRTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKESIIVGATMFDYWGQGTLVTVSS	754	SSELTQDPAVSVALGQTVRITCQGDSFRNYY ASWYQQMPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
567	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVISYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKGIAALGYYYMDVWGKGTTVTVSS	755	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
568	EVQLVQSGAEMKKPGESLKISCKDSGYRFSN YWIGWVRQLPGKGLEWMGIIYPGDSDTRYSP SFQGQVTISADKSINTAYLQWNSLKASDTAI YYCAKRRITGSHNWFDPWGQGTLVTVSS	756	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
569	QVQLVQSGSELKKPGASVKVSCKASGYTFTS YAMNWVRQAPGQGLEWMGWINTNTGNPTYAQ GFTGRFVFSLDTSVSTAYLQISSLKAEDTAV YYCARGGTIFGVVNFDYWGQGTLVTVSS	757	QTVVTQEPSLTVSPGGTVTLTCASSTGAVTS GYYPNWFQQKPGQAPRALIYSTSNKHSWTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCLLY YGGARVFGGGTKLTVL
570	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YVMHWVRQAPGKGLEWVAVIWYDGSNKYFAD SVKGRFTISRDNSNNTLYLQMNSLRAEDTGV YYCLSRSGYSAHNDGDYWGQGTLVTVSS	758	QSALTQPASVSGSPGQSITISCTGTSSDVGV YNFVSWYQQHPGKAPKLMIYDVTKRPSGASE RFSGSKSGSTASLTISGLQAEDEADYYCCSY AGSSTWVFGGGTKLTVL
571	QVQLVQSGAEVKKPGASVKVSCKASGYTFTG YYIFWVRQAPGQGLEWMGWINPNSGGTNYAQ KFQGRVTMTRDTSITTAYMELSRLRHDDTAV YYCTKEGLVVRPDWFDPWGQGTLVTVSS	759	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKILIYVNNNRPSGVPD RFSGSKSGTSASLAITGLQAEDEADYYCQSY DSSLSGPVFGGGTKLTVL
572	QVQLQQSGPGLVKPTQTLSLTCAISGDSVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYND YAVSVRSRITINPDTSKNQFSLHLNSVTPED TAVYYCARKGRDVFDIWGQGTMVTVSS	760	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDETDYYCCSY AGSSTYWVFGGGTKLTVL
573	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCAREGSGSYSDAFDIWGQGTMVTVSS	761	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIYGNSNRPSGVPD RFSGSKSGTSASLAITGLQAEDEADYYCQSY DSSLSGSYVFGTGTKVTVL
574	QITLKESGPTLVKPTQTLTLTCTFSGFSITT SGVGVGWIRQPSGKALEWLALIYWNDDKRYS PSLKSRLTITKDTSKNQVVLTMTNMDPVDTA TYYCTHTEYRNTWCVDYWGQGTLVTVSS	762	QAVLTQPASLSASPGASASLTCTLRSGIHVD TSRIYWYQQKPGSPPQYLLRYKSDSDKHQDS GVPSRFSGSKDASTNAGILLISGLQSEDEAD YYCMIWHSSAIVFGGGTKLTVL
575	QITLKESGPTLVKPTQTLTLTCTFSGFSLST SGVGVGWIRQPPGKALEWLALIYWNDDKRYS PSLKSRLTITKDTSKNQVVLTMTNMDPVDTA TYYCAHSPYTSGWPFDYWGQGTLVTVSS	763	QAVLTQPASLSASPGASASLTCTLRSGINVG SYRIYWFQQRPGSPPQYLLRYKSDSDKQQGS GVPSRFSGSKDASANAGILLISGLQSEDEAD YYCMIWHSSASVFGGGTKVTVL
576	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARVSYSSSWSLFDYWGQGTLVTVSS	764	QAVLTQPASLSASPGASASLTCTLRSGINVG TYRIYWYQQKPGSPPQYLLRYKSDSDKQQGS GVPSRFSGSKDASANAGILLISGLQSEDEAD YYCMIWHSSAWVFGGGTKLTVL
577	QVTLRESGPALVKPTQTLTLTCTFSGFSLST SGMSLSWIRQPPGKALEWLALIDWDDDQYYS TSLKTRLTISKDTSKNQVVLSMTNMDPVDTA TYYCARIRGVGALDGFDFWGQGTMVTVSS	765	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
578	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISGYKGNTNCAQ ELQGRVTITSDTSTSTAYMELRSLRSDDTAV YYCARPLDYGDYEGWFDPWGQGTLVTVSS	766	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
579	QVQLAQSGIEMRKPGASVKVSCRASGDTFTN CGFGWVRQAPGQGLEWMGWISAYNGNTNYAQ KFQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCAREGRTNYFYYYMDVWGKGTTVTVSS	767	SSELTQDPTVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
580	EVQLVESGGGLVQPGRSLRLSCAASGFTFDD YAMHWVRQAPGKGLEWVSGISKNSGSIGYAD SVKGRFTISRDNAKKSLYLQMNSLRVEDTAL YYCAKDITASGDYYYMDVWGKGTTVTVSS	768	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
581	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSSTIYFAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCARDRVYNWNDGAFDIWGQGTMVTVSS	769	SSELTPDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPILVIYHKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL
582	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGSTYYAD SVKGRFTISRDNSKNTMYLQMNSLRAEDTAV YYCAKDQRYNWNSWYFDLWGRGTLVTVSS	770	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
583	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARDHGGVTTYNWFDPWGQGTLVTVSS	771	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
584	QVQLVQSGAEVKKPGASVKVSCKASGYTFTG YYMHWVRQAPGQGLEWMGWINPNSGGTNYAQ KFQGRVTMTRDTSISTAYMELSRLRSDDTAV YYCARDRMVRGVLDAFDIWGQGTMVTVSS	772	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNVVFGGGTKLTVL
585	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCVRGYSSGWYNWYFDLWGRGTLVTVSS	773	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNLVFGGGTKLTVL
586	QVQLVESGGGLVKPGGSLRLSCAASGFTFSD YYMSWIRQAPGKGLEWVSYISSSGSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARKVPGIAAAGAFDYWGQGTLVTVSS	774	QTVVTQEPSLTVSPGGTVTLTCASSTGAVTS GYYPNWFQQKPGQAPRALIYSTSNKHSWTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCLLY YGGAQLVFGGGTKLTVL
587	QVQLVQSGSELKKPGASVKVSCKASGYTFNS YAMNWVRQAPGLGLEWMGWINTNTGNPTYAQ GFSGRFVFSLDTSVNTAYLQISSLQAEDTAV YFCARGGYGYNFWIRFDPWGQGTLVTVSS	775	QSVLTQPPSVSGAPGQRVTISCTGSNSNIGA GYDIHWYQQLPVTAPKLLIYGNSNRPSGVPD RFSGSKSGSSASLAITGLQAEDEADYYCQSY DNSLSGSVFGGGTKLTVL
588	QLQLQESGPGLVKPSETLSLTCTVSGGSISR SSYYWGWIRQPPGRGLEWIGSIYYSGSTYYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTG VYYCASYWNFDYWGRGTLVTVSS	776	SYELTQPSSVSVSPGQTARITCSGDVLAKKF ARWFQQKPGQAPLLVIYKDSERPSGIPERFS GSNSGTTVTLTISGAQVEDEADYYCYSAADN NLVFGGGTKLTVL
589	QVQLQESGPGLVKPSGTLSLTCAVSGGSISS SFWLSWVRQPPGKGLEWIGEIYHSGSTNYNP SLKSRVTISVDKSKNQFSLKLTSVTAADTAV YSCARVLGYSYGYRRWFDPWGQGTLVTVSS	777	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
590	EVQLVESGGGLVNPGGSLRLSCAASGFTFSN AWMSWVRQGPGRGLEWVGRIKSKSDGETIDY AAPVKGRFSFSRDDAENTLYLEMNSLKTEDT AVYYCTTEGSFNFYYFMDVWGKGTAVTVSS	778	SHMLTQPPSVSVAPGTTARITCGGNNFGSKS VHWYQQKPGQAPVLVIYYDSDRPSGIPERFS GSNSGNTATLTISRVEAGDEADYYCQVWDST SDHYVFGTGTKVTVL
591	QVQLQESGPGLVKPSETLSLTCTVSGGSISS YYWSWIRQPPGKGLEWIGHIYYSGSTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARDPFYYDFSDYYYMDVWGKGTTVTVSS	779	QSALTQPASVSGSPGQSITISCTGTSSDVGA YNYVSWYQQHPGKAPKLMIYAVSKRPSGVSY RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGTISWVFGGGTKLTVL
592	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKNEARDYYGSGSFDYWGQGTLVTVSS	780	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTYVFGTGTKVTVL
593	EVQLVESGGGVVRPGGSLRLSCAASGFTFGD FGMSWVRQAPGKGLEWVSGINWNGGSTGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCASLVGATDYYFYYMDVWGKGTTVTVSS	781	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVNKRPSGVPD RLSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNWVFGGGTKLTVL
594	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYND YAVSVKSRITINPDTSKNQFSLQLNSVTPED TAVYYCARKWELLDAFDIWGQGTMVTVSS	782	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTWVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
595	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCAREERDDYSNYGYFQHWGQGTLVTVSS	783	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIYGNSNRPSGVPD RFSGSKSGTSASLAITGLQAEDEADYYCQSY DSSLSGWVFGGGTKLTVL
596	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSS NSATWNWIRQSPSRGLEWLGRSYYMSKWYND YAVSVKSRITINPDTSKNQFSLQLNSVTPED TAVYYCARGDWNYGVLDSWGQGTLVTVSS	784	QSALTQPPSVSGSPGQSVTISCTGTSSDVGS YNRVSWYQQPPGTAPKLMIYDVSNRPSGVPD RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTYVVFGGGTKLTVL
597	QVQLVQSGAEVKKPRASVKVSCEASGYTFTT YGISWVRQAPGQGLEWMGWISAYNGNTKYTQ KLQGRVAMTTDTSTSTAYMEVRSLRSDDTAV YYCARSGYNWNYDYYFMDVWGTGTTVTVSS	785	QSILTQPPSVSATPGQRVTISCTGSDSNIGA GYDVHWYQQLPGAVPRLLIHDNIIRPSGVPD RFSGSKSDTSASLAISGLHAEDEADYYCQSY DISLSGSVVFGGGTKLTVL
598	EVQLVESGGGVVRPGGSLRLSCAASGFTFDD YGMSWVRQAPGKGLEWVSGINWNGGSTGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCARDGCSSTSCYGNWFDPWGQGTLVTVSS	786	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TAVFGGGTKLTVL
599	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYSD YAVSVKSRITINPDTSKNQFSLQLNSVTPED TAVYYCARVDFGIVGAIDYWGQGTLVTVSS	787	SYELTQPPSVSVSPGQTARITCSGDGLSKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTVSGAQVEDEADYYCYSTDSS GKIFGGGTKLTVL
600	EVQLVESGGGLVKPGGSLRLSCAASAFTFSN YNMNWVRQAPGKGLEWVSSISSSTSYIYYAD SVKGRFTVSRDNAKNSLYLQMNSLRAEDTAV YYCARDRDDFWSGYSPYFDYWGQGTLVTVSS	788	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
601	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCAREKYDILTGYSPYFDYWGQGTLVTVSS	789	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
602	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTDQVSGSYGDAFDIWGQGTMVTVSS	790	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
603	EVQMVESGGGLVQPGGSLRLSCAASGFTFSS HVMSWVRQAPGKGLEWVSVISGSESSTYYAD SVKGRFTISSDNSKNTLYLQMNSLRAEDTAI YYCAKRAGSGTYYRGYYFDYWGQGTLVTVSS	791	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
604	LVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVTLIWYDGSNTYYAE SVKGRFTISRDNSKSTLYLHMNSLRAEDSAV YYCAGTYYYDSSGYLNYMDVWGKGTTVTVSS	792	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
605	QLQLQESGPGLVKPSETLSLTCTVSGGSISS SSYYWGWIRQPPGKGLEWIGSIHYSGSTYYN PSLKSRVTTSVDTSKNQFSLKLSSVTAADTA VYYCASEGPYFDYWGQGTLVTVSS	793	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
606	QVQLVQSGAEVKKPGASVKVSCKASGYSFSS YGIGWVRQAPGQGLEWMGWISGYNGNTNYAQ KFQGRVTMTTDTSTSTAHMEVKSLRSDDTAA YYCARAYCGGDCYYSNAFDAWGQGTMVTVSS	794	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTVVFGGGTKLTVL
607	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTDRVTIFGLARMDVWGKGTTVTVSS	795	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTWVFGGGTKLTVL
608	EVQLVESGGGLVQPGGSLRLSCAASGFTFST YSVKWVRQAPGKGLEWVSYISSGSSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCARDPTTIFGVVPYYYMDVWGTGTTVTVS S	796	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ATWYQQKPGQAPVLVIYGRNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCYSRDSS GNHLVFGGGTNLTVL
609	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTDRDYYGSGSYYFDYWGQGTLVTVS S	797	SYVLTQPPSVSVAPGKTARITCGGNNIGSKS VHWYQQKPGQAPVLVIYYDSDRPSGIPERFS GSNSGNTATLTISRVEAGDEADYYCQVWDSS SDHRVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
610	QLQLQESGPGLVKPSETLSLTCTVSGGSITT RSYYWGWLRQPPGKGLEWIGTFYYSGNTYYN PSLQSRVSISVDASKNQFSLQLSSVTAADTA VFYCAREDLIGNDYWGQGTLVTVSS	798	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
611	QVHLQQSGPGLVKPSQTLSLTCAISGDSVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYND YAVSVKSRITINSDTSKNQFSLQLNSVTPED TAVYYCSRDRLIVGASYFDLWGRGTLVTVSS	799	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVFYGKNKRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSN GNHWVFGGGTKLSVL
612	EVQLVESGGGVVRPGGSLRLSCAASGFTFDD YGMSWVRQAPGKGLEWVSGINWNGGSTGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAREKAPAHRSSWSWYFDLWGRGTLVTVS S	800	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSWVFGGGTKLTVL
613	QVQLVHSGAEVKKPGASVKVSCKASGYTFTG NYIHWVRQAPGQGLEWMGWINPTSGVTNYAQ KFQGRVTLTRDTSISTAYMELSRLRSDDTAV YYCTREGIAAANPGYFYYMDVWGKGTTVTVS S	801	QPVLTQPPSVSGVPGQRVTISCTGSSSNIGA RYDVHWYQQLPGTAPKLLIYGNSNRPSGVPD RFSGSKSGTSASLAITGLQAEDEADYYCQSY DGTLGGWIFGGGTNLTVL
614	QVQLVQSGAEVKKPGASVKVSCKASGYTFTD YYMHWVRQAPGQGLEWMGWINPNSGGTNYAQ KFQGRVTMTRDTSISTAYMELSRLRSDDTAV YFCARCDMVRGVIDHYYNYMDVWGKGTTVTV SS	802	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
615	QMQLQGSGPGLMKPSETLSLTCTVSGGSISS RSYYWGWIRQPPGKGLEWIGSVFYSGSTYYN PSLKSRVTISVDTSKNQFSLKVISVTAADTA VYYCVRQTYDSWTGYSFFYFDYWGQGTLVTV SS	803	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSWVFGGGTKLTVL
616	EVQLVESGGGLVQPGGSLKLSCAASGFTFSG SAMHWVRQASGKGLEWVGRIRSKANSYATAY AASVKGRFTISRDDSKNTAYLQMNSLKTEDT AVYYCTRPMITFGGVIVYDAFDIWGQGTMVT VSS	804	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVIFGGGTKLTVL
617	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSG YYWSWIRQPPGKGLEWIGEINHSGSTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARGWGSSSWYYFDYWGQGTLVTVSS	805	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDNKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
618	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSG YYWSWIRQPPGKGLEWIGEINRSGSTNYNPS LKTRVTISVDTSKNQFSLQLSSVTAADTAVY YCARGIFGVGGNWFDPWGQGTLVTVSS	806	SSELTQDPAVSVALGQTVRITCQGDSLRNYY ASWYQQKPGQAPVIVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
619	QLQLQESGPGLVKPSETLSLTCTVSGGSISS SSYYWGWIRQPPGKGLEWIGSIYYSGSTYYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTA VYYCARYSSSWSGFDYWGQGTLVTVSS	807	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNFGGGTKLTVL
620	QLQLQESGPGLVKPSETLSLTCTVSGGSISS SSYYWGWIRQPPGKGLEWIGSIYYSGSTYYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTA VYYCARGGSYYVYFDYWGQGTLVTVSS	808	SSELTQDPAVSVALGQTVRITCQGDSLRTYY ASWYQQKPGQAPVLVIYGKNKRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
621	KVQLVESGGGLVQPGGSLRLSCAASGFTFRS YWMSWVRQAPGKGLEWVANINQDGSEKYYVD SVKGRFTISRDNAKNSLYLHMNSLRAEDTAV YYCSRDTDCSSTSCYFNWNPFFDYWGQGTLV TVSS	809	SYVLTQPPSVSVAPGQTARIICGGDNIGIKN VHWYQQKPGQAPVLVIYDDSDRPSGIPERFS GSNSGNTATLTISRVEAGDEADYCCQVWDSS SDHVVFGGGTKLTVL
622	QLQLQESGPGLVKPSETLSLTCTVSGGSINS SNFYWGWIRQPPGKGLEWFGSIFYSGFTYYN PSLKSRVTISVDTSKNQFSLKLTSVTAADTA VYYCARGGYSYGLNWFDPWGQGTLVTVSS	810	SYELTQPPSVSVSPGQTASITCSGDKLGDKY TCWYQQKPGQSPVLVIYQDIKRPSGIPDRFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
623	QLQLQESGPGLVKPSETLSLTCTVSGGSISS SSYYWGWIRQPPGKGLEWIGSIYYSGSTYYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTA	811	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL

SEQ ID NO	Full HC AA sequence	SEQ ID NO	Full LC AA sequence
	VYYCARTYYDFWSGYLNWFDPWGQGTLVTVSS		
624	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINRGGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARWRNYYDSSGSPYWYFDLWGRGSLVTVSS	812	QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNNWVFGGGTKLTVL
625	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSGYYWGWIRQSPGKGLEWIGSFYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARQGRITMVRGVIPFDYWGQGTLVTVSS	813	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTLVFGGGTKLTVL
626	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGYYWSWIRQPPGKGLEWIGEINHSGSTNYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCAGGYCSSTSCRYNWNYGGWFDPWGQGTLVTVSS	814	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGHYPYWFQQKPGQAPRTLIYDTSNKHSWTPARFSGSLLGGKAALTLSGAQPEDEAEYYCLLSYSGARVFGGGTKLTVL

[00647] **Table 6.** VH-CDR3 and VL-CDR3 Sequences for Anti-CD131 Antibodies

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype8	10	IGHV4-39	IGLV2-14	CASLTGDRFDYW	815	CSSYTSSSTVVF	944	1073	1202
clonotype11	6	IGHV3-15	IGLV3-10	CTGRPSIAARHFDYW	816	CYSTDSSGNHSVF	945	1074	1203
clonotype14	6	IGHV3-20	IGLV1-40	CARERLTIFGVVNYYMDVW	817	CQSYDSSLSGWVF	946	1075	1204
clonotype15	5	IGHV3-48	IGLV3-27	CARDGWDYW	818	CYSAADNNRVF	947	1076	1205
clonotype16	5	IGHV3-13	IGLV3-10	CARGYSGSYYGDFDYW	819	CYSTDSSGNRVF	948	1077	1206
clonotype17	5	IGHV3-23	IGLV1-40	CAKKPPRDSAFDYW	820	CQSYDSSLSGSVF	949	1078	1207
clonotype25	3	IGHV1-18	IGLV2-8	CARENSGSYYWFDPW	821	CSSYAGSNNVVF	950	1079	1208
clonotype27	3	IGHV3-23	IGLV2-23	CAKLEYSSPDYW	822	CCSYAGSSTLVF	951	1080	1209
clonotype36	2	IGHV4-34	IGLV3-19	CAREGLLVGATLDAFDIW	823	CNSRDSSGNHLVF	952	1081	1210
clonotype37	2	IGHV3-33	IGLV3-21	CARDTGITMVRGVFDYW	824	CQVWDSSSDHPVF	953	1082	1211
clonotype44	2	IGHV1-18	IGLV1-44	CARDRTGISAAGPSNWFDPW	825	CAAWDDSLNGPVF	954	1083	1212
clonotype45	2	IGHV4-34	IGLV2-8	CARTSLAAADFDYW	826	CSSYAGSNNYVF	955	1084	1213
clonotype47	2	IGHV3-53	IGLV1-36	CARAPDYYGSGSLFDYW	827	CAAWDDRLNGPVF	956	1085	1214
clonotype52	2	IGHV3-21	IGLV3-9	CASHWGHFDYW	828	CQVWDSSTVVF	957	1086	1215
clonotype115	1	IGHV3-13	IGLV3-10	CARDRTLDYW	829	CYSTDSSGNHWVF	958	1087	1216
clonotype116	1	IGHV1-18	IGLV2-8	CARQIGDYW	830	CSAYAGSNNVVF	959	1088	1217

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype118	1	IGHV3-73	IGLV3-1	CTGPFDNW	831	CQAWDSSTGVF	960	1089	1218
clonotype119	1	IGHV3-15	IGLV3-25	CTTGGHYW	832	CQSADSSGTWVF	961	1090	1219
clonotype122	1	IGHV3-43	IGLV3-10	CAKARSFDIW	833	CYSTDSSGNHRVF	962	1091	1220
clonotype123	1	IGHV3-15	IGLV3-10	CRADMDVW	834	CYSIDSSGNHRVF	963	1092	1221
clonotype124	1	IGHV3-20	IGLV3-10	CARDRGFDYW	835	CYSTDSSGNHRVF	964	1093	1222
clonotype125	1	IGHV3-53	IGLV3-10	CARGGDYFDYW	836	CYSTDSSGNHRVF	965	1094	1223
clonotype126	1	IGHV1-18	IGLV2-14	CARGASFDFW	837	CSSYTRSSTCVF	966	1095	1224
clonotype127	1	IGHV3-73	IGLV2-14	CTGPFDYW	838	CSSYTSSSTWVF	967	1096	1225
clonotype128	1	IGHV3-53	IGLV2-23	CARSFDAFDIW	839	CCSYAGSSTFVVF	968	1097	1226
clonotype130	1	IGHV3-21	IGLV3-27	CAGLTGELDYW	840	CYSAADNNLVF	969	1098	1227
clonotype132	1	IGHV3-13	IGLV3-25	CARWGTGGFDYW	841	CQSADSSGTWVF	970	1099	1228
clonotype133	1	IGHV3-21	IGLV3-10	CARREGFFDYW	842	CYSTDSSGNHRVF	971	1100	1229
clonotype134	1	IGHV3-7	IGLV3-10	CARDQLAPDYW	843	CYSTDSSGNHRVF	972	1101	1230
clonotype135	1	IGHV3-23	IGLV3-10	CAKDSSGFDYW	844	CYSTDSSGNHRVF	973	1102	1231
clonotype136	1	IGHV3-23	IGLV3-10	CAKDPQFFDYW	845	CYSTDSSGNHRVF	974	1103	1232
clonotype137	1	IGHV3-23	IGLV3-10	CAKDGTAFDIW	846	CYSTDSSGNHRVF	975	1104	1233
clonotype138	1	IGHV3-33	IGLV3-9	CARDRGWGLDYW	847	CQVWDSSTGVF	976	1105	1234
clonotype140	1	IGHV3-30	IGLV3-19	CARGELGDFDYW	848	CNSRDSSGNHLVF	977	1106	1235
clonotype141	1	IGHV1-2	IGLV7-43	CARVLELYFDYW	849	CLLYYGGAVVF	978	1107	1236
clonotype143	1	IGHV3-15	IGLV1-44	CTTRSDFQHW	850	CAAWDDSLNGWVF	979	1108	1237
clonotype145	1	IGHV1-8	IGLV3-1	CARDQELRVFDYW	851	CQAWDSSTVVF	980	1109	1238
clonotype146	1	IGHV3-30	IGLV3-1	CAKASGYGPFDYW	852	CQAWDSSTVVF	981	1110	1239
clonotype147	1	IGHV5-51	IGLV3-1	CARHSSSSHFDYW	853	CQAWDSSTVVF	982	1111	1240
clonotype148	1	IGHV3-21	IGLV3-10	CARDRGNSLFDYW	854	CYSTDSSGNHRVF	983	1112	1241
clonotype150	1	IGHV1-2	IGLV3-10	CARDKSLEWFDYW	855	CYSTDSSGNHRVF	984	1113	1242
clonotype151	1	IGHV3-13	IGLV3-10	CARGDWNYGGFDYW	856	CYSTDSSGNHRVF	985	1114	1243

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype152	1	IGHV3-15	IGLV3-10	CTTAPDAFDIW	857	CYSTDSSGNHRVF	986	1115	1244
clonotype153	1	IGHV3-23	IGLV3-10	CASGITGTTGDYW	858	CYSTDSSGNHRVF	987	1116	1245
clonotype154	1	IGHV3-23	IGLV3-10	CAKEGAHDAFDIW	859	CYSTDSSGNHRVF	988	1117	1246
clonotype156	1	IGHV3-23	IGLV3-10	CAKDKGELPFDYW	860	CYSTDSSGNHRVF	989	1118	1247
clonotype157	1	IGHV3-33	IGLV3-19	CAKLGVRDYMDVW	861	CNSRDSSGNHWVF	990	1119	1248
clonotype158	1	IGHV3-20	IGLV3-19	CAREGGGWVFDYW	862	CNSRDSSGNHWVF	991	1120	1249
clonotype159	1	IGHV5-51	IGLV3-10	CARGGGGDPFDYW	863	CYSTDSSGNHRVF	992	1121	1250
clonotype160	1	IGHV1-2	IGLV2-14	CARPYNWNSFDYW	864	CSSYTTSSTWVF	993	1122	1251
clonotype161	1	IGHV3-43	IGLV2-14	CAKDNDWNGFDYW	865	CNSYTTNTTRVF	994	1123	1252
clonotype162	1	IGHV3-43	IGLV2-14	CAKDNWNYAFDIW	866	CSSYTSSSTRVF	995	1124	1253
clonotype164	1	IGHV3-74	IGLV5-45	CARDLDWTLFDYW	867	CMTWHSSAVVF	996	1125	1254
clonotype165	1	IGHV3-7	IGLV3-1	CAGDYSNYGWFDPW	868	CQAWDSSTVF	997	1126	1255
clonotype166	1	IGHV1-8	IGLV3-1	CARARDSGYYMDVW	869	CQAWDSSTVVF	998	1127	1256
clonotype167	1	IGHV3-33	IGLV3-27	CARATAMVTGIDYW	870	CYSAADNNWVF	999	1128	1257
clonotype168	1	IGHV3-73	IGLV3-27	CTGSSGSYFDYW	871	CYSAADNNLVF	1000	1129	1258
clonotype169	1	IGHV3-21	IGLV3-10	CARSPYNWNYVDYW	872	CYSTDSSGNHRVF	1001	1130	1259
clonotype170	1	IGHV1-24	IGLV3-10	CATEGPSTFSFDYW	873	CYSTDSSGNHRVF	1002	1131	1260
clonotype171	1	IGHV1-24	IGLV3-19	CATANWNDEAFDIW	874	CNSRDSSGNHLVF	1003	1132	1261
clonotype172	1	IGHV3-48	IGLV3-10	CARDELTGDAFDIW	875	CYSTDSSGNHRVF	1004	1133	1262
clonotype173	1	IGHV3-15	IGLV3-10	CTTEALGIFDYW	876	CYSTDSSGNHRVF	1005	1134	1263
clonotype174	1	IGHV3-21	IGLV7-43	CARDGSSGFLFDYW	877	CLLYYGGAWVF	1006	1135	1264
clonotype175	1	IGHV3-23	IGLV2-8	CAKHYYDSRSFDYW	878	CSSYAGSNNLVF	1007	1136	1265
clonotype176	1	IGHV4-4	IGLV1-40	CARDFQGTGPFDYW	879	CQSYDGSLNGWVF	1008	1137	1266
clonotype178	1	IGHV4-59	IGLV3-19	CARGRLYSGSFSFDYW	880	CKSRDRSGNHWVF	1009	1138	1267
clonotype179	1	IGHV3-7	IGLV3-19	CARDGGYNWNFFDYW	881	CNSRDSSGNHVVF	1010	1139	1268
clonotype180	1	IGHV2-5	IGLV3-19	CTHRDAAMVYFDYW	882	CNSRDSSGNHWVF	1011	1140	1269

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype181	1	IGHV1-18	IGLV3-10	CARWYYGSGSYFDYW	883	CYSTDSSGNHRVF	1012	1141	1270
clonotype182	1	IGHV3-13	IGLV3-19	CARGWNYGSGSCFDNW	884	CNSRDISGKHWVF	1013	1142	1271
clonotype183	1	IGHV3-13	IGLV3-10	CARGFSGTYYGDFDYW	885	CYSTDSSGNHWVF	1014	1143	1272
clonotype184	1	IGHV3-48	IGLV3-10	CAREGEWEPLHMDVW	886	CYSTDSSGNHRVF	1015	1144	1273
clonotype185	1	IGHV3-23	IGLV3-10	CAKSLSGSYVYMDVW	887	CYSTDSSGNHRVF	1016	1145	1274
clonotype186	1	IGHV3-30	IGLV3-19	CAKGFLEWLLGFDYW	888	CNSRDSSGNHWVF	1017	1146	1275
clonotype187	1	IGHV3-11	IGLV3-21	CARDGGSSGYYSDYW	889	CQVWDSSSDHVVF	1018	1147	1276
clonotype188	1	IGHV3-74	IGLV3-19	CTRDLVYSSGWYDYW	890	CNSRDSSGNHWVF	1019	1148	1277
clonotype189	1	IGHV3-74	IGLV3-19	CAREGIKASDAFDIW	891	CNSRDSSGSHVVF	1020	1149	1278
clonotype190	1	IGHV3-43	IGLV3-10	CAKDIDPSITGTDYW	892	CYSTDSSGNHSVVF	1021	1150	1279
clonotype191	1	IGHV3-11	IGLV7-43	CAGLRHFDWLGFDSW	893	CLLYYGGAWVF	1022	1151	1280
clonotype192	1	IGHV3-23	IGLV2-14	CAKEDNWNYGWFDPW	894	CSSYTSSSTWVF	1023	1152	1281
clonotype193	1	IGHV3-13	IGLV2-14	CAREETGTTSWYFDLW	895	CSSYTSSSTLYVF	1024	1153	1282
clonotype194	1	IGHV3-48	IGLV2-14	CARGYSYGYWYFDLW	896	CSSYTSSSTPYVF	1025	1154	1283
clonotype195	1	IGHV1-24	IGLV3-1	CATPYCSGGSCHFDYW	897	CQAWDSSTVVF	1026	1155	1284
clonotype196	1	IGHV3-21	IGLV3-10	CARDDYGGNSVYFDYW	898	CYSTDSSGNHRVF	1027	1156	1285
clonotype198	1	IGHV3-33	IGLV3-21	CVRAARYSGTYIFDYW	899	CQVWDSSSYHYVF	1028	1157	1286
clonotype199	1	IGHV3-15	IGLV3-10	CTTDPGYSYGVDYW	900	CYSTDSSGNHRVF	1029	1158	1287
clonotype200	1	IGHV5-51	IGLV3-10	CARPEYSSSSGYFQHW	901	CYSTDSSGNHRVF	1030	1159	1288
clonotype201	1	IGHV3-7	IGLV7-43	CAREYNWNYEDAFDIW	902	CLLYYGGAQVF	1031	1160	1289
clonotype202	1	IGHV2-5	IGLV2-23	CAHRRGSYSNWFDPW	903	CCSYAGSSTWVF	1032	1161	1290
clonotype203	1	IGHV1-18	IGLV1-36	CARTLFGVVKNWFDPW	904	CAAWDGRLNEWVF	1033	1162	1291
clonotype204	1	IGHV1-2	IGLV1-44	CAREVLGGGDCPFDYW	905	CAAWDDSLNGVVF	1034	1163	1292
clonotype205	1	IGHV1-2	IGLV1-36	CARSDGGSHYVFFDDW	906	CTAWDDRLNGPVF	1035	1164	1293
clonotype206	1	IGHV3-43	IGLV2-8	CAKDIAYSSSGHFDYW	907	CSSYAGSNNLVF	1036	1165	1294
clonotype207	1	IGHV4-4	IGLV1-40	CARAPLTGTTNWFDPW	908	CQSYDSSLSGWVF	1037	1166	1295

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype209	1	IGHV3-21	IGLV3-27	CAGVLYYDSSGYPFDYW	909	CYSAADNNLVF	1038	1167	1296
clonotype210	1	IGHV7-4-1	IGLV3-1	CARDPLAARPVGWFDPW	910	CQAWDSSTAVF	1039	1168	1297
clonotype211	1	IGHV3-21	IGLV3-19	CAREDGYSSGWNYFDYW	911	CNSRDSSGNHWVF	1040	1169	1298
clonotype212	1	IGHV1-24	IGLV3-21	CATGGQTIVAARVFDYW	912	CQVWDSSSDHVVF	1041	1170	1299
clonotype213	1	IGHV7-4-1	IGLV3-19	CARDQTPSDHYYYMDVW	913	CNSRDSSGNHYVF	1042	1171	1300
clonotype214	1	IGHV1-2	IGLV3-19	CARDRGITMRLDNMDVW	914	CNSRDSSGNHLVF	1043	1172	1301
clonotype215	1	IGHV3-73	IGLV2-23	CTRRYNWNDVGFDYW	915	CCSYAGSNTYVF	1044	1173	1302
clonotype217	1	IGHV2-5	IGLV3-1	CAHRPGITGNTGYFDYW	916	CQAWDSSTVVF	1045	1174	1303
clonotype218	1	IGHV1-18	IGLV3-1	CARCRYSGSLTSYYMDVW	917	CQAWDSSTVVF	1046	1175	1304
clonotype219	1	IGHV3-43	IGLV3-1	CAKDMITGTTNYYYMDVW	918	CQAWDSSTVVF	1047	1176	1305
clonotype220	1	IGHV3-43	IGLV3-9	CAKGGYDFWSGYYPFDPW	919	CQVWDNNTPWVF	1048	1177	1306
clonotype223	1	IGHV3-15	IGLV3-10	CTTEGTTVTTWAFDIW	920	CYSTDSSGNHRVF	1049	1178	1307
clonotype225	1	IGHV6-1	IGLV3-10	CASSGSYSDAFDIW	921	CYSTDSSGNHRVF	1050	1179	1308
clonotype226	1	IGHV7-4-1	IGLV1-44	CAKDRTGYYHYYYFMDVW	922	CAAWDDSLNGWLF	1051	1180	1309
clonotype228	1	IGHV1-18	IGLV1-40	CARSGYNWKYDYYYMDVW	923	CQSYDSSLSGSLVF	1052	1181	1310
clonotype230	1	IGHV3-7	IGLV3-10	CAREGGYDFWSGLNWFDPW	924	CYSTDSSGNHRVF	1053	1182	1311
clonotype232	1	IGHV1-18	IGLV3-10	CARAGGIAAAGTGYWFDPW	925	CYSTDSSGNHRVF	1054	1183	1312
clonotype234	1	IGHV3-15	IGLV3-19	CTTADYDFWSGYYMDVW	926	CNSRDSSGNHWVF	1055	1184	1313
clonotype236	1	IGHV6-1	IGLV3-10	CARDLELRGGAFDIW	927	CYSTDSSGNHRVF	1056	1185	1314
clonotype242	1	IGHV3-21	IGLV3-10	CTRGEGATWGNYHCYYMDVW	928	CYSTDSSGNHRVF	1057	1186	1315
clonotype245	1	IGHV1-2	IGLV3-19	CARDQITMVRGFLGDWFDPW	929	CNSRDSSGNHLVF	1058	1187	1316
clonotype247	1	IGHV4-39	IGLV3-10	CARGYSYEFDYW	930	CYSTDSSGNHRVF	1059	1188	1317
clonotype248	1	IGHV6-1	IGLV3-21	CAREEIVGATTAFDIW	931	CQVWDSSSDHWVF	1060	1189	1318
clonotype249	1	IGHV6-1	IGLV3-10	CARDYGGNSGWYFDLW	932	CYSTDSSGNHRVF	1061	1190	1319
clonotype251	1	IGHV4-34	IGLV2-14	CAREGLTGHVFDIW	933	CSSYTSSITWVF	1062	1191	1320
clonotype252	1	IGHV6-1	IGLV2-14	CARGGGSGSYDWFDPW	934	CSSYTSSSTWVF	1063	1192	1321

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype255	1	IGHV3-21	IGLV3-19	CAREGVLCSGGSCYREIFDYW	935	CNSRDSSGNHLVF	1064	1193	1322
clonotype261	1	IGHV3-15	IGLV1-40	CSTSPYYDFWSGYYGYIDYW	936	CQSFDSSLSGVMF	1065	1194	1323
clonotype262	1	IGHV3-15	IGLV1-40	CSTSPYFDFWSGYYGYLDYW	937	CQSYDSSLSGVVF	1066	1195	1324
clonotype263	1	IGHV4-39	IGLV5-45	CARHAAAGGWFDPW	938	CMIWHSSAVVF	1067	1196	1325
clonotype264	1	IGHV4-39	IGLV3-1	CARRSSSGIGAFDIW	939	CQAWDSSTVVF	1068	1197	1326
clonotype266	1	IGHV4-34	IGLV3-21	CARGRGIAARPPYFDYW	940	CQVWDSSSDHVVF	1069	1198	1327
clonotype269	1	IGHV4-39	IGLV3-10	CASEYSSSSLDAFDIW	941	CYSTDSSGNHRVF	1070	1199	1328
clonotype270	1	IGHV4-34	IGLV3-1	CARGTTVVTPTEYYYMDVW	942	CQAWDSSTVVF	1071	1200	1329
clonotype272	1	IGHV1-8	IGLV1-40	CARRGDFWSGYYSTSQNIVIHWFDSW	943	CQSYDSSLSGSVF	1072	1201	1330

[00648] **Table 7.** Full Heavy Chain (HC) and Light Chain (LC) Sequences for Anti-CD131 Antibodies

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
1073	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCASLTGDRFDYWGQGTLVTVSS	1202	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCSSYTSSSTVVFGGGTKLTVL
1074	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNAWMSWVRQAPGKGLEWVGRIKSKTDGGTTDYAAPVKGRFTISRDDSKNTLYLQMNSLKTEDTAVYYCTGRPSIAARHFDYWGQGTLVTVSS	1203	SYELTQPPSVSVSPGQTARITCSGDALPKKYAYWYQQKSGQAPVLVIYEDSKRPSGIPERFSGSSSGTMATLTISGAQVEDEADYYCYSTDSSGNHSVFGTGTKVTVL
1075	EVQLVESGGGVVRPGGSLRLSCAASGFTFDDYGMSWVRQAPGKGLEWVSGINWNGGSTGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCARERLTIFGVVNYYMDVWGKGTTVTVSS	1204	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTKLTVL
1076	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSYISSSSSTIYYADSVKGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARDGWDYWGQGTLVTVSS	1205	SYELTQPSSVSVSPGQTARITCSGDVLAKKYARWFQQKPGQAPVLVIYKDSERPSGIPERFSGSSSGTTVTLTISGAQVEDEADYYCYSAADNNRVFGGGTKLTVL
1077	EVQLVESGGGLVQPGGSLKLSCAASGFTFSSSDMHWVRQTTGKGLEWVSAIYTTGDTYYPGSVKGRFTISRENAKNSLYLQMNSLRAGDTAVYYCARGYSGSYYGDFDYWGQGTLVTVSS	1206	SYELTQPPSVSVSPGQTARITCSGDALPKKYAYWYQQKSGQAPVLVIYEDSKRPSGIPERFSGSSSGTMATLTISGAQVEDEADYYCYSTDSSGNRVFGGGTKLTVL
1078	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKKPPRDSAFDYWGQGTLVTVSS	1207	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIYGNSNRPSGVPDRFSGSKSGTSASLAITGLQAEDEADYYCQSYDSSLSGSVFGGGTKLTVL
1079	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGWISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARENSGSYYWFDPWGQGTLVTVSS	1208	QSALTQPPSASGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSKRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYCSSYAGSNNVVFGGGTKLTVL
1080	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAISGSGGSTYYADSV	1209	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPS

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKLEYSSPDYWGQGTLVTVSS		GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCCSYAGSSTLVFGGGTKLTVL
1081	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGY YWSWIRQPPGKGLEWIGEINHSGSTNYNPSLK SRVTISVDTSKNQFSLKLSSVTAADTAVYYCA REGLLVGATLDAFDIWGQGTMVTVSS	1210	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHLVFGTGTKVTVL
1082	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSY GMHWVRQAPGKGLEWVAVIWYDGSNKYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARDTGITMVRGVFDYWGQGTLVTVSS	1211	SYVLTQPPSVSVAPGKTARITCGGNNIGS KSVHWYQQKPGQAPVLVIYYDSDRPSGIP ERFSGSNSGNTATLTISRVEAGDEADYYC QVWDSSSDHPVFGGGTKLTVL
1083	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSY GISWVRQAPGQGLEWMGWISAYNGNTNYAQKF QGRVTMTTDTSTNTAYMELRSLRSDDKAVFYC ARDRTGISAAGPSNWFDPWGQGTLVTVSS	1212	QSVLTQPPSASGTPGQRVTISCSGSSSNI GSNTVNWYQQLPGTAPKLLIYSNNQRPSG VPDRFSGSKSGTSASLAISGLQSEDEADY YCAAWDDSLNGPVFGGGTKLTVL
1084	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGY YWSWIRQPPGKGLEWIGEINHSGSTNYNPSLK SRVTISVDTSKNQFSLKLSSVTAADTAVYYCA RTSLAAADFDYWGQGTLVTVSS	1213	QSALTQPPSASGSPGQSVTISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVSKRPS GVPDRFSGSKSGNTASLTVSGLQAEDEAD YYCSSYAGSNNYVFGTGTKVTVL
1085	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSN YMSWVRQAPGKGLEWVSVIYSGGSTYYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA RAPDYYGSGSLFDYWGQGTLVTVSS	1214	QSVLTQPPSVSEAPRQRVTISCSGSSSNI GNNAVNWYQQLPGKAPKLLIYYDDLLPSG VSDRFSGSKSGTSASLAISGLQSEDEADY YCAAWDDRLNGPVFGGGTKLTVL
1086	EVQLVESGGGLVKPGGSLRLSCIASGFTFSTY SMNWVRQAPGKGLEWVSSISGSSSYIYYSDSV KGRFTISRDNAKNSLYLQLNSLRAEDTAVYYC ASHWGHFDYWGRGTLVTVSS	1215	SYELTQPLSVSVALGQTARITCGGNNIGS KNVHWYQQKPGQAPVLVIYRDSNRPSGIP ERFSGSNSGNTATLTISRAQAGDEADYYC QVWDSSTVVFGGGTKLTVL
1087	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY DMHWVRQATGKGLEWVSAIGTAGDTYYPGSVK GRFTISRENAKNSLYLQMNSLRAGDTAVYYCA RDRTLDYWGQGTLVTVSS	1216	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHWVFGGGTKLTVL
1088	QVQLVQSGAEAKKPGASVKVSCMASGYTFTTY GISWVRQAPGQGLEWMGWISAYNGNTKYAQKL QGRVTMTTDTSTRTAYMELRSLRSDDTAVYYC ARQIGDYWGQGTLVTVSS	1217	QSALTQPPSASGSPGQSVTISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVIKRPS GVPDRFSGSKSGNTASLTVSGLQAEDEAD YYCSAYAGSNNVVFGGGTQLTVL
1089	EVQLVESGGGLVQTGGSLKLSCAASGFTFSVS PIHWVRQASGKGLEWVGRIRSKANSYATAYGA SVKGRFTISRDDSKNTAYLQMNSLKTEDTAVY YCTGPFDNWGQGTLVTVSS	1218	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTGVFGGGTKLTVL
1090	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDGGTTDYTA PVKGRFTISRDDSKNTLYLQMNSLRTEDTAVY YCTTGGHYWGQGTLVTVSS	1219	SYELTQPPSVSVSPGQTARITCSADALPN QYAYWYQQKPGQAPVLVIYKDSERPSGIP ERFSGSSSGTTVTLTISGVQAEDEADYYC QSADSSGTWVFGGGTKLTVL
1091	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY AMHWVRQAPGKGLEWVSGISWNSGSIGYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTALYYC AKARSFDIWGQGTMVTVSS	1220	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1092	EVQLVESGGGLVKPGGSLRLSCAASGFTFSDA WMYWDRQAPGKGLEWVGRIKSKTDGGTTDYAA PVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCRADMDVWGKGTTVTVSS	1221	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSIDSSGNHRVFGGGTKLTVL
1093	EVQLVESGGGVVRPGGSLRLSCAASGFTFDDY GMSWVRQAPGKGLEWVSGINWNGGSTGYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTALYYC ARDRGFDYWGQGTLVTVSS	1222	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1094	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSN YMSWVRQAPGKGLEWVSVIYSGGSTYYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA RGGDYFDYWGQGTLVTVSS	1223	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1095	QVQLVQSGAEVKKPGASVKVSCKTSGYTFTSF GISWVRQAPGQGLEWMGWISAYNDNINYAQKL	1224	QSALTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVSDRPS

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	QDRVTMTTDTSTSTACMELRSLRSDDTAVYFC ARGASFDFWGQGTLVTVSS		GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCSSYTRSSTCVFGGGTKLTVL
1096	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGS AMHWVRQASGKGLEWVGRIRSKANSYATAYAA SVKGRFTISRDDSKNTAYLQMNSLKTEDTAVY YCTGPFDYWGQGTLVTVSS	1225	QSALTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVSNRPS GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCSSYTSSSTWVFGGGTKLTVL
1097	EVQLVESGGGLIQPGGSLRLSCAASGFTVSSN YMSWVRQAPGKGLEWVSVIYSGGSTYYADSVK GRFTISRDNSKNTLYLQMNSLRAEDTAVYYCA RSFDAFDIWGQGTMVTVSS	1226	QSALTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYDVSKRPS GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCCSYAGSSTFVVFGGGTKLTVL
1098	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSSISSSSSYIYYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AGLTGELDYWGQGTLVTVSS	1227	SYELTQPSSVSVSPGQTARITCSGDVLAK KYARWFQQKPGQAPVLVIYKDSERPSGIP ERFSGSSSGTTVTLTISGAQVEDEADYYC YSAADNNLVFGGGTKLTVL
1099	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY DMHWVRQATGKGLEWVSAIGTAGDTYYPGSVK GRFTISRENAKNSLYLQMNSLRAGDTAVYYCA RWGTGGFDYWGQGTLVTVSS	1228	SYELTQPPSVSVSPGQTARITCSADALPK QYAYWYQQKPGQAPVLVIYKDSERPSGIP ERFSGSSSGTTVTLTISGVQAEDEADYYC QSADSSGTWVFGGGTKLTVL
1100	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSSISSSSSYIYYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC ARREGFFDYWGQGTLVTVSS	1229	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1101	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY WMSWVRQAPGKGLEWVANIKQDGSEKYYVDSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC ARDQLAPDYWGQGTLVTVSS	1230	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1102	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKDSSGFDYWGQGTLVTVSS	1231	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1103	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKDPQFFDYWGQGTLVTVSS	1232	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1104	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKDGTAFDIWGQGTMVTVSS	1233	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1105	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSY GMHWVRQAPGKGLEWVAVIWYDGSNKYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARDRGWGLDYWGQGTLVTVSS	1234	SYELTQPLSVSVALGQTARITCGGNNIGS KNVHWYQQKPGQAPVLVIYRDSNRPSGIP ERFSGSNSGNTATLTISRAQAGDEADYYC QVWDSSTGVFGGGTKLTVL
1106	QVQLVESGGGVVQPGRSLRLSCAASGFPFSNS GMHWVRQAPGKGLEWVTIISYDGNSKYYADSV KGRFTISRDNSKNTLYLQMNSLRTEDTAVYYC ARGELGDFDYWGRGTLVTVSS	1235	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHLVFGGGTKLTVL
1107	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGY YMHWVRQAPGQGLEWMGWINPNSGGTNYAQKF QGRVTMTRDTSISTAYMELSRLRSDDTAVYYC ARVLELYFDYWGQGTLVTVSS	1236	QTVVTQEPSLTVSPGGTVTLTCASSTGAV TSGYYPNWFQQKPGQAPRALIYSTSNKHS WTPARFSGSLLGGKAALTLSGVQPEDEAE YYCLLYYGGAVVFGGGTKLTVL
1108	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDGGTTDYAA PVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCTTRSDFQHWGQGTLVTVSS	1237	QSVLTQPPSASGTPGQRVTISCSGSSSNI GSNTVNWYQQLPGTAPKLLIYSNNQRPSG VPDRFSGSKSGTSASLAISGLQSEDEADY YCAAWDDSLNGWVFGGGTKLTVL
1109	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSY DINWVRQATGQGLEWMGWMNPNSGNTGYAQKF QGRVTMTRNTSISTAYMELSSLRSEDTAVYYC ARDQELRVFDYWGQGTLVTVSS	1238	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVVFGGGTKLTVL
1110	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSY GMHWVRQAPGKGLEWVAVISYDGSNKYYADSV	1239	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKASGYGPFDYWGQGTLVTVSS		ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVVFGGGTKLTVL
1111	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSY WIGWVRQMPGKGLEWMGIIYPGDSDTRYSPSF QGQVTISADKSISTAYLQWSSLKASDTAMYYC ARHSSSSHFDYWGQGTLVTVSS	1240	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVVFGGGTKLTVL
1112	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSSISSSSSYIYYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC ARDRGNSLFDYWGQGTLVTVSS	1241	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1113	QVQLVQSGAEVKKPGASVKVSCKASGYTFTGY YMHWVRQAPGQGLEWMGWINPNSGGTNYAQKF QGRVTMTRDTSISTAYMELSRLRSDDTAVYYC ARDKSLEWFDYWGQGTLVTVSS	1242	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1114	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY DMHWVRQATGKGLEWVSAIGTAGDTYYPGSVK GRFTISRENAKNSLYLQMNSLRAGDTAVYYCA RGDWNYGGFDYWGQGTLVTVSS	1243	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1115	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDGGTTDYAA PVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCTTAPDAFDIWGQGTMVTVSS	1244	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1116	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ASGITGTTGDYWGQGTLVTVSS	1245	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1117	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKEGAHDAFDIWGQGTMVTVSS	1246	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1118	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKDKGELPFDYWGQGTLVTVSS	1247	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1119	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSY GMHWVRQAPGKGLEWVAVIWYDGSNKYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKLGVRDYMDVWGKGTTVTVSS	1248	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHWVFGGGTKLTVL
1120	EVQLVESGGGVVRPGGSLRLSCAASGFTFDDY GMSWVRQAPGKGLEWVSGINWNGGSTGYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTALYYC AREGGGWVFDYWGQGTLVTVSS	1249	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHWVFGGGTKLTVL
1121	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSY WIGWVRQMPGKGLEWMGIIYPGDSDTRYSPSF QGQVTISADKSISTAYLQWSSLKASDTAMYYC ARGGGGDPFDYWGQGTLVTVSS	1250	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1122	QVQLVQSGAEVKKPGASVQVSCKASGYTFTGY YIHWVRQAPGQGLEWMGWINPNSGGTNYAQKF QGRVIMTRDTSISIAYIELSRLRSDDTAVYYC ARPYNWNSFDYWGQGTLVTVSS	1251	QSALTQPASVSGSLGQSITISCTGTSSDV GGYNYVSWYQHHPGKAPKIMIYDVSNRPS GVSNRFSASKSGNTASLTISGLQTEDEAD YYCSSYTTSSTWVFGGGTNLTVL
1123	EVQLVESGGDLVQPGRSLRLSCAASGFTFDDH AIHWVRQAPGKGLEWVSGVTWNSNIIGYADSV KGRFTISRDIAKNSLYLQMNSLRPEDTALYYC AKDNDWNGFDYWGQGTLVTVSS	1252	QSALTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVSNRPS VISYRFSGSKSGNTASLTISGLQAEDEAD YYCNSYTTNTTRVFGGGTKLTVL
1124	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY AMHWVRQAPGKGLEWVSGISWNSGSIGYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTALYYC AKDNWNYAFDIWGQGTMVTVSS	1253	QSALTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVSNRPS GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCSSYTSSSTRVFGGGTKLTVL
1125	EVQLVESGGGLVQPGGSLRLSCTASGFTFSSY WMHWVRQAPGKGLVWVSRVNSDGGNTIYADSV	1254	QAVLTQPASLSASPGASASLTCTLRSGIY VGTYRIYWYQQKPGSPPQYLLRYKSDSDK

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	KGRFTISRDNAKNTLYLQMNSLRAEDTAIYYC ARDLDWTLFDYWGQGTLVTVSS		QQGSGVPSRFSGSKDVSANAGILLISGLQ SEDEADYYCMTWHSSAVVFGGGTKLTVL
1126	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY WMSWVRQAPGKGLEWVANIKQDGSEKYYVDSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AGDYSNYGWFDPWGQGTLVTVSS	1255	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVFGGGTKLTVL
1127	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSY DINWVRQATGQGLEWMGWMNPNSGNTGYAQKF QGRVTMTRNTSISTAYMELSSLRSEDTAVYYC ARARDSGYYMDVWGKGTTVTVSS	1256	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVVFGGGTKLTVL
1128	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSY GMHWVRQAPGKGLEWVAVIWYDGSNKYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARATAMVTGIDYWGQGTLVTVSS	1257	SYELTQPSSVSVSPGQTARITCSGDVLAK KYARWFQQKPGQAPVLVIYKDSERPSGIP ERFSGSSSGTTVTLTISGAQVEDEADYYC YSAADNNWVFGGGTKLTVL
1129	EVQLVESGGGLVQPGGSLKLSCAASGFTFSGS AMHWVRQASGKGLEWVGRIRSKANSYATAYAA SVKGRFTISRDDSKNTAYLQMNSLKTEDTAVY YCTGSSGSYFDYWGQGTLVTVSS	1258	SYELTQPSSVSVSPGQTARITCSGDVLAK KYARWFQQKPGQAPVLVIYKDSERPSGIP ERFSGSSSGTTVTLTISGAQVEDEADYYC YSAADNNLVFGGGTKLTVL
1130	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSSISSSSSYIYYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC ARSPYNWNYVDYWGQGTLVTVSS	1259	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1131	QVQLVQSGAEVKKPGASVKVSCKVSGYTLTEL SMHWVRQAPGKGLEWMGGFDPEDGETIYAQKF QGRVTMTEDTSTDTAYMDLSSLRSEDTAVYYC ATEGPSTFSFDYWGQGTLVTVSS	1260	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1132	QVQLVQSGAEVKKPGASVKVSCKVSGYTLTEL SMHWVRQAPGKGLEWMGGFDPEDGETIYAQKF QGRVTMTEDTSTDTAYMDLSSLRSEDTAVYYC ATANWNDEAFDIWGQGTMVTVSS	1261	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHLVFGGGTKLTVL
1133	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSYISSSSSTIYYADSV KGRFTISRDNAKNSLYLQMNSLRDEDTAVYYC ARDELTGDAFDIWGQGTMVTVSS	1262	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1134	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDGGTTDYAA PVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCTTEALGIFDYWGQGTLVTVSS	1263	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1135	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSSISSSSSYIYYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC ARDGSSGFLFDYWGQGTLVTVSS	1264	QTVVTQEPSLTVSPGGTVTLTCASSTGAV TSGYYPNWFQQKPGQAPRALIYSTSNKHS WTPARFSGSLLGGKAALTLSGVQPEDEAE YYCLLYYGGAWVFGGGTKLTVL
1136	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKHYYDSRSFDYWGQGTLVTVSS	1265	QSALTQPPSASGSPGQSVTISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVSKRPS GVPDRFSGSKSGNTASLTVSGLQAEDEAD YYCSSYAGSNNLVFGGGTKLTVL
1137	QVQLQESGPGLVKPSGTLSLTCAVSGGSISSS DWWTWVRQPPGRGLEWIGEINHSGTTNYNPSL KSRVTISVDKSKNQFSLKLSSVTAADTAVYYC ARDFQGTGPFDYWGQGTLVTVSS	1266	QSALTQPPSVSGAPGQRVTISCTGSSSNI GAGYDVHWFQQLPGTAPKLLIYDNNNRPS GVPNRFSGSKSGTSASLAITGLQADFEAD YYCQSYDGSLNGWVFGGGTKLTVL
1138	QVQLQQWGAGLLKPSETLSLTCAVFGGSFSGY YWSWIRQPPGKGLEWIGEINHSGSTNYNPSLK SRVTISVDTSKNQFSLKLTSVTAADTTVYYCA RGRLYSGSFSFDYWGQGTLVTVSS	1267	SSELTQDPAVSVALGQTVRITCQGDSLRN YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNIASLTITGAQAEDEADYYC KSRDRSGNHWVFGGGTKVTVL
1139	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY WMSWVRQAPGKGLEWVANIKQDGSEKYYVDSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC ARDGGYNWNFFDYWGQGTLVTVSS	1268	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHVVFGGGTKLTVL
1140	QITLKESGPMLVKPTQTLTLTCTFSGFSLSTS GVGVGWIRQPPGKALEWLALIYWNDDKRYSPS	1269	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	LKSRLTITRDTSKNQVVLTMTNMDPVDTATYY CTHRDAAMVYFDYWGQGTLVTVSS		DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHWVFGGGTKLTVL
1141	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSY GISWVRQAPGQGLEWMGWISAYNGNTNYAQKL QGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC ARWYYGSGSYFDYWGQGTLVTVSS	1270	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1142	EVQLVESGGGLVQPGGSRRLSCAASGFTFSRY DMHWVRQGTGKGLEWVSGINTAGDTYYSGSVK GRFTISRENAKNSLHLQMNSLRAGDTAVYYCA RGWNYGSGSCFDNWGQGTLVTVSS	1271	SSELTQDPAVSVALGQTVRITCQGDNLRN YSVSWCQQRPGQAPTLVIFGKNNRPSGIP DRFSGSNSGNTASLTITGAQAEDEADYYC NSRDISGKHWVFGGGTKLTVL
1143	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSS DMHWVRQAPGEGLEWVSAIYTTGDTYYPGSVQ GRFTISRENAKNSLYLQMNSLRAGDTAVYYCA RGFSGTYYGDFDYWGQGTLVTVSS	1272	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHWVFGGGTKLTVL
1144	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSYISSSSSTIYYADSV KGRFTISRDNAKNSLYLQMNSLRDEDTAVYYC AREGEWEPLHMDVWGKGTTVTVSS	1273	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1145	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMSWVRQAPGKGLEWVSAISGSGGSTYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKSLSGSYVYMDVWGKGTTVTVSS	1274	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1146	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSY GMHWVRQAPGKGLEWVAVISYDGSNKYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AKGFLEWLLGFDYWGQGTLVTVSS	1275	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHWVFGGGTKLTVL
1147	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDY YMSWIRQAPGKGLEWVSYISSSGSTIYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARDGGSSGYYSDYWGQGTLVTVSS	1276	SYVLTQPPSVSVAPGKTARITCGGNNIGS KSVHWYQQKPGQAPVLVIYYDSDRPSGIP ERFSGSNSGNTATLTISRVEAGDEADYYC QVWDSSSDHVVFGGGTKLTVL
1148	EVQLVESGGGLVQPGGSLRLSCAASGFTFSEY WMHWVRQAPGKGLVWVARINSDGSRTDYADSV KGRFTISRNNAKNRLNLQIDSLRAEDTAVYYC TRDLVYSSGWYDYWGQGTLVTVSS	1277	SSELTQDPAVSVALGQTVRITCQGDSLRS YYANWYQQKPGQAPILVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDESDYYC NSRDSSGNHWVFGGGTKLTVL
1149	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY WMHWVRQAPGKGLVWVSRINSDGSGTSYADSV KGRFTISRDNAKNTLYLQMNSLRAEDTAVYYC AREGIKASDAFDIWGQGTMVTVSS	1278	SSELTQDPAVSVALGQTVRITCQGDSLRT YYASWYQQKPGQAPILVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYSC NSRDSSGSHVVFGGGTKLTVL
1150	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY AMHWVRQAPGKGLEWVSGISWNSGSIGYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTALYYC AKDIDPSITGTDYWGQGTLVTVSS	1279	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHSVVFGGGTKLTVL
1151	QVQLVESGGGLVKPGGSLRLSCAASGFTFSDY YMSWIRQAPGKGLEWVSYISHSGTTVYYADSV KGRFTISRDNAKISLYLQMNSLRAEDTAVYYC AGLRHFDWLGFDSWGQGTLVTVSS	1280	QTVVTQEPSLTVSPGGTVTLTCASSTGAV TSGYYPNWFQQKPGQAPRALIYSTSNKHS WTPARFSGSLLGGKAALTLSGVQPEDEAE YYCLLYYGGAWVFGGGTKLTVL
1152	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY AMNWVRQAPGKGLEWVSIINDSGYSTYYADSV KGRFTISRDNSKNTLYLQMNSLRAEDTALYYC AKEDNWNYGWFDPWGQGTLVTVSS	1281	QSALTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKVIIYEVIIRPS GVSPRFSGSKSGKMASLTISGLQAEDEAD YYCSSYTSSSTWVFGGGTKLTVL
1153	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY DMHWVRQATGKGLEWVSAIGTAGDTYYPGSVK GRFTISRENAKNSLYLQMNSLRAGDTAVYYCA REETGTTSWYFDLWGRGTLVTVSS	1282	QSALTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVSNRPS GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCSSYTSSSTLYVFGTGTKVTVL
1154	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSYISSSSSTIYYADSV KGRFTISRDNAKNSLYLQMNSLRDEDTAVYYC ARGYSYGYWYFDLWGRGTLVTVSS	1283	QSALTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVSNRPS GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCSSYTSSSTPYVFGTGTKVTVL
1155	QVQLVQSGAEVKKPGASVKVSCKVSGYTLTEL SMHWVRQAPGKGLEWMGGFDPEDGETIYAQKF	1284	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	QGRVTMTEDTSTDTAYMDLSSLRSEDTAVYYC ATPYCSGGSCHFDYWGQGTLVTVSS		ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVVFGGGTKLTVL
1156	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSSISSSSSYIYYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC ARDDYGGNSVYFDYWGQGTLVTVSS	1285	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1157	QVQLVESGGGAVQPGRSLRLSCVASGFTFSNY DMHWVRQAPGKGLEWVAVIWSDGSNKYYSDSV KGRFTISRDNSKNTLYLQMTSLSAEDSALSYC VRAARYSGTYIFDYWGQGTLVTVSS	1286	SYVLTQSPSMSVAPGKTARITCGGNNIGS KSVHWYQQRPGQAPVLVIYYDSDRPSGIP ERFSGSNSGNTATLTISRVEAGDEAVYYC QVWDSSSYHYVFGTGTKVAVL
1158	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDGGTTDYAA PVKGRFAISRDDSKNTLYLQMNSLKTEDTAVY YCTTDPGYSYGVDYWGQGTLVTVSS	1287	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1159	EVQLVQSGAEVKKPGESLKISCKGSGYSFTSY WIGWVRQMPGKGLEWMGIIYPGDSDTRYSPSF QGQVTISADKSISTAYLQWSSLKASDTAMYYC ARPEYSSSSGYFQHWGQGTLVTVSS	1288	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1160	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY WMSWVRQAPGKGLEWVANIKQDGSEKYYVDSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AREYNWNYEDAFDIWGQGTMVTVSS	1289	QTVVTQEPSLTVSPGGTVTLTCASSTGAV TSGYYPNWFQQKPGQAPRALIYSTSNKHS WTPARFSGSLLGGKAALTLSGVQPEDEAE YYCLLYYGGAQVFGGGTKLTVL
1161	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTS GVGVGWIRQPPGKALEWLALIYWNDDKRYSPS LKSRLTITKDTSKNQVVLTMTNMDPVDTATYY CAHRRGSYSNWFDPWGQGTLVTVSS	1290	QSALTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYDVSKRPS GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCCSYAGSSTWVFGGGTKLTVL
1162	QIQLVQSGAEVKKPGASVKVSCTASGYTFSSY GITWVRQAPGQGLEWMGWISAYNGNTHYAQNL QGRVTMTTDTSTTTAYMDLRSLRSDDTAIYYC ARTLFGVVKNWFDPWGQGTLVTVSS	1291	QSVLSQPPSVSEAPRQRVTISCSGSSSNI GNNAVNWYQKLPGKAPKLLISHDVLLSSG VSDRFSGSKSGTSASLAISGLQSEDEADY YCAAWDGRLNEWVFGGGTKLTVL
1163	QVQLVQSGASVKVSCKASGYTFTGYYMHWVRQ APGQGLEWMGWINPNSGGTNYAQKFQGRVTMT RDTSISTAYMELSRLRSDDTAVYYCAREVLGG GDCPFDYWGQGTLVTVSS	1292	QSVLTQPPSASGTPGQRVTISCSGSSSNI GSNTVNWYQQLPGTAPKLLIYSNNQRPSG VPDRFSGSKSGTSASLAISGLQSEDEADY YCAAWDDSLNGVVFGGGTKLTVL
1164	QVQLVQSGAEVRKPVASVKVSCKASGYTFTDH SIHWVRQAPGQGLEWMGSINPNSGGTNYAQKF QGRVTMTWDTYNSTAFMELSRLRSDDTAVYYC ARSDGGSHYVFFDDWGQGTLVTVSS	1293	QSVLTQPPSVSEAPRQRVTISCSGSISNI GNNAVSWYQQVPGKAPKLLIYYDDLLPSG VSDRFSGSRSVTSASLAISGLQSEDDADY YCTAWDDRLNGPVFGGGTKLTVL
1165	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY AMHWVRQAPGKGLEWVSGISWNSGSIGYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTALYYC AKDIAYSSSGHFDYWGQGTLVTVSS	1294	QSALTQPPSASGSPGQSVTISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVSKRPS GVPDRFSGSKSGNTASLTVSGLQAEDEAD YYCSSYAGSNNLVFGGGTKLTVL
1166	QVQLQESGPGLVKPSGTLSLTCVVSGGSITSS NWWSWVRQPPGKGLEWIGEIYHSGNTNYNPSL KSRVTISVDKSKNQFSLRLSSVTAADTAVYYC ARAPLTGTTNWFDPWGQGTLVTVSS	1295	QSVLTQPPSVSGAPGQRVTISCSGSSSNI GAGYDVHWYQQLPGTGPKVLIYGNRNRPS GVPDRFSGSKSGTSASLVITGLQAEDEAD YSCQSYDSSLSGWVFGGGTKLTVL
1167	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSSISSSSSYIYYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AGVLYYDSSGYPFDYWGQGTLVTVSS	1296	SYELTQPSSVSVSPGQTARITCSGDVLAK KYARWFQQKPGQAPVLVIYKDSERPSGIP ERFSGSSSGTTVTLTISGAQVEDEADYYC YSAADNNLVFGGGTKLTVL
1168	QVQLVQSGSELKKPGASVKVSCKASGYTFTSY AMNWVRQAPGQGLEWMGWINTNTGNPTYAQGF TGRFVFSLDTSVSTAYLQISSLKAEDTAVYYC ARDPLAARPVGWFDPWGQGTLVTVSS	1297	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTAVFGGGTKLTVL
1169	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY SMNWVRQAPGKGLEWVSSISSSSSYIYYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AREDGYSSGWNYFDYWGQGTLVTVSS	1298	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHWVFGGGTKLTVL
1170	QVQLVQSGAEVKKPGASVKVSCKVSGYTLTEL SMHWVRQAPGKGLEWMGGFDPEDGETIYAQKF	1299	SYVLTQPPSVSVAPGKTARITCGGNNIGS KSVHWYQQKPGQAPVLVIYYDSDRPSGIP

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	QGRVTMTEDTSTDTAYMDLSSLRSEDTAVYYC ATGGQTIVAARVFDYWGQGTLVTVSS		ERFSGSNSGNTATLTISRVEAGDEADYYC QVWDSSSDHVVFGGGTKLTVL
1171	QVQLVQSGSELKKPGASVKVSCKASGYTVTRH ALNWVRQAPGQGLEWMGWINTNTGTPTYAQGF IGRFVFTLDTSVSTAYLQINSLKAEDTAVYYC ARDQTPSDHYYYMDVWGKGTTVTVSS	1300	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHYVFGTGTKVTVL
1172	LAHLVQSGAEVKRPGASVKVSCKAFGYAFRGQ HIHWVRQAPGQGLEWMGWIRPNSGDTNYSQKF QGRVTMTRDTSITTAYMELTRLRSDDSAVYYC ARDRGITMRLDNMDVWGKGTMVTVSS	1301	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHLVFGGGTKLTVL
1173	EVQLVESGGTLVQPGGSLTLSCAASGFTFSDS AMHWVRQASGKGLEWVGRIRGKPNTYATAYAA SVKGRFTISKDDSKNTAFLQMNSLKTEDRAVY YCTRRYNWNDVGFDYWGQGTLVTVSS	1302	QSALTQPASVSGSPGQSITISCTGTSSDV GAYNYVSWYQQHPGKAPKFMIYDVSKRPS GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCCSYAGSNTYVFGTGTRVTVL
1174	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTS GVGVGWIRQPPGKALEWLALIYWNDDKRYSPS LKSRLTITKDTSKNQVVLTMTNMDPVDTATYY CAHRPGITGNTGYFDYWGQGTLVTVSS	1303	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVVFGGGTKLTVL
1175	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSY GISWVRQAPGQGLEWMGWISAYNGNTNYAQKL QGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC ARCRYSGSLTSYYMDVWGKGTTVTVSS	1304	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVVFGGGTKLTVL
1176	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY AMHWVRQAPGKGLEWVSGISWNSGSIGYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTALYYC AKDMITGTTNYYYMDVWGKGTTVTVSS	1305	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVVFGGGTKLTVL
1177	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDY AMHWVRQAPGKGLEWVSGISRNSGSVGYADSV RGRFTISRDNAKNSLYLQMNSLRAEDTALYYC AKGGYDFWSGYYPFDPWGQGTLVTVSS	1306	SYELTQPLSVSVALGQTARITCGENNIVN KNVHWYQQKPGQAPVLVIYRDGNRPSGIP ERFSGSNSGNTATLTISRAQAGDEADYYC QVWDNNTPWVFGGGTKLTVL
1178	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDGGTTDYAA PVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCTTEGTTVTTWAFDIWGQGTMVTVSS	1307	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1179	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSN SAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYA VSVKSRITINPDTSKNQFSLQLNSVTPEDTAV YYCASSGSYSDAFDIWGQGTMVTVSS	1308	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1180	QVQLVQSGSELKKPGASVMVSCKASGYTFTRN GINWLRQAPGQGLEWMGWIDTHTGNPTYVQGF TGRFVFSLDTSVNTAYLQISSLRAEDTAVYYC AKDRTGYYHYYYFMDVWGKGTAVTVSS	1309	QSVLTQPPSASGAPGQRVTMSCSGSSSNI ERTAVNWYSHLPGAAPKLLIYSNDQRPLG VPDRFAGSKSGSSASLAISGLQSEDEAAY FCAAWDDSLNGWLFGGGTKLTVL
1181	QVQLVQSGTEMKKPGASVKVSCKASGYTFTTY GISWVRQAPGQGLEWMGWISAYNGNTNYAQKL QARVTMTTDTSTNTAYMELRSLRSDDTAVYYC ARSGYNWKYDYYYMDVWGKGTTVTVSS	1310	QSVLTQPPSVSGAPGQRVTISCTGNSSNI GADYDVQWYQQFPGTAPKLLIYANIIRPS GVPDRFSGSKSGTSASLAITGLQAEDEAD YYCQSYDSSLSGSLVFGGGTKLTVL
1182	EVQLVESGGGLVQPGGSLRLSCAASGFTFSSY WMSWVRQAPGKGLEWVANIKQDGSEKYYVDSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AREGGYDFWSGLNWFDPWGQGTLVTVSS	1311	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1183	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSY GISWVRQAPGQGLEWMGWISAYNGNTNYAQKL QGRVTMTTDTSTSTAYMELRSLRSDDTAVYYC ARAGGIAAAGTGYWFDPWGQGTLVTVSS	1312	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1184	EVQLVESGGGLVKPGGSLRLSCAASGFTFSNA WMSWVRQAPGKGLEWVGRIKSKTDGGTTDYAA PVKGRFTISRDDSKNTLYLQMNSLKTEDTAVY YCTTADYDFWSGYYMDVWGKGTTVTVSS	1313	SSEMTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHWVFGGGTKLTVL
1185	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSN SAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYA	1314	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	VSVKSRITINPDTSKNQFSLQLNSVTPEDTAV YYCARDLELRGGAFDIWGQGTMVTVSS		ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1186	EVHLVESGGGLVRPGGSLRLSCEVSGFTFSTY SMNWVRQAPGKGLEWVSSISSRSSYIYYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC TRGEGATWGNYHCYYMDVWGKGTTVIVSS	1315	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1187	QVQLVQSGAEVKKPGASVKVSCKASGYSFTGY YMHWVRQAPGQGLEWMGWINPNSGGTNYAQKF QGRVTMTWDTSISTAYMELSRLRSDDTAVYYC ARDQITMVRGFLGDWFDPWGQGTLVTVSS	1316	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHLVFGGGTKLTVL
1188	QLQLQESGPGLVKPSETLSLTCTVSGGSISSS SYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CARGYSYEFDYWGQGTLVTVSS	1317	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1189	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSN SAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYA VSVKSRITINPDTSKNQFSLQLNSVTPEDTAV YYCAREEIVGATTAFDIWGQGTMVTVSS	1318	SYVLTQPPSVSVAPGKTARITCGGNNIGS KSVHWYQQKPGQAPVLVIYYDSDRPSGIP ERFSGSNSGNTATLTISRVEAGDEADYYC QVWDSSSDHWVFGGGTKLTVL
1190	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSSN SAAWNWIRQSPSRGLEWLGRTYYRSKWYNDYA VSVKSRITINPDTSKNQFSLQLNSVTPEDTAV YYCARDYGGNSGWYFDLWGRGTLVTVSS	1319	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1191	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGH YWNWIRQPPGKGLEWIGEINHSGFTNYNPSLK SRVTISVDTPKNQFSLNLSSVTAADTAVYYCA REGLTGHVFDIWGQGTMVTVSS	1320	QSALTQPASVSGSPGQSITISCTGTSSDV GVYNYVSWYQQHPTKAPKLMIYEVSNRPS GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCSSYTSSITWVFGGGTKLTVL
1192	QVQVQQSGPGLVKPSQTLSLTCAISGDSVSSN SAAWNWIRQSPSRGLEWLGRTYYRSKWYNDFA VSVKSRITINPDTSKNQFSLQLNSVTPEDTAV YYCARGGGSGSYDWFDPWGQGTLVTVSS	1321	QSALTQPASVSGSPGQSITISCTGTSSDV GGYNYVSWYQQHPGKAPKLMIYEVSNRPS GVSNRFSGSKSGNTASLTISGLQAEDEAD YYCSSYTSSSTWVFGGGTKLTVL
1193	EVRLVESGGGLVKPGGSLRLSCAASGFIFSSY SMTWVRQAPGKGLEWVSSISGSSSFVKYGDSV KGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AREGVLCSGGSCYREIFDYWGQVTLVTVSS	1322	SSELTQDPAVSVALGQTVRITCQGDSLRS YYASWYQQKPGQAPVLVIYGKNNRPSGIP DRFSGSSSGNTASLTITGAQAEDEADYYC NSRDSSGNHLVFGGGTKLTVL
1194	EVQLVESGEGLVKPGGSLRLSCVASGFDFTNA WMSWVRQAPGRGLEWVGRIKSKTDGGSIDYAA PVKGRFTISRDDSKTTLYLQMTSLRTEDTAVY YCSTSPYYDFWSGYYGYIDYWGQGTLVTVSS	1323	QSVLTQPPSVSGAPGQRVTISCTGSSSNI GAGYAVHWYQQFPGIAPKLLIYGNINRPS GVPDRFSGSKSDTSASLAITGLQAEDEAD YYCQSFDSSLSGVMFGGGTKLTVL
1195	EVHLVESGGGLVKPGGSLRLSCVASRFTFSSA WMTWVRQVPGKGLEWIGRIKTKTEGGTTEYAA PVKGRFAISRDDSKKTLYLQMNSLKTEDTAVY YCSTSPYFDFWSGYYGYLDYWGQGTLVTVSS	1324	WAQSVLTQPPSVSGAPGQRVTISCSGSSS NIGAGYAVHWYQLLPGTVPKLLIYGNLNR PSGVPDRFSGSMSDTSVSLAITGLQAEDE ADYYCQSYDSSLSGVVFGGGTKVTVL
1196	QLQLQESGPGLVKPSETLSLTCTVSGGSISSS SYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CARHAAAGGWFDPWGQGTLVTVSS	1325	QAVLTQPASLSASPGASASLTCTLRSGIN VGTYRIYWYQQKPGSPPQYLLRYKSDSDK QQGSGVPSRFSGSKDASANAGILLISGLQ SEDEADYYCMIWHSSAVVFGGGTKLTVL
1197	QLQLQESGPGLVKPSETLSLTCTVSGGSISSS SYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CARRSSSGIGAFDIWGQGTMVTVSS	1326	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVVFGGGTKLTVL
1198	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGY YWSWIRQPPGKGLEWIGEINHSGSTNYNPSLK SRVTISVDTSKNQFSLKLSSVTAADTAVYYCA RGRGIAARPPYFDYWGQGTLVTVSS	1327	SYVLTQPPSVSVAPGKTARITCGGNNIGS KSVHWYQQKPGQAPVLVIYYDSDRPSGIP ERFSGSNSGNTATLTISRVEAGDEADYYC QVWDSSSDHVVFGGGTKLTVL
1199	QLQLQESGPGLVKPSETLSLTCTVSGGSISSS SYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVYY CASEYSSSSLDAFDIWGQGTMVTVSS	1328	SYELTQPPSVSVSPGQTARITCSGDALPK KYAYWYQQKSGQAPVLVIYEDSKRPSGIP ERFSGSSSGTMATLTISGAQVEDEADYYC YSTDSSGNHRVFGGGTKLTVL
1200	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSGY YWSWIRQPPGKGLEWIGEINHSGSTNYNPSLK	1329	SYELTQPPSVSVSPGQTASITCSGDKLGD KYACWYQQKPGQSPVLVIYQDSKRPSGIP

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	SRVTISVDTSKNQFSLKLSSVTAADTAVYYCA RGTTVVTPTEYYYMDVWGKGTTVTVSS		ERFSGSNSGNTATLTISGTQAMDEADYYC QAWDSSTVVFGGGTKLTVL
1201	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSY DINWVRQATGQGLEWMGWLNPKNGYTGYSHKF QGRVTMTRNTSISTAYMELSSLRSEDAAVYFC ARRGDFWSGYYSTSQNIVIHWFDSWGLGTLVT VSS	1330	QSVLTQPPSVSGAPGQRVTISCTGSSSNI GAGYDVHWYQQLPGTAPKLLIYGNSNRPS GVPDRFSGSKSGTSASLAITGLQAEDEAD YYCQSYDSSLSGSVFGGGTKLTVL

[00649] Table 8. VH-CDR3 and VL-CDR3 Sequences for EPOR/CD131 Binders

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype7	17	IGHV1-8	IGLV3-1	CARWGRGFDPW	1331	CQAWDSSTAVF	1467	1603	1739
clonotype9	10	IGHV1-69D	IGLV2-23	CARERLELRWFDPW	1332	CCSYAGSSTWVF	1468	1604	1740
clonotype14	8	IGHV4-39	IGLV2-23	CARQTDYWFDPW	1333	CCSYAGSSTLVF	1469	1605	1741
clonotype15	6	IGHV3-21	IGLV2-14	CAREGGIAVAGFDYW	1334	CSSYTSSSTLVF	1470	1606	1742
clonotype17	5	IGHV3-13	IGLV3-9	CARDSSSWYEDAFDIW	1335	CQVWDSSTVVF	1471	1607	1743
clonotype19	5	IGHV3-11	IGLV2-14	CAREETMVRGVIAYW	1336	CSSYTSSSTVVF	1472	1608	1744
clonotype22	4	IGHV3-21	IGLV3-10	CARDWGSFDLW	1337	CYSTDSSGNHWVF	1473	1609	1745
clonotype29	4	IGHV3-53	IGLV2-8	CARDGGEYSSSYYFDYW	1338	CSSYAGSNNVVF	1474	1610	1746
clonotype32	4	IGHV4-39	IGLV4-3	CARHDPSFDYW	1339	CGESHTIDGQVGVVF	1475	1611	1747
clonotype38	3	IGHV1-18	IGLV3-21	CARERSNWDFDYW	1340	CQVWDSSSDHRVF	1476	1612	1748
clonotype42	2	IGHV3-7	IGLV3-1	CARDGGVRGVITYFDYW	1341	CQAWDSSNVVF	1477	1613	1749
clonotype43	2	IGHV1-8	IGLV3-1	CARGRGSSWYWYFDLW	1342	CQAWDSSTAVF	1478	1614	1750
clonotype44	2	IGHV3-13	IGLV3-9	CARGSSSSAFDIW	1343	CQVWDSSTWVF	1479	1615	1751
clonotype45	2	IGHV3-21	IGLV3-27	CARDGGIAAAGTDYW	1344	CYSAADNNLVF	1480	1616	1752
clonotype56	2	IGHV3-21	IGLV3-10	CARADSLTGGFFDYW	1345	CYSTDSSGNHSWVF	1481	1617	1753
clonotype57	2	IGHV7-4-1	IGLV7-46	CAERGWNYDYW	1346	CLLSYSGAWVF	1482	1618	1754
clonotype65	2	IGHV3-53	IGLV2-14	CARDSTTVTLFDYW	1347	CSSYTSSSTYVF	1483	1619	1755
clonotype68	2	IGHV3-21	IGLV2-8	CARGIAVAGPHAFDIW	1348	CSSYAGSNNFVVF	1484	1620	1756
clonotype70	2	IGHV3-53	IGLV1-40	CARGYSGSYAYW	1349	CQSYDSSLSGYVF	1485	1621	1757

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype72	2	IGHV6-1	IGLV2-23	CARKWELRDAFDIW	1350	CCSYAGRSTLGIDWVF	1486	1622	1758
clonotype74	2	IGHV5-51	IGLV3-21	CAKRRMTGSHSWFDPW	1351	CQVWDNGSDHVVF	1487	1623	1759
clonotype215	1	IGHV3-74	IGLV2-14	CARIDYW	1352	CSSYTSSSTWVF	1488	1624	1760
clonotype216	1	IGHV3-7	IGLV3-10	CARDGGTP	1353	CYSTDSSGNHRVF	1489	1625	1761
clonotype219	1	IGHV4-59	IGLV3-27	CAIVGARFDYW	1354	CYSAADNNLVF	1490	1626	1762
clonotype221	1	IGHV3-15	IGLV3-25	CTTGGTHW	1355	CQSADSSGTWVF	1491	1627	1763
clonotype223	1	IGHV3-15	IGLV3-25	CTTGGYRW	1356	CQSADSSGTNWVF	1492	1628	1764
clonotype224	1	IGHV3-15	IGLV3-10	CTTDLYYW	1357	CYSTDSSGNHRVF	1493	1629	1765
clonotype225	1	IGHV1-18	IGLV2-14	CARGWYFDYW	1358	CSSYTSSSTLVF	1494	1630	1766
clonotype226	1	IGHV3-23	IGLV2-14	CAKRVFFDYW	1359	CSSYTISSTWVF	1495	1631	1767
clonotype228	1	IGHV3-13	IGLV3-10	CARDLGRVFDYW	1360	CYSTDSSGNHRVF	1496	1632	1768
clonotype229	1	IGHV3-7	IGLV2-14	CATDLNWNGYW	1361	CSSYTRSRTWVF	1497	1633	1769
clonotype230	1	IGHV3-13	IGLV5-45	CATGYNWNPDYW	1362	CMIWHSSASVF	1498	1634	1770
clonotype231	1	IGHV3-33	IGLV3-27	CARDRSSSSDYW	1363	CYSAADNNRVF	1499	1635	1771
clonotype232	1	IGHV3-74	IGLV3-27	CAGITGTYFDYW	1364	CYSAADNNLVF	1500	1636	1772
clonotype233	1	IGHV3-43	IGLV3-10	CAKDSGYSPDYW	1365	CYSTDSSGKGVF	1501	1637	1773
clonotype234	1	IGHV1-18	IGLV3-10	CARDRPYYFDYW	1366	CYSTDSSGNHRVF	1502	1638	1774
clonotype235	1	IGHV1-46	IGLV3-19	CARGGWGTMDVW	1367	CNSRDSSGNHYVF	1503	1639	1775
clonotype236	1	IGHV3-13	IGLV3-19	CARAWELDAFDIW	1368	CNSRDSSGNHVVF	1504	1640	1776
clonotype237	1	IGHV3-23	IGLV3-10	CAKDNWNYFDYW	1369	CYSTDSSGNHRVF	1505	1641	1777
clonotype238	1	IGHV3-33	IGLV3-10	CARVYNWIFDYW	1370	CYSTDSSGNHRVF	1506	1642	1778
clonotype239	1	IGHV3-21	IGLV2-23	CARITVVSFDYW	1371	CCSYAGSSTWVF	1507	1643	1779
clonotype240	1	IGHV3-23	IGLV2-8	CAKAAAGKGDYW	1372	CSSYSGSNNYVF	1508	1644	1780
clonotype241	1	IGHV1-46	IGLV2-14	CARGDWGTMDVW	1373	CTSYTRNNTYVF	1509	1645	1781
clonotype242	1	IGHV3-7	IGLV1-40	CARDGTGWFDPW	1374	CQSYDSSLSGWVF	1510	1646	1782

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype243	1	IGHV1-18	IGLV2-23	CARRGTVVFDYW	1375	CCSYAGSSTYVVF	1511	1647	1783
clonotype244	1	IGHV1-18	IGLV2-23	CARPLSGTLDNW	1376	CCSYAGRSTLGIDWVF	1512	1648	1784
clonotype246	1	IGHV3-48	IGLV3-19	CARESIAALFDYW	1377	CNSRDSSGNHLVF	1513	1649	1785
clonotype247	1	IGHV3-13	IGLV3-16	CARGDHSYGGLDYW	1378	CLSADSSGTYRVF	1514	1650	1786
clonotype249	1	IGHV1-8	IGLV2-14	CARGDWAWSFDLW	1379	CSSYTSSSSLVF	1515	1651	1787
clonotype250	1	IGHV1-46	IGLV2-14	CARGLRRDWFDPW	1380	CSSYTSSSTWVF	1516	1652	1788
clonotype251	1	IGHV3-15	IGLV2-11	CTTGTGRSDYW	1381	CCSYSGSYTYVF	1517	1653	1789
clonotype252	1	IGHV3-33	IGLV2-14	CVRGGVGDGFDMW	1382	CISYTNTNTRVF	1518	1654	1790
clonotype253	1	IGHV3-33	IGLV2-14	CASVGSYGYFQHW	1383	CSSYTSSSTWVF	1519	1655	1791
clonotype254	1	IGHV3-20	IGLV2-8	CARKGNWNSFDYW	1384	CSSYAGSNNWVF	1520	1656	1792
clonotype255	1	IGHV3-21	IGLV2-8	CARDSAYYTFDYW	1385	CSSYAGSNNFWVF	1521	1657	1793
clonotype256	1	IGHV3-23	IGLV2-14	CGSGWYEGAFDYW	1386	CSSYTSSSTYWVF	1522	1658	1794
clonotype259	1	IGHV3-13	IGLV3-1	CARDRDSSHDAFDIW	1387	CQAWDSSTVVF	1523	1659	1795
clonotype260	1	IGHV3-20	IGLV3-27	CVRDEIWNYYFDYW	1388	CYSAADNNRVF	1524	1660	1796
clonotype262	1	IGHV3-21	IGLV3-10	CARDSYDFHAFDIW	1389	CYSTDSSGNHRVF	1525	1661	1797
clonotype264	1	IGHV3-74	IGLV3-19	CARVGWGGHAFDIW	1390	CNSRDSSGNHVVF	1526	1662	1798
clonotype265	1	IGHV3-21	IGLV2-14	CARGYNWNYVGDYW	1391	CSSYTSSSTLVF	1527	1663	1799
clonotype266	1	IGHV3-23	IGLV1-40	CAKDANWGYAFDIW	1392	CQSYDSSLSGSVF	1528	1664	1800
clonotype270	1	IGHV1-18	IGLV3-1	CARRFIWNYGDFDYW	1393	CQAWDSSTVVF	1529	1665	1801
clonotype271	1	IGHV3-48	IGLV3-1	CARGRLGIEDYFDYW	1394	CQAWDSSTVVF	1530	1666	1802
clonotype272	1	IGHV3-48	IGLV3-19	CARECYSSSWAFDYW	1395	CNSRDSSGWVF	1531	1667	1803
clonotype273	1	IGHV4-4	IGLV3-1	CARDVGVDGRGFDYW	1396	CQAWDSTTAWVF	1532	1668	1804
clonotype274	1	IGHV3-7	IGLV3-19	CARDILWSGGYLDVW	1397	CYSRDSSGSLWIF	1533	1669	1805
clonotype275	1	IGHV3-7	IGLV3-19	CARKQLWLNWYFDFW	1398	CNSRDSSGNHLVF	1534	1670	1806
clonotype276	1	IGHV1-18	IGLV3-19	CARENNWNYGWFDPW	1399	CNSRDSSGNHYVF	1535	1671	1807

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype277	1	IGHV3-13	IGLV3-10	CAREGYGDYPLPMDVW	1400	CYSTDSSGNHRVF	1536	1672	1808
clonotype278	1	IGHV3-15	IGLV3-10	CTTDNWNSYFDYW	1401	CYSTDSSGNHRVF	1537	1673	1809
clonotype279	1	IGHV3-23	IGLV3-10	CAGNSGYDSPYFDYW	1402	CYSTDSSGNHRVF	1538	1674	1810
clonotype280	1	IGHV3-33	IGLV3-10	CAREYSSSSDWFDPW	1403	CYSTDSSGNHRVF	1539	1675	1811
clonotype281	1	IGHV3-21	IGLV2-11	CARDGGITGRYFDLW	1404	CCSYAGSYTWVF	1540	1676	1812
clonotype282	1	IGHV3-21	IGLV2-23	CAREGNWGPYYFDYW	1405	CCSYAGSSTVVF	1541	1677	1813
clonotype283	1	IGHV1-2	IGLV2-8	CARGVWSGYYTFDPW	1406	CSSYAGSNNWVF	1542	1678	1814
clonotype284	1	IGHV3-15	IGLV2-14	CTPHSSSPVFDYW	1407	CSSYTSSSHVVF	1543	1679	1815
clonotype286	1	IGHV1-2	IGLV3-1	CARDDTGTTGGYFQHW	1408	CQAWDSSTVVF	1544	1680	1816
clonotype287	1	IGHV1-8	IGLV3-1	CARAVAVAGTGWFDPW	1409	CQAWDSSTVVF	1545	1681	1817
clonotype288	1	IGHV3-15	IGLV3-27	CTTNYGDYVGFDYW	1410	CYSAADNNLVF	1546	1682	1818
clonotype289	1	IGHV3-7	IGLV3-10	CAREIDWNYGFHFDYW	1411	CFSTDSSGNKVF	1547	1683	1819
clonotype290	1	IGHV1-8	IGLV3-10	CARGYYDFWSGPFDYW	1412	CYSTDSSGNRVF	1548	1684	1820
clonotype291	1	IGHV3-33	IGLV3-10	CARDSKWELLNWFDPW	1413	CYSTDSSGNRVF	1549	1685	1821
clonotype292	1	IGHV4-59	IGLV3-19	CARGRHFDWLLSYFDYW	1414	CNSRDSSGNHYVF	1550	1686	1822
clonotype293	1	IGHV3-21	IGLV3-19	CARDRAIVGATWFDPWGQGTLVIV	1415	CNSRDSSYNHWVF	1551	1687	1823
clonotype294	1	IGHV3-21	IGLV3-19	CARDRYNWNYRYFDLW	1416	CNSRDSSGNHLVF	1552	1688	1824
clonotype295	1	IGHV3-21	IGLV3-10	CARDSHDYGDSYFDYW	1417	CYSTDSSGNHRVF	1553	1689	1825
clonotype296	1	IGHV1-18	IGLV3-19	CARDGAARPPRYMDVW	1418	CNSRDSSGNHLVF	1554	1690	1826
clonotype297	1	IGHV1-2	IGLV3-19	CARSDSGSHYVFFDDW	1419	CNSRDSSGNHWVF	1555	1691	1827
clonotype298	1	IGHV1-2	IGLV3-19	CARDLDYYGSGNYDYW	1420	CNSRDSSDNHRVF	1556	1692	1828
clonotype300	1	IGHV3-74	IGLV3-19	CARNRDYHGSGSFDYW	1421	CNSRDSSGNHWVF	1557	1693	1829
clonotype301	1	IGHV6-1	IGLV3-19	CARDWNFAFDIW	1422	CNSRDSSGNHLVF	1558	1694	1830
clonotype302	1	IGHV1-18	IGLV1-36	CARTIFGVVNNWFDPW	1423	CAAWDARLNGWVF	1559	1695	1831
clonotype303	1	IGHV1-2	IGLV2-11	CARDGEQLALNWFDPW	1424	CCSYAGSYTWVF	1560	1696	1832

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype304	1	IGHV3-21	IGLV1-40	CARETPVTLFDAFDIW	1425	CQSYDSSLSGSVF	1561	1697	1833
clonotype305	1	IGHV3-43	IGLV1-40	CAKDIFTGRAGYFDYW	1426	CQSYDSSLSGWVF	1562	1698	1834
clonotype306	1	IGHV3-33	IGLV1-40	CARAITGTTGNWFDPW	1427	CQSYDSSLSGWVF	1563	1699	1835
clonotype307	1	IGHV2-5	IGLV5-45	CTHTEYGSSWSVDYW	1428	CMIWHSSAVVF	1564	1700	1836
clonotype308	1	IGHV3-20	IGLV5-45	CARHFDWLLSNAFDIW	1429	CMIWHSSASVVF	1565	1701	1837
clonotype309	1	IGHV1-8	IGLV3-1	CVRRITVVRGVISLDYW	1430	CQAWDSSTAVF	1566	1702	1838
clonotype310	1	IGHV3-21	IGLV3-10	CARETYYYDSSGYFDYW	1431	CYSTDSSGNHRVF	1567	1703	1839
clonotype316	1	IGHV3-7	IGLV3-19	CARDDTIFGVVTDAFDIW	1432	CNSRDSSGNLF	1568	1704	1840
clonotype318	1	IGHV6-1	IGLV3-1	CARGVGARGWFDPW	1433	CQAWDSSTAVF	1569	1705	1841
clonotype319	1	IGHV3-21	IGLV3-19	CARDPPLSGSYAGEFDYW	1434	CNSRDSSGNHWVF	1570	1706	1842
clonotype320	1	IGHV2-70	IGLV3-10	CARRRGYSYGWGDFDYW	1435	CYSTDSSGNHRVF	1571	1707	1843
clonotype322	1	IGHV3-48	IGLV3-10	CARGGLLNWNYEGWFDPW	1436	CYSTDSSGNHRVF	1572	1708	1844
clonotype323	1	IGHV3-11	IGLV3-10	CARDGGIAARPDWYFDLW	1437	CYSTDSSGNHRVF	1573	1709	1845
clonotype326	1	IGHV3-48	IGLV1-40	CARTYYYGSGSYYTLDYW	1438	CQSYDSSLSGVVF	1574	1710	1846
clonotype327	1	IGHV1-8	IGLV5-45	CARGGITIFGVVTPFDYW	1439	CMIWHSSAWVF	1575	1711	1847
clonotype328	1	IGHV4-30-4	IGLV3-1	CARDALHYYGSGSAFDYW	1440	CQAWDSSTVVF	1576	1712	1848
clonotype333	1	IGHV3-7	IGLV3-19	CAREGVLWFGEFYYYMDVW	1441	CNSRDSSGNHLVF	1577	1713	1849
clonotype339	1	IGHV3-48	IGLV3-10	CARDGDYYDSSGYYHFDYW	1442	CYSTDSSGNHRVF	1578	1714	1850
clonotype340	1	IGHV3-23	IGLV3-10	CAKDRGGENWNYGGWFDPW	1443	CYSTDSSGNHRVF	1579	1715	1851
clonotype341	1	IGHV3-33	IGLV3-21	CAGAYYYDSSGYLNYMDVW	1444	CQVWDSSSDHPVF	1580	1716	1852
clonotype342	1	IGHV3-15	IGLV1-44	CTTDHIEYSSLYYFDYW	1445	CSSYAGSNNFVF	1581	1717	1853
clonotype343	1	IGHV1-18	IGLV2-8	CARQLAYCGGDCYLYFDYW	1446	CSSYAGSNNLVF	1582	1718	1854
clonotype345	1	IGHV6-1	IGLV2-8	CAREAYWNYGGFDYW	1447	CSSYAGSNNFGVF	1583	1719	1855
clonotype349	1	IGHV3-21	IGLV3-1	CARDGRITMVRGVRNWFDPW	1448	CQAWDSSTVVF	1584	1720	1856
clonotype350	1	IGHV3-48	IGLV3-1	CARMSSQLELHYYCYYMDVW	1449	CQAWDSSTVVF	1585	1721	1857
clonotype351	1	IGHV3-15	IGLV3-1	CTTDLGYSGYDWGAFDYW	1450	CQAWDSSTVVF	1586	1722	1858

clonotype_id	frequency	VH Gene	VL Gene	VH-CDR3 AA	SEQ ID NO	VL-CDR3 AA	SEQ ID NO	Full HC AA Sequence SEQ ID NO	Full LC AA Sequence SEQ ID NO
clonotype352	1	IGHV6-1	IGLV3-1	CARDRVNWNDVGFDYW	1451	CQAWDSSTVVF	1587	1723	1859
clonotype356	1	IGHV3-7	IGLV3-10	CARTPGYSSSWYEGPYFDYW	1452	CYSTDSSGNHVVF	1588	1724	1860
clonotype358	1	IGHV4-39	IGLV3-10	CAREDLIGNDYW	1453	CYSTDSSGNHRVF	1589	1725	1861
clonotype359	1	IGHV4-39	IGLV1-44	CAREDLIGNDYW	1454	CAAWDDSLKVF	1590	1726	1862
clonotype360	1	IGHV4-34	IGLV7-43	CAREGLTGHVFDIW	1455	CLLYYGGAQVF	1591	1727	1863
clonotype361	1	IGHV4-34	IGLV2-23	CAREGLTGHTFDIW	1456	CCSYAGSSTVVF	1592	1728	1864
clonotype363	1	IGHV1-18	IGLV3-27	CARGVWGSYRSHSYYTFMDVW	1457	CFSAADNTSVF	1593	1729	1865
clonotype364	1	IGHV3-21	IGLV3-19	CARDYRPYYDILTGYSHFDYW	1458	CNSRDSSGNHVVF	1594	1730	1866
clonotype365	1	IGHV1-46	IGLV3-10	CARRVLWFGELRDYFYYMDVW	1459	CYSTDSSGNHVVF	1595	1731	1867
clonotype366	1	IGHV4-30-4	IGLV2-8	CVRQGYDSWTGYSFFYFDYW	1460	CSSYAGSNNLVF	1596	1732	1868
clonotype367	1	IGHV4-34	IGLV1-44	CARGGGYSFGGFDYW	1461	CTSWDDSLNTWVF	1597	1733	1869
clonotype368	1	IGHV4-39	IGLV3-9	CARQNWGSDAFDIW	1462	CQVWDSSTAVF	1598	1734	1870
clonotype369	1	IGHV4-34	IGLV3-19	CARGELGIGYWYFDLW	1463	CNSRDSSGNHVVF	1599	1735	1871
clonotype370	1	IGHV4-34	IGLV3-10	CAREGGTTHEPLFDYW	1464	CYSTDSSGNHRVF	1600	1736	1872
clonotype379	1	IGHV1-18	IGLV2-23	CARAPGGSCGSTNCYKWNYDPYYFDYW	1465	CCSYAGSSTLVF	1601	1737	1873
clonotype380	1	IGHV1-18	IGLV2-23	CARAPGGDCSSTSCYKWNYDPYYFDYW	1466	CCSYAGSSTLVF	1602	1738	1874

[00650] **Table 9.** Full Heavy Chain (HC) and Light Chain (LC) Sequences for EPOR/CD131 Binders

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
1603	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYDINWVRQATGQGLEWMGWMNPNSGNTGYAQKFQGRVTMTRNTSISTAYMELSSLRSEDTAVYYCARWGRGFDPWGQGTLVTVSS	1739	SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQKPGQSPVLVIYQDSKRPSGIPERFSGSNSGNTATLTISGTQAMDEADYYCQAWDSSTAVFGGGTKLTVL
1604	QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYCARERLELRWFDPWGQGTLVTVSS	1740	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSSTWVFGGGTKLTVL
1605	QLQLQESGPGLVKPSETLSLTCTVSGGSISSSSYYWGWIRQPPGKGLEWIGSIYYSGSTYYNPSLKSRVTISVDTSKNQFSLKLSSVTAADTAVYYCARQTDYWFDPWGQGTLVTVSS	1741	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVSKRPSGVSNRFSGSKSGNTASLTISGLQAEDEADYYCCSYAGSSTLVFGGGTKLTVL
1606	EVQLVESGGGLVRPGGSLRLSCAASGFTFSSYSIHWVRQAPGKGLEWVSSISSSSTYIYYAD	1742	QSALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	SLKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCAREGGIAVAGFDYWGQGTLVTVSS		RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTLVFGGGTKLTVL
1607	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCARDSSSWYEDAFDIWGQGTMVTVSS	1743	SYELTQPLSVSVALGQTARITCGGNNIGSKN VHWYQQKPGQAPVLVIYRDSNRPSGIPERFS GSNSGNTATLTISRAQAGDEADYYCQVWDSS TVVFGGGTKLTVL
1608	EVQLVESGGGLVKPGGSLRLSCAASGFTFSD YYMSWIRQAPGKGLEWVSYISSSGSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCAREETMVRGVIAYWGQGTLVTVSS	1744	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTVVFGGGTKLTVL
1609	EVQLVESGGGLVKPGGSLRLSCAVSGFTFST DSMNWVRQAPGKGLEWVSSISGSSSYIYYTD SVKGRFTISRDNAKNSLFLQMNSLRAEDTAV YYCARDWGSFDLWGRGTLVTVSS	1745	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHWVFGGGTKLTVL
1610	EVQLVESGGGLIQPGGSLRLSCAASGFTVSS NYMSWVRQAPGKGLEWVSVIYSGGSTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARDGGEYSSSYYFDYWGQGTLVTVSS	1746	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNVVFGGGTKLTVL
1611	QLQLQESGPGLVKPSETLSLTCTVSGGSISS SSYYWGWIRQPPGKGLEWIGSIYYSGSTYYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTA VYYCARHDPSFDYWGQGTLVTVSS	1747	LPVLTQPPSASALLGASIKLTCTLSSEHSTY TIEWYQQRPGRSPQYIMKVKSDGSHSKGDGI PDRFMGSSSGADRYLTFSNLQSDDEAEYHCG ESHTIDGQVGVVFGGGTKLTVL
1612	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARERSNWDFDYWGQGTLVTVSS	1748	SYVLTQPPSVSVAPGKTARITCGGNNIGSKS VHWYQQKPGQAPVLVIYYDSDRPSGIPERFS GSNSGNTATLTISRVEAGDEADYYCQVWDSS SDHRVFGGGTKLTVL
1613	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDGGVRGVITYFDYWGQGTLVTVSS	1749	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS NVVFGGGTKLTVL
1614	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARGRGSSWYWYFDLWGRGTLVTVSS	1750	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TAVFGGGTKLTVL
1615	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCARGSSSSAFDIWGQGTMVTVSS	1751	SYELTQPLSVSVALGQTARITCGGNNIGSKN VHWYQQKPGQAPVLVIYRDSNRPSGIPERFS GSNSGNTATLTISRAQAGDEADYYCQVWDSS TWVFGGGTKLTVL
1616	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDGGIAAAGTDYWGQGTLVTVSS	1752	SYELTQPSSVSVSPGQTARITCSGDVLAKKY ARWFQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGAQVEDEADYYCYSAADN NLVFGGGTKLTVL
1617	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARADSLTGGFFDYWGQGTLVTVSS	1753	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHSWVFGGGTKLTVL
1618	QVQLVQSESELKKPGASVKVSCKASGYTFIS YAMSWVRQAPGQGLEWMGWINTNTGNPTYAQ GFTGRFVFSLDTSVSTAYLQISSLKAEDTAV YYCAERGWNYDYWGQGTLVTVSS	1754	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTS GHYPYWFQQKPGQAPRTLIYDTSNKHSWTPA RFSGSLLGGKAALTLSGAQPEDEAEYYCLLS YSGAWVFGGGTKLTVL
1619	EVQLVESGGGLIQPGGSLRLSCAASGFTVSS NYMSWVRQAPGKGLEWVSVIYSGGSTYYADS VKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARDSTTVTLFDYWGQGTLVTVSS	1755	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTYVFGTGTKVTVL
1620	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGIAVAGPHAFDIWGQGTMVTVSS	1756	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNFVVFGGGTKLTVL
1621	EVQLVESGGGLIQPGGSLRLSCAASGFTVSS NYMSWVRQAPGKGLEWVSVIYSGGSTYYADS	1757	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIYGNSNRPSGVPD

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	VKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCARGYSGSYAYWGQGTLVTVSS		RFSGSKSGTSASLAITGLQAEDEADYYCQSY DSSLSGYVFGTGTKVTVL
1622	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYND YAGSVKSRIIINPDTSKNQLSLQLKSVTPED TAVYYCARKWELRDAFDIWGQGTMVTVSS	1758	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGRSTLGIDWVFGGGTKLTVL
1623	EVQLVQSGAVVKKPGESLKISCKGSGYSFSS YWIGWVRQMPGKGLEWMGIIYPGDSDTRYSP SFQGQVTISADKSISTAYLQWSSLQASDTAM YFCAKRRMTGSHSWFDPWGQGTLVTVSS	1759	SYVLTQPPSVSVAPGKTARITCEGDNIGSES VHWYQQKPGQAPVLVIYFDSDRPSGIPERFS GSNSGITATLTISRVEAGDEADFYCQVWDNG SDHVVFGGGTKLTVL
1624	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMHWVRQAPGKGLVWVSRINSDGSSTSYAD SVKGRFTISRDNAKNTLYLQMNSLRAEDTAV YYCARIDYWGQGTLVTVSS	1760	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTWVFGGGTKLTVL
1625	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDGGTPGQGTLVTVSS	1761	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1626	QVQLQESGPGLVKPSETLSLTCTVSGGSISS YYWSWIRQPPGKGLEWIGYIYYSGSTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCAIVGARFDYWGQGTLVTVSS	1762	SYELTQPSSVSVSPGQTARITCSGDVLAKKY ARWFQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGAQVEDEADYYCYSAADN NLVFGGGTKLTVL
1627	EVQLVESGGGLVKPGGSLRLSCAASGFTFIN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTGGTHWGQGTLVTVSS	1763	SYELTQPPSVSVSPGQTARITCSADALPNQY AYWYQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGVQAEDEADYYCQSADSS GTWVFGGGTKLTVL
1628	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTGGYRWGQGTLVTVSS	1764	SYELTQPPSVSVSPGQTARITCSADALSKQY AYWYQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGVQAEDEADYYCQSADSS GTNWVFGGGTKLTVL
1629	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTDLYYWGQGTLVTVSS	1765	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1630	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARGWYFDYWGQGTLVTVSS	1766	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTLVFGGGTKLTVL
1631	EVQLVESGGGLVQPGGSLRLSCAASGFTFST YAMNWVRQAPGKGLEWVSAISGGGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKRVFFDYWGQGTLVTVSS	1767	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYSCSSY TISSTWVFGGGTKLTVL
1632	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCARDLGRVFDYWGQGTLVTVSS	1768	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1633	VVQLVESGGGLVQPGGSLRLSCAASGFTFSR YWMSWVRQAPGKGLEWVANINQDGSEEYYVD SVKGRFTISRDNAKSSLSLQMNSLRAEDTAL YYCATDLNWNGYWGQGTLVTVSS	1769	QSALTQPASVSGSPGQSITISCTGTSSDVGG YDYVSWYQQHPGKAPKFMISGVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TRSRTWVFGGGTKLTVL
1634	EVQLVESGGGLVQPGGSLRLSCAASGFTFSR CDMYWVRQATGKGLEWVSAIGAAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCATGYNWNPDYWGQGTLVTVSS	1770	QAVLTQPASLSASPGASASLTCTLRSGINVG TYRIYWYQQKPGSPPQYLLRYKSDSDKQQGS GVPSRFSGSKDASANAGILLLISGLQSEDEAD YYCMIWHSSASVFGGGTKLTVL
1635	QVQLVESGGGVVQPGRSLRLSCEASGFTFIN YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARDRSSSSDYWGQGTLVIVSS	1771	SYELTQPSSVSVSPGQTARITCSGDVLAKKY ARWFQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGAQVEDEADYYCYSAADN NRVFGGGTKLTVL
1636	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMHWVRQAPGKGLVWVSRINSDGSSTSYAD	1772	SYELTQPSSVSVSPGQTARITCSGDVLAKKY ARWFQQKPGQAPVLVIYKDSERPSGIPERFS

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	SVKGRFTISRDNAKNTLYLQMNSLRAEDTAV YYCAGITGTYFDYWGQGTLVTVSS		GSSSGTTVTLTISGAQVEDEADYYCYSAADN NLVFGGGTKLTVL
1637	EVQLVESGGGLVQPGRSLRLSCAASGFTFDD YAMHWVRQAPGKGLEWVSGISWNSGSIGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDSGYSPDYWGQGTLVTVSS	1773	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GKGVFGGGTKLTVL
1638	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARDRPYYFDYWGQGTLVTVSS	1774	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1639	QVQVVQSGAEVRKSGASVKVSCKASGYTFTS YYIHWVRQVPGQGLEWMGLINPSGGSTIYAQ KFQGRVTMTRDTSTSSVYMELSSLRSEDTAA YYCARGGWGTMDVWGKGTTVTVSS	1775	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHYVFGTGTKVTVL
1640	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCARAWELDAFDIWGQGTMVTVSS	1776	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL
1641	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKDNWNYFDYWGQGTLVTVSS	1777	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1642	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARVYNWIFDYWGQGTLVTVSS	1778	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1643	EVQVMESGGGLVKPGGSLRLSCAASGFSFSS HSLNWVRQAPGKGLEWVSSISGISNYIAYAD SVRGRFTISRDNAKNSLFLQMNSLRAEDTGV YYCARITVVSFDYWGQGTLVTVTS	1779	QSALTQPASVSGSPGQSITISCTGTNNDVGY YNYVSWYQQHPDKAPKLMIYDVIKRPSGVSD RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTWVFGGGTKLSVL
1644	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGNTYNAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKAAAGKGDYWGQGTLVTVSS	1780	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY SGSNNYVFGTGTKVTVL
1645	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YYIHWVRQAPGQGLEWMGIINPSGGTTNYAQ KFQGRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARGDWGTMDVWGKGTTVTVSS	1781	QSALTQPASVSGSPGQSITISCTGTSSDVGN YNYVSWYQQHPGKVPKLMIYEVIYRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCTSY TRNNTYVFGSGTKVTVL
1646	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDGTGWFDPWGQGTLVTVSS	1782	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIYGNSNRPSGVPD RFSGSKSGTSASLAITGLQAEDEADYYCQSY DSSLSGWVFGGGTKLTVL
1647	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARRGTVVFDYWGQGTLVTVSS	1783	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTYVVFGGGTKLTVL
1648	QVQLVQSGAEVKKPGASVKVSCKASGYTFTN YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ NLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARPLSGTLDNWGQGTLVTVSS	1784	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGRSTLGIDWVFGGGTKLTVR
1649	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSSTIYYAD SVKGRFTISRDNAKNSLYLQMNSPRDEDTAV YYCARESIAALFDYWGQGTLVTVSS	1785	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
1650	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCARGDHSYGGLDYWGQGTLVTVSS	1786	SYELTQPPSVSVSLGQMARITCSGEALPKKY AYWYQQKPGQFPVLVIYKDSERPSGIPERFS GSSSGTIVTLTISGVQAEDEADYYCLSADSS GTYRVFGGGTKLTVL
1651	QVQLVQSGAEVEKPGASVKVSCKASGYTFTS YDIYWVRQATGQGLEWMGWMIPNSGNTGYAQ	1787	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSHRPSGVSN

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	RFEDRVTMTRSTSMNTAYMELNSLRSEDTAV YYCARGDWAWSFDLWGRGTLVTVSS		RFSGSKSGNTASLTISGLQAEDESDYYCSSY TSSSSLVFGGGTKLTVL
1652	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YYMHWVRQAPGQGLEWMGIINPSGGSTSYAQ KFQGRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARGLRRDWFDPWGQGTLVTVSS	1788	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTWVFGGGTKLTVL
1653	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTGTGRSDYWGQGTLVTVSS	1789	QSALTQPRSVSGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVTTRPSGVPD RFSGSKSGNTASLTISGLQAEDEADYYCCSY SGSYTYVFGTGTKVTVL
1654	QVQLVESGGGVVQPGRSLRLSCAASGFTFSN YGMHWVRQAPGKGLDWVAVIWYDGNNEYYAD SVKDRFTISRDNSQNTLYLQMNSLRAEDRAV YYCVRGGVGDGFDMWGQGTMVTVSS	1790	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKVPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCISY TNTNTRVFGGGTKLTVL
1655	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCASVGSYGYFQHWGQGTLVTVSS	1791	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTWVFGGGTKLTVL
1656	EVQLVESGGGVVRPGGSLRLSCAASGFTFDD YGMSWVRQAPGKGLEWVSGINWNGGSTGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCARKGNWNSFDYWGQGTLVTVSS	1792	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNWVFGGGTKLTVL
1657	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDSAYYTFDYWGQGTLVTVSS	1793	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNFWVFGGGTKLTVL
1658	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCGSGWYEGAFDYWGQGTLVTVSS	1794	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTYWVFGGGTKLTVL
1659	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCARDRDSSHDAFDIWGQGTMVTVSS	1795	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
1660	EVQLVESGGGVVRPGGSLRLSCAASGFPFDD FGLNWVRQAPGKGLEWVSGINWNGGTTTYAD SVKGRFTISRDNAKKSLYLQMSSLRVEDTAL FYCVRDEIWNYYFDYWGQGTLVTVSS	1796	SYELTQPSSVSVSPGQTARITCSGDVLAKKY ARWFQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGAQVEDEADYYCYSAADN NRVFGGGTKLTVL
1661	EVQMVESGGGRVKPGGSLRLSCTASGFSISI NNMNWVRQAPGKGLEWVSSISSSSTYIYYAD SVKGRFTISRDNAENSLYLQMNSLRAEDTGV YYCARDSYDFHAFDIWGQGTMVTVSS	1797	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1662	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMHWVRQAPGKGLVWVSRINSDGSSTSYAD SVKGRFTISRDNAKNTLYLQMNSLRAEDTAV YYCARVGWGGHAFDIWGQGTMVTVSS	1798	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL
1663	EVQLVESGGGLVKPGGSLRLSCAASGFTFST YSMNWVRQAPGKGLEWVSSISSSSTYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARGYNWNYVGDYWGQGTLVTVSS	1799	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSTLVFGGGTKLTVL
1664	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKDANWGYAFDIWGQGTMVTVSS	1800	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIYGNSNRPSGVPD RFSGSKSGTSASLAITGLQAEDEADYYCQSY DSSLSGSVFGGGTKLTVL
1665	QVQLVQSVSEVNKPGASVKVSCKASGYTFTT YGISWVRQAPGQGLEWMGWISGYSGYTSYAQ KFQGRLTMTTDTSANTAYMELRSLRSDDTAV YYCARRFIWNYGDFDYWGQGTLVTVSS	1801	SYELTQPPSVSVSPGQTASITCSRDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
1666	EVQLVESGGDLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISRSSGTIYYAD	1802	SYELTQPPSVSVSPGQTASITCSGDKLGDRY ACWYQQKPGQSPVLVIYQGSKRPSGIPERFS

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCARGRLGIEDYFDYWGQGTLVTVSS		GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
1667	EVQLVESGGGLVQPGGSLRLSCAASGFTFNR YNMNWVRQAPGKGLEWVSYISSSSDTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAM YYCARECYSSSWAFDYWGQGTLVTVSS	1803	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGILDRFS GSSSGNTASLTITGAQAEDEGDYYCNSRDSS GWVFGGGTKLTVL
1668	QVQLQESGPGLVKPSGTLSLTCAISGGSISS SNWWSWVRQPPGKGLEWIGEIYHSGSTNFNP SLKSRVTISVDKSKNQFSLHLSSVTAADTAV YYCARDVGVDGRGFDYWGQGIVVIVSS	1804	SYELTQPPSVSVSPGQTANITCSGDKLENKY TCWYQQKPGQSPLVVIYQDNKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDST TAWVFGGGTKLTVL
1669	EVQLVESGGGLVQPGGSLRLSCGVSGFTFSI YWMSWVRQAPGKGLEWVANINLDGSEKYHVD SVKGRFTISRDNAKNSLFLQMTSLRAEDTAV YYCARDILWSGGYLDVWGKGTTVTVSS	1805	SSELTQDPAVSVALGQTVRITCQGDNIRNYY ASWYQQKPGQAPLLVISGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEAYYYCYSRDSS GSLWIFGGGTKLTVL
1670	EVQLVESGGGLVQPGGSLRLSCAASGFTFSG YWMTWVRQAPGKGLEWVANIKHDGSEKYYVD SVKGRFTISRDNAQNSLYLQMNSLRAEDTAV YYCARKQLWLNWYFDFWGRGILVTVSS	1806	SSELTQDPAVSVALGQTVRITCQGDSLRRYY ASWYQQKPGQAPVLVIYGKDNRPSGIPDRFS GSSSGNTASLTITGTQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
1671	QVQLVQSGAEVKKPGASVKVSCKASGYTFTT YGISWVRQAPGQGLEWMGWISAFNGNTNYAQ NLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARENNWNYGWFDPWGQGTLVTVSS	1807	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHYVFGTGTKVTVL
1672	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YDMHWVRQATGKGLEWVSAIGTAGDTYYPGS VKGRFTISRENAKNSLYLQMNSLRAGDTAVY YCAREGYGDYPLPMDVWGKGTTVTVSS	1808	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1673	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTDNWNSYFDYWGQGTLVTVSS	1809	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1674	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGGGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAGNSGYDSPYFDYWGQGTLVTVSS	1810	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1675	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAREYSSSSDWFDPWGQGTLVTVSS	1811	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDIKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1676	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDGGITGRYFDLWGRGTLVTVSS	1812	QSALTQPRSVSGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVPD RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSYTWVFGGGTKLTVL
1677	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCAREGNWGPYYFDYWGQGTLVTVSS	1813	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTVVFGGGTKLTVL
1678	QVQLVQSGAEVKKPGASVKVSCKASGYTFTG YYMHWVRQAPGQGLEWMGWINPNSGGTNYAQ KFQGRVTMTRDTSISTAYMELSRLRSDDTAV YYCARGVWSGYYTFDPWGQGTLVTVSS	1814	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNWVFGGGTKLTVL
1679	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTPHSSSPVFDYWGQGTLVTVSS	1815	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSNRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCSSY TSSSHVVFGGGTKLTVL
1680	QVQLVQSGAEVKKPGASVKVSCKASGYTFTG YYMHWVRQAPGQGLEWMGWINPNSGGTNYAQ KFQGRVTMTRDTSISTAYMELSRLRSDDTAV YYCARDDTGTTGGYFQHWGQGTLVTVSS	1816	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
1681	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ	1817	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARAVAVAGTGWFDPWGQGTLVTVSS		GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
1682	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTNYGDYVGFDYWGQGTLVTVSS	1818	SYELTQPSSVSVSPGQTARITCSGDVLAKKY ARWFQQKPGQAPVLVIYKDSERPSGIPERFS GSSSGTTVTLTISGAQVEDEADYYCYSAADN NLVFGGGTKLTVL
1683	EVHLVESGGGLVQPGGSLRLSCAASGFTFSG YWMSWVRQAPGKGLEWVANIKQDGSDKYYVD SVKGRFTISRDNAINSLFLQLTSLRAEDTAV YYCAREIDWNYGFHFDYWGQGTLITVSS	1819	SYELTQPPSVSVSPGQTARITCSGDALPQKY AFWYQQKSGQAPVLVIYEDSERPSGIPERFS GSTSGTMATLTISGAQVEDEADYYCFSTDSS GNKVFGGGTKLTVL
1684	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARGYYDFWSGPFDYWGQGTLVTVSS	1820	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNRVFGGGTKLTVL
1685	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARDSKWELLNWFDPWGQGTLVTVSS	1821	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNRVFGGGTKLTVL
1686	QVQLQESGPGLVKPSETLSLTCTVSGGSISD YYWNWIRQPPGKGLEWIGYISSRGRTNYNPS LKSRVTLSVDSSKNQFSLKLTSVTAADTAVF YCARGRHFDWLLSYFDYWGQGTLVTVSS	1822	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHYVFGTGTKVTVL
1687	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS DNMNWVRQAPGKGLEWVSSIGSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDRAIVGATWFDPWGQGTLVIVSS	1823	SSELTQDPAVSVALGQTVRITCQGDSLRNYY ASWYQQKPGQAPILVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS YNHWVFGGGTKLTVL
1688	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDRYNWNYRYFDLWGRGTLVTVSS	1824	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
1689	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDSHDYGDSYFDYWGQGTLVTVSS	1825	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1690	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARDGAARPPRYMDVWGKGTTVTVSS	1826	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
1691	QVQLVQSGAEVRKPVASVKVSCKASGYTFTD HSIHWVRQAPGQGLEWMGSINPNSGGTNYAQ KFQGRVTMTRDTYNCTAYMELSRLRSDDTAV YYCARSDSGSHYVFFDDWGQGTLVTVSS	1827	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
1692	QVQLVQSGSEVKKPGASVKVSCKASGYTFTG YYMYWVRQAPGQGLEWMGWINPNSGGTNYAQ KFQDRVTMTRDTSISTAYMELSRLRSDDTAI YYCARDLDYYGSGNYDYWGQGTLVTVSS	1828	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS DNHRVFGGGTKLTVL
1693	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMHWVRQAPGKGLVWVSRVNSDGSNTTYAD SVKGRFTISRDNAKNTLYLQMNSLRAEDTAV YYCARNRDYHGSGSFDYWGQGTLVTVSS	1829	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGQNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
1694	QVQLQQSGPGLVKPSQTLSLTCAISGDNVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYND YAVSVKSRITINPDTSKNQFSLHLNSVTPED TALYYCARDWNFAFDIWGQGTMVTVSS	1830	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
1695	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGITWVRQAPGQGLEWMGWISAYNGNTHYAQ KLQGRVTMTTDTSTSTAYMDLRSLRSDDTAV YYCARTIFGVVNNWFDPWGQGTLVTVSS	1831	QSVLSQPPSVSEAPRQRVTISCSGSSSNIGY NAVNWYQQLPGKAPKLLISHDDLLPSGVSDR FSGSKSGTSASLAISGLQSDDEADYYCAAWD ARLNGWVFGGGTKLTVL
1696	QVQLVQSGAEVKKPGASVKVSCKASGYTFTG YYMHWVRQAPGQGLEWMGWINPNSGGTNYAQ	1832	QSALTQPRSVSGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVPD

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	KFQGRVTMTRDTSISTAYMELSRLRSDDTAV YYCARDGEQLALNWFDPWGQGTLVTVSS		RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSYTWVFGGGTKLTVL
1697	EVQLVESGGGLVKPGGSLRLSCAASGFTFSR YSMNWVRQAPGKGLEWVSSIISSTSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARETPVTLFDAFDIWGQGTMVTVSS	1833	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA RYDVHWYQLLPGSAPKLLIYDNSDRPSGVPD RFSGSRSGTSASLAITGLQAEDEADYFCQSY DSSLSGSVFGGGTKLTVL
1698	EVHLVESGGGLVQPGRSLRLSCAASGFTFDE YAMHWVRQVPGKGLEWVSGISWNSGSIGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCAKDIFTGRAGYFDYWGQGTLVTVSS	1834	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIYGNSNRPSGVPD RFSGSKSGTSASLAITGLQAEDEADYYCQSY DSSLSGWVFGGGTKLTVL
1699	QVQLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAVIWYDGSNKYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCARAITGTTGNWFDPWGQGTLVTVSS	1835	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIHGNSNRPSGVPD RFSGSKSGTSASLAITGLQAEDETDYYCQSY DSSLSGWVFGGGTKLTVL
1700	QITLKESGPTLVKPTQTLTLTCTFSGFSIST SGVGVGWIRQPPGKALEWLAFIFWNDDKRYS PSLKSRLTITKDTSKNQVVLTMTNMDPVDTA TYYCTHTEYGSSWSVDYWGQGTLVTVSS	1836	QAVLTQPASLSASPGASASLTCTLRSGINVG TSRIYWYQQKPGSPPQYLLRYKSDSDKHQDS GVPSRFSGSKDASANAGILLISGLQSEDEAD YYCMIWHSSAVVFGGGTKLTVL
1701	EVQLVESGGGVVRPGGSLRLSCAASGFTFDD YGMSWVRQAPGKGLEWVSGINWNGGSTGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAL YYCARHFDWLLSNAFDIWGQGTMVTVSS	1837	QAVLTQPASLSASPGASASLTCTLRSGINVG TYRIYWYQQKPGSPPQYLLRYKSDSDKQQGS GVPSRFSGSKDASANAGILLISGLQSEDEAD YYCMIWHSSASVVFGGGTKLTVL
1702	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCVRRITVVRGVISLDYWGQGTLVTVSS	1838	SYELTQPPSVSVSPGQTAIITCSGAKLGDKY ACWYQKKPGQSPVMVIYQDRKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TAVFGGGTKLTVL
1703	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARETYYYDSSGYFDYWGQGTLVTVSS	1839	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1704	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDDTIFGVVTDAFDIWGQGTMVTVSS	1840	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNLFGGGTKLTVL
1705	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYND YAVSVKSRITINPDTSKNQFSLQLNSVTPED TAVYYCARGVGARGWFDPWGQGTLVTVSS	1841	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERIS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TAVFGGGTKLTVL
1706	EVQLVESGGGLVKPGGSLRLSCAASGFTFST YSMNWVRQAPGKGLEWVSSISSSSTYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRADDTAV YYCARDPPLSGSYAGEFDYWGQGTLVTVSS	1842	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHWVFGGGTKLTVL
1707	QVTLRESGPALVKPTQTLTLTCTFSGFSLST SGMCVSWIRQPPGKALEWLALIDWDDDKYYS TSLKTRLTISKDTSKNQVVLTMTNMDPVDTA TYYCARRRGYSYGWGDFDYWGQGTLVTVSS	1843	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1708	EVQLVESGGGLVQPGGSLRLSCAASEFIFRS YNMNWVRQAPGKGLEWVSYISISSSRTIYYAD SVKGRFTISRDNAKNSLFLQMNSLRDEDTAV YYCARGGLLNWNYEGWFDPWGQGTLVTVSS	1844	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1709	QVQLVESGGGLVKPGGSLRLSCAASGFTFSD YYMSWIRQAPGKGLEWVSYISSSGSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDGGIAARPDWYFDLWGRGTLVTVSS	1845	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1710	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCARTYYYGSGSYYTLDYWGQGTLVTVSS	1846	QSVLTQPPSVSGAPGQRVTISCTGSSSNIGA GYDVHWYQQLPGTAPKLLIYGNSNRPSGVPD RFSGSKSGTSASLAITGLQAEDEADYYCQSY DSSLSGVVFGGGTKLTVL
1711	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YDINWVRQATGQGLEWMGWMNPNSGNTGYAQ	1847	QAVLTQPASLSASPGASASLTCTLRSGINVG TYRIYWYQQKPGSPPQYLLRYKSDSDKQQGS

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
	KFQGRVTMTRNTSISTAYMELSSLRSEDTAV YYCARGGITIFGVVTPFDYWGQGTLVTVSS		GVPSRFSGSKDASANAGILLISGLQSEDEAD YYCMIWHSSAWVFGGGTKLTVL
1712	QVQLQESGPGLVKPSQTLSLTCTVSGGSISS GGYYWSWIRQHPGKGLEWIGYIYYSGSTYYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTA VYYCARDALHYYGSGSAFDYWGQGTLVTVSS	1848	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
1713	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCAREGVLWFGEFYYYMDVWGKGTTVTVSS	1849	SSELTQDPAVSVALGQTVRITCQGDSLRRYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHLVFGGGTKLTVL
1714	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSSSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLRDEDTAV YYCARDGDYYDSSGYYHFDYWGQGTLVTVSS	1850	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1715	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YAMSWVRQAPGKGLEWVSAISGSGGSTYYAD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAV YYCAKDRGGENWNYGGWFDPWGQGTLVTVSS	1851	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1716	QVHLVESGGGVVQPGRSLRLSCAASGFTFSS YGMHWVRQAPGKGLEWVAIIWYDGSNEYYAD SVKGRFTISRDNSKNTLYLQMNTLRAEDTAV YYCAGAYYYDSSGYLNYMDVWGKGTTVTVSS	1852	SYVLIQPPSVSVAPGKTARITCGGNNIGGKS VHWYQLKPGQAPVLVICYNRDRPSGIPERFS GSNSGNTATLTISRVEAGDEADYYCQVWDSS SDHPVFGGGTKLTVL
1717	EVQLVESGGGLVKPGGSLRLSCAASGFTFRN AWMSWVRQAPGKGLEWVGRIKTKTDGGATQY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTDHIEYSSLYYFDYWGQGTLVTVSS	1853	QSVLTQSPSASGTPGQRVTISCSGSNSNIGF NTVNWYQQLPGTAPKLLIDSNNQRPSGVPDR FSGSTSGTSASLAISGLQSEDEADYYCSSYA GSNNFVFGTGTKVTVL
1718	QVQLVQSGAEVKKPGASVKVSCKASGYTFTS YGISWVRQAPGQGLEWMGWISAYNGNTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARQLAYCGGDCYLYFDYWGQGTLVTVSS	1854	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNLVFGGGTKLTVL
1719	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYND YAVSVKSRITINPDTSKNQFSLQLNSVTPED TAVYYCAREAYWNYGGFDYWGQGTLVTVSS	1855	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNFGVFGGGTKLTVL
1720	EVQLVESGGGLVKPGGSLKLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDGRITMVRGVRNWFDPWGQGTLVTVS S	1856	SYELTQPPSVSVSPGQTANITCSGDKLGNKY ACWYQQKPGQSPVLVIFQDNKRPSGIPERFS GSNSGNTATLTIGGTQAMDEADYYCQAWDSS TVVFGGGTKVTVL
1721	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSYISSSTSTIYYAD SVKGRFTISRDNAKNSLYLQMNSLTDEDTAV YYCARMSSQLELHYYCYYMDVWGKGTTVTVS S	1857	SYDLTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDIKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
1722	EVQLVESGGGLVKPGGSLRLSCAASGFTFSN AWMSWVRQAPGKGLEWVGRIKSKTDGGTTDY AAPVKGRFTISRDDSKNTLYLQMNSLKTEDT AVYYCTTDLGYSGYDWGAFDYWGQGTLVTVS S	1858	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSMRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
1723	QVQLQQSGPGLVKPSQTLSLTCAISGDSVSS NSAAWNWIRQSPSRGLEWLGRTYYRSKWYND YAVSVKSRITINPDTSKNQFSLQLNSVTPED TAVYYCARDRVNWNDVGFDYWGQGTLVTVSS	1859	SYELTQPPSVSVSPGQTASITCSGDKLGDKY ACWYQQKPGQSPVLVIYQDSKRPSGIPERFS GSNSGNTATLTISGTQAMDEADYYCQAWDSS TVVFGGGTKLTVL
1724	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YWMSWVRQAPGKGLEWVANIKQDGSEKYYVD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARTPGYSSSWYEGPYFDYWGQGTLVTVS S	1860	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHVVFGGGTKLTVL
1725	QLQLQESGPGLVKPSETLSLTCTVSGGSITT RSYYWGWLRQPPGKGLEWIGTFYYSGNTYYN PSLQSRVSISVDASKNQFSLQLSSVTAADTA VFYCAREDLIGNDYWGQGTLVTVSS	1861	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL

SEQ ID NO	Full HC AA Sequence	SEQ ID NO	Full LC AA Sequence
1726	QLQLQESGPGLVKPSETLSLTCTVSGGSIST RSYYWGWLRQPPGKGLEWIGTFYYSGSTYYN PSLKSRVSISVDTSKNQFSLQLSSVTAADTA VYYCAREDLIGNDYWGQGTLVTVSS	1862	QSVLTQPPSASGTPGQRVTISCSGSSSNIGI NTVNWYQQVPGTAPKLLIYFNNQRPSGVPDR FSGSKSGTSASLAISGLQSEDEADYYCAAWD DSLKVFGGGTKLTVL
1727	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSG HYWNWIRQPPGKGLEWIGEINHSGFTNYNPS LKSRVTISVDTPKNQFPLNLSSVTAADTAVY YCAREGLTGHVFDIWGQGTMVTVSS	1863	QTVVTQEPSLTVSPGGTVTLTCASSTGAVTS GYYPNWFQQKPGQAPRALIYSTSNKHSWTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCLLY YGGAQVFGGGTKLTVL
1728	QVQLQQWGAGLLKPSETLSLTCAVYGGFLRG YYWSWIRQPPGKGLEWIGEINHSGSTNYNPS LKSRVTISVDTAENQFSLKLNSVTAADTAVY YCAREGLTGHTFDIWGQGTMVTVSS	1864	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTVVFGGGTKLTVL
1729	QVQLVQSGAEVKKPGASVKVSCKASGYIFSN YGICWVRQAPGQGLEWMGWINPYNVNRNYAQ SLQGRVTMTTDTSTNSAYMELRSLKSDDTAV YFCARGVWGSYRSHSYYTFMDVWGKGTTVTV SS	1865	SYELTQPSSVSVSPGQAARITCSGNLLAKKY PRWFLQKPGQAPIMLTHTDCERPSGIPERFS GSSSGTTVTLTISGAQVEDEADYYCFSAADN TSVFDGGTNLTVL
1730	EVQLVESGGGLVKPGGSLRLSCAASGFTFSS YSMNWVRQAPGKGLEWVSSISSSSSYIYYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTAV YYCARDYRPYYDILTGYSHFDYWGQGTLVTV SS	1866	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL
1731	QVQLVQSGAEVKKPGASVKVSCKASGFTFTS YYIHWVRQAPGQGLEWMGIITPSGGTTSYAQ KFQGRVTMTRDTSTSTVYMELSSLRSEDTAV YYCARRVLWFGELRDYFYYMDVWGKGTTVTI SS	1867	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWFQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLIISGAQVEDEADYYCYSTDSS GNHVVFGGGTKLTVL
1732	QMQLQESGPGLVRPSETLSLTCTVSGGSIST RSYYWGWIRQPPGKGLEWIGSVFYSGSTYYN PSLKSRVAISVDTSKNQFSLKVNSVTAADTA VFYCVRQGYDSWTGYSFFYFDYWGQGTLVTV SS	1868	QSALTQPPSASGSPGQSVTISCTGTSSDVGG YNYVSWYQQHPGKAPKLMIYEVSKRPSGVPD RFSGSKSGNTASLTVSGLQAEDEADYYCSSY AGSNNLVFGGGTKLTVL
1733	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSV YYWSWIRQPPGKGLEWIGEINHSGSTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARGGGYSFGGFDYWGQGTLVTVSS	1869	QSVLNQPPSASGTPGQRVTISCSGSSSNIGS KTVNWYQQVPGTAPKLLIYSSNQRPSGVPDR FSGSKSGTSASLAISELQSEDEADYYCTSWD DSLNTWVFGGGTKLTVL
1734	QLQLQESGPGLVKPSETLALTCTVSGGSISS IIYYWGWIRQPPGKGLEWIGNVYYSGSIYYN PSLKSRVTISVDTSKNQFSLKLSSVTAADTA VYYCARQNWGSDAFDIWGQGTMVTVSS	1870	SYELTQPLSLSVALGQTARITCGENNIGSRN VHWYQQKPGQAPVLVIYRDSDRPSGIPERFS GSNSGNTATLTISRAQAGDEADYFCQVWDSS TAVFGGGTKLTVL
1735	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSG YYWSWIRQPPGKGLEWIGEINHSGNTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCARGELGIGYWYFDLWGRGTLVTVSS	1871	SSELTQDPAVSVALGQTVRITCQGDSLRSYY ASWYQQKPGQAPVLVIYGKNNRPSGIPDRFS GSSSGNTASLTITGAQAEDEADYYCNSRDSS GNHVVFGGGTKLTVL
1736	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSG YYWSWIRQPPGKGLEWIGEINHSGSTNYNPS LKSRVTISVDTSKNQFSLKLSSVTAADTAVY YCAREGGTTHEPLFDYWGQGTLVTVSS	1872	SYELTQPPSVSVSPGQTARITCSGDALPKKY AYWYQQKSGQAPVLVIYEDSKRPSGIPERFS GSSSGTMATLTISGAQVEDEADYYCYSTDSS GNHRVFGGGTKLTVL
1737	QVQLVQSGAEVKKPGASMKVSCKASGYTFIT YGITWVRQAPGQGLEWMGWISAYNGNANYAQ KVQDRVTMTTDTSTSTAYMELRSLRSDDTAV YYCARAPGGSCGSTNCYKWNYDPYYFDYWGQ GTLVTVSS	1873	RSALTQPASVSGSPGQSITISCTGTSSDVGG YNYVSWYHQHPGKAPKLMIYDVSKRPSGVSN RFSGFKSGNTASLTISGLQAEDEADYFCCSY AGSSTLVFGGGTKLTVL
1738	QVQLVQSGAEVKKPGASVKVSCKASGYTFIT YGISWVRQAPGQGLEWMGWISSYNGNTNYAQ KLQGRVTMTRDTSTSTAYMELRSLRSDDTAV YYCARAPGGDCSSTSCYKWNYDPYYFDYWGQ GTLVTVSS	1874	QSALTQPASVSGSPGQSITISCTGTSSDVGG YNHVSWYQQNPGKAPKLMIYDVSKRPSGVSN RFSGSKSGNTASLTISGLQAEDEADYYCCSY AGSSTLVFGGGTKLTVL

[00651] Table 10. Hybridoma Antibody Sequences

Hybridoma clone	SEQ ID NO	VH Sequence	SEQ ID NO	VK Sequence
M1	1739	QVQLQESGPGLVKPSQTLSLTCTVSG GSISSGGYYWSWIRQHPGKGLEWIGN IYYSGNPYYNPSLKSRLIISVDTSKN QFSLRLNSVTAADTAVYYCATFYYGS GSYYNEDYWGQGTLVTVSS	1956	DIQMTQSPSSLSASVGDRVTITCR ASQGIRIDLGWYQQKPGKAPKRLI YAASSLKSGVPSRFSGSGSGTEFT LTISSLQPEDFTTYFCLQHNSYPY TFGQGTKLEIK
M2	1740	QVQLVESGGGLVKPGGSLRLSCAASG FTFSDSYMSWIRQAPGKGLEWVSYIS NSGSYMYYADSVKGRFTISRDNAKNS LYLQMNNLRAEDTAVYYCARDKLGIG DYWGQGTLVTVSS	1957	DIQMTQSPSSLSASVGDRVTITCR ASQGIRNDLGWFQQKPGKAPKRLI YAASRLQSGVPSRFSGSGSGTEFT LTISSLQPEDFATYCCLQHHTYPP TFGQGTKVEIK
M3	1741	QVQLQESGPGLVKPSETLSLTCTVSG GSISSYDWSWIRQPPGKGLEWIGYIY YSGSTNYNPSLKSRVTISVDTSKNQF SLKLRSVTAADTAVYYCARKYSYGPF DNWGQGTLVTVSS	1958	DIVMTQSPSSLSPSVGDRVTITCR ASQGINNYLAWYQQKPGKVPQLLI YAASTLQSGVPSRFSGSGSGTDFT LTISSLQPEDVATYYCQKYNSXPF TFGPGTKVDIK
M9	1742	QVQLQESGPGLVKPSQTLSLTCDISG DSVSSNSAAWNWIRQSPSRGLEWLGR TYYRSKWYNDYAVAVKSRITINPDTS KNQFSLQLNSVTPEDTAVYYCARESS GWYEDYYYYYMDVWGKGTTVTVSS	1959	DIQMTQSPSSLSASVGDRVTITCR ASQSISSYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQSYSTPF TFGPGTKVDIK
M19	1743	QLQLQESGPGLVKPSETLSLTCTVSG GSISSSNHYWGWIRQPPGKGLEWIGT LYYSGSTYYEPSLKSRVTISVDTSMN QFSLNLSSVTATDTAVYNCARGDRYG PFDYWGQGTLVTVSS	1960	DIVMTQSPSSLSASVGDRVTITCR ASQGIRDDLGWYQQKPEKAPKRLI CAASSLQSGVPSRFSGSGSGTEFT LTISSLQPEDFATYYCLQYNRYPW TFGQGTKVEIK
M24	1744	EVQLVESGGGLVKPGGSLRLSCAASG FTFTNAWMNWVRQAPGKGLEWIGRIK SKTAGETTDYAAPVKGRFTISRDDSK NTLYLQMNSLKTEDTAVYYCTTDPDY GDPYYYYYFMDVWGKGTTVTVSS	1961	DIQMTQSPSSLSASIGDRVTISCR ASQSISSYLNWYQQKPGKAPKLLI YGASSLQSGVPSRFSGSGSGTDFT LTISSLQPEDFATYYCQQSYSLPL TFGGGTKVEIK
M26	1745	QVQLVQSGVEVKKPGASVKVSCKASG YAFSNNDISWVRQAPGQGLEWMAWIT TSNGNTNYAPKLQGRVTMTTDTSTST AYMELRSLKSDDTAVYYCARGGRTGY FDYWGQGTLVTVSS	1962	DIVMTQSPLSLPVTPGEPASISCR SSQSLLHSNGYNYLDWYLQKPGQS PQLLIYLGSNRASGVPDRFSGSGS GTDSTLKISRVEAEDVGVYYCMQV LQIPLTFGGGTKVEIR
M37	1746	QVQLQESGPGLVKPSGTLSLTCAVSG GSITTNNWWSWVRQSPGKGLEWIGEI YHSGNTNYNPSLKSRVTMSVDKSKNQ FSLNLNSVIVADTAVYYCASALGTYY GAFDTWGQGTMVTVSA	1963	DIQMTQSPSSLSASVGDRVTITCR ASQSISNYLNWYQQKPGKAPKLLI YAASSLQSGVPSRFSGSGSGTDFT LTISSLQPEDFTTYYCQQSYGTPY TFGQGAKLQIK
M38	1747	QVQLVESGGGVVQPGRSLRLSCAASG FTFSSYGMHWVRQAPGKGLEWVAFIW YDGRNKNYVDSVKGRFTISRDNSKNT LYLQMNSLRAEDTAVYYCARDRGDYV FDYWGQGTLVTVSS	1964	DIQMTQSPSSLSASVGDRVTITCQ ASQDIRNYLNWYQQKPGKAPKLLI YDASNLETGVPSRFSGSGSGTDFT FTISSLKPEDIATYYCQQYDNLLF TFGPGTKVDIK
M41	1748	QVQLVESGGGLVQPGRSLRLSCAASG FTFDDYAIHWVRQAPGKGLEWVSGIS YNSENIGYADSVKGRFTISRDNAKNS LYLQMNSLRSEDTALYYCAKDMFLTW FSSFDYWGQGTLVTVSS	1965	ETKLTQSPGTLSLSPGERTTLSCR ASQSISNNYLAWYQQKPGQAPRLL IYRASTRATGIPDRFSGSGSGTDF TLTIRRLEPEDFAVYYCQRYGRSP LTFGGGTKVEIK
M43	1749	QVQLQESGPGLVKPSGTLSLTCAVSG GSISSSNWWSWVRQPPGKGLEWIGEI YHSGSINYNPSLKSRVTISVDKSKNQ FSLKLTSVTAADTAVYYCASALGNYY GAFDLWGQGTMVTVSS	1966	DIVMTQSPSSLSASVGDRVTITCR ASQTISSYLNWYQQKPGKAPKLLI CAASSLQGGVPSRFSGSGSGTDFT LTISSLQPEDFAPYYCQQSYSTPY TFGQGTKLEIK
M52	1750	QLQLQESGPGLAKPSETLSLTCTVSG VSISSNSYYWGWIRQPPGKGLEWIGN IYHSGRTYYNPSLRSRVTISVDTSKN QFSLKLNSVTAADTAVYYCARGYSYG AFDYWGQGTLVTVSS	1967	DIQMTQSPSSLSASVGDRVTITCR ASQGIRNDLGWYQQKPGKAPKRLI YAASSLQSGIPSRFSGSGSGTEFT LTISSLQPEDFATYYCLQHNNYPW TFGQGTKVEIK

Hybridoma clone	SEQ ID NO	VH Sequence	SEQ ID NO	VK Sequence
M54	1751	QLQLQESGPGLVKPSETLSLTCSVSG GSISSSGYYWGWIRQPPGKGLDWIGT IYYSGNTNYNPSLNSRVTISVDTSRN QFSLKLRSVTAADTAVYYCARGYSYG PFDYWGQGTLVTVSS	1968	EIVMTQSPATLSVSPGERATLSCR ASQSVSSNLAWYQLKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFT LTISSLQSEDFAVYYCHPYNNWPL TFGGGTKVEIK
M71	1752	QVQLVESGAEVKKPRASVKVSCKTSG YTFTRHYMHWVRQAPGQGLEWMGIIN PNNNSTSYAQKFQGRITMTRDTSTST VYMELSSLRSEDTAVYYCARFRIVGT TLYFDYWGQGTLVTVSS	1969	EIVMTQSPATLSVSPGERATLSCR ASQSVSSNLAWYQLKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFT LTISSLQSEDFAVYYCHPYNNWPL TFGGGTKVEIK
M80	1753	QVQLVESGGGLVKPGGSLRLSCAASG FTFSDSYMSWIRQAPGKGLEWVSYIS NSGSYMYYADSVKGRFTISRDNAKNS LYLQMNNLRAEDTAVYYCARDKLGIG DYWGQGTLVTVSS	1970	DIVMTQSPLSLPVTPGEPASISCR SSQSLLHSNGYNYLDWYLQKPGQS PQLLIYLGSNRASGVPDRFSGSGS GTDSTLKISRVEAEDVGVYYCMQV LQIPLTFGGGTKVEIR
M82	1754	QVQLVQSGAEVKKPGASVKVSCKASG YTFSSFGITWIRQAPGQGLEWMGWIS GYTGNTNYAQNLQGRVTITTDTSTNT AYMELRSLKSDDTAVYYCAREPVLNP NYYYFYYMDVWGQGTTVTVSS	1971	EIQLTQSPGTLSLSPGERATLSCR ASQSVRNSYLAWYQQKPGQAPRLL TYGASSRATGIPDRFSGSGSGTDF TLTISRLEPEDCAVYFCQQYGSSP TFGGGTKVDIK
M87	1755	QVQLVQSGAEVKKPGASMKVSCKASG YTFTQNHISWVRQAPGQGLEWMGWIS AYSGNTNYAWKFQGRVTMTTDTSTNT AYMELRSLRSDDTAVYYCARDRGNWN DFAYWGRGTLVTVSS	1972	DIVMTQSPDSLAVSLGERATINCK SSQSVLYSSNNKNYLAWYQQKPGQ PPKLLIYWASTRESGVPDRFSGSG SGTDFTLTISSLQAEDVAVYYCQQ YYSTPYTFGQGTKLEIK

[00652] Table 11. Hybridoma Clones and EPO/EPOR Blocking Efficiency

Antibody ID	EPO Conc. (nM)	% Inhibition	Antibody ID	EPO Conc. (nM)	% Inhibition	Antibody ID	EPO Conc. (nM)	% Inhibition
EPORab-M1	10	31.2%	EPORab-M30	10	88.6%	EPORab-M59	10	34.5%
EPORab-M2	10	93.6%	EPORab-M31	10	22.4%	EPORab-M60	10	30.0%
EPORab-M3	10	13.4%	EPORab-M32	10	20.9%	EPORab-M61	10	11.2%
EPORab-M4	10	35.0%	EPORab-M33	10	28.6%	EPORab-M62	10	36.3%
EPORab-M5	10	100.7%	EPORab-M34	10	99.6%	EPORab-M63	10	15.0%
EPORab-M6	10	97.2%	EPORab-M35	10	25.4%	EPORab-M64	10	102.0%
EPORab-M7	10	100.4%	EPORab-M36	10	90.2%	EPORab-M65	10	104.2%
EPORab-M8	10	93.9%	EPORab-M37	10	-7.1%	EPORab-M66	10	102.8%
EPORab-M9	10	18.1%	EPORab-M38	10	0.5%	EPORab-M67	10	8.9%
EPORab-M10	10	87.4%	EPORab-M39	10	99.1%	EPORab-M68	10	110.3%
EPORab-M11	10	92.3%	EPORab-M40	10	97.6%	EPORab-M69	10	99.2%
EPORab-M12	10	35.6%	EPORab-M41	10	18.7%	EPORab-M70	10	34.3%
EPORab-M13	10	94.3%	EPORab-M42	10	-5.4%	EPORab-M71	10	0.1%
EPORab-M14	10	95.1%	EPORab-M43	10	-11.4%	EPORab-M72	10	14.8%

Antibody ID	EPO Conc. (nM)	% Inhibition	Antibody ID	EPO Conc. (nM)	% Inhibition	Antibody ID	EPO Conc. (nM)	% Inhibition
EPORab-M15	10	101.4%	EPORab-M44	10	26.3%	EPORab-M73	10	100.6%
EPORab-M16	10	96.5%	EPORab-M45	10	19.5%	EPORab-M74	10	5.1%
EPORab-M17	10	92.0%	EPORab-M46	10	98.4%	EPORab-M75	10	32.7%
EPORab-M18	10	28.8%	EPORab-M47	10	26.5%	EPORab-M76	10	88.6%
EPORab-M19	10	10.4%	EPORab-M48	10	1.3%	EPORab-M77	10	106.6%
EPORab-M20	10	31.8%	EPORab-M49	10	22.4%	EPORab-M78	10	104.8%
EPORab-M21	10	96.8%	EPORab-M50	10	99.0%	EPORab-M79	10	-0.8%
EPORab-M22	10	0.6%	EPORab-M51	10	89.8%	EPORab-M80	10	-1.8%
EPORab-M23	10	94.9%	EPORab-M52	10	7.4%	EPORab-M81	10	9.7%
EPORab-M24	10	9.5%	EPORab-M53	10	101.6%	EPORab-M82	10	24.8%
EPORab-M25	10	1.6%	EPORab-M54	10	16.0%	EPORab-M83	10	10.1%
EPORab-M26	10	31.3%	EPORab-M55	10	98.3%	EPORab-M84	10	114.7%
EPORab-M27	10	23.8%	EPORab-M56	10	112.1%	EPORab-M85	10	28.5%
EPORab-M28	10	21.0%	EPORab-M57	10	31.5%	EPORab-M86	10	12.6%
EPORab-M29	10	13.2%	EPORab-M58	10	102.8%	EPORab-M87	10	11.5%

[00653] Table 12. Engineered EPO Variants Amino Acid Sequences

Plasmid	Protein	Mutations	SEQ ID NO	Amino Acid Sequences (without the signal peptide sequence)
IME002	EPO-Fc	N24Q/N38Q/N83Q	1973	APPRLICDSRVLERYLLEAKEAEQITTGCAEHCSLNEQITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVQS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME005	EPO-Fc	K45D	1974	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTDVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME006	EPO-Fc	N147K	1975	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSKFLRGKLKLYTGEACRTGDR
IME007	EPO-Fc	R150E	1976	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLEGKLKLYTGEACRTGDR
IME008	EPO-Fc	R103A	1977	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLASLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME009	EPO-Fc	K45D/R103A	1978	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTDVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLASLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR

Plasmid	Protein	Mutations	SEQ ID NO	Amino Acid Sequences (without the signal peptide sequence)
IME010	EPO-Fc	N147K/R103A	1979	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLASLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSKFLRGKLKLYTGEACRTGDR
IME011	EPO-Fc	R150E/R103A	1980	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLASLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLEGKLKLYTGEACRTGDR
IME012	EPO-Fc	E62R	1981	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVRVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME013	EPO-Fc	Q65A	1982	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWAGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME014	EPO-Fc	E72R	1983	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSRAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME015	EPO-Fc	R76E	1984	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLEGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME016	EPO-Fc	E62A/Q65A/E72A/R76A	1985	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVAVWAGLALLSAAVLAGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME028	EPO-Fc	N24A/N38A/N83A	1986	APPRLICDSRVLERYLLEAKEAEAITTGCAEHCSLNEAITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVAS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME029	EPO-Fc	N24S/N38S/N83S	1987	APPRLICDSRVLERYLLEAKEAESITTGCAEHCSLNESITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVSS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME032	EPO-Fc	E62A	1988	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVAVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME033	EPO-Fc	E72A	1989	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSAAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME034	EPO-Fc	R76A	1990	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLAGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME035	EPO-Fc	G151A	1991	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRAKLKLYTGEACRTGDR
IME036	EPO-Fc	R103A/G151A	1992	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLASLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRAKLKLYTGEACRTGDR
IME037	EPO-Fc	Q58A	1993	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGAQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR

Plasmid	Protein	Mutations	SEQ ID NO	Amino Acid Sequences (without the signal peptide sequence)
IME038	EPO-Fc	L69A	1994	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLAALSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME039	EPO-Fc	L80A	1995	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQAALVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME040	EPO-Fc	N83A	1996	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVAS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME041	EPO-Fc	S84A	1997	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNA SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME042	EPO-Fc	S85A	1998	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS AQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME043	EPO-HSA	R103A	1999	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLASLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME044	EPO-HSA	Q65A/E72R	2000	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWAGLALLSRAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME045	EPO-HSA	Q65A/E72R/N83A	2001	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWAGLALLSRAVLRGQALLVAS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME046	EPO-HSA	K20A/K45A/K52A	2002	APPRLICDSRVLERYLLEAAEAENITTGCAEHCSLNENITVP DTAVNFYAWARMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME047	EPO-HSA	K140A/K152A	2003	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRALFRVYSNFLRGALKLYTGEACRTGDR
IME048	EPO-HSA	K140A/K152A/K154A	2004	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRALFRVYSNFLRGALALYTGEACRTGDR
IME049	EPO-HSA	K20A/K45A/K52A/K140A/K152A/K154A	2005	APPRLICDSRVLERYLLEAAEAENITTGCAEHCSLNENITVP DTAVNFYAWARMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRALFRVYSNFLRGALALYTGEACRTGDR
IME050	EPO-HSA	K97A/K116A	2006	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDAAVSGLRSLTTLLRALGAQAEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME051	EPO-HAS	K20A/K45A/K52A/K97A/K116A/K140A/K152A/K154A	2007	APPRLICDSRVLERYLLEAAEAENITTGCAEHCSLNENITVP DTAVNFYAWARMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDAAVSGLRSLTTLLRALGAQAEAISPPDAAS AAPLRTITADTFRALFRVYSNFLRGALALYTGEACRTGDR
IME077	EPO-HSA	K45D/R103A	2008	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTDVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLASLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR

Plasmid	Protein	Mutations	SEQ ID NO	Amino Acid Sequences (without the signal peptide sequence)
IME085	EPO-HSA	K97A	2009	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDAAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME086	EPO-HSA	K116A	2010	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQAEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME087	EPO-HSA	K140A	2011	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRALFRVYSNFLRGKLKLYTGEACRTGDR
IME088	EPO-HSA	K152A	2012	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGALKLYTGEACRTGDR
IME089	EPO-HSA	Q58A/Q65A/E72R	2013	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGAQAVEVWAGLALLSRAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME090	EPO-HSA	L80A/N83A/S84A/S85A	2014	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLALLSEAVLRGQAALVAA AQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME091	EPO-HSA	Q58A/Q65A/E72R/ L80A/N83A/S84A/S85A	2015	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGAQAVEVWAGLALLSRAVLRGQAALVAA AQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME092	EPO-HSA	Q58A/L69A	2016	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGAQAVEVWQGLAALSEAVLRGQALLVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME093	EPO-HSA	Q58A/L80A	2017	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGAQAVEVWQGLALLSEAVLRGQAALVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME094	EPO-HSA	L69A/L80A	2018	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGQQAVEVWQGLAALSEAVLRGQAALVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR
IME095	EPO-HSA	Q58A/L69A/L80A	2019	APPRLICDSRVLERYLLEAKEAENITTGCAEHCSLNENITVP DTKVNFYAWKRMEVGAQAVEVWQGLAALSEAVLRGQAALVNS SQPWEPLQLHVDKAVSGLRSLTTLLRALGAQKEAISPPDAAS AAPLRTITADTFRKLFRVYSNFLRGKLKLYTGEACRTGDR

[00654] Table 13. Engineered EPO Variants Nucleic Acid Sequences

Plasmid	SEQ ID NO	Nucleic Acid Sequence (without the signal peptide)
IME001 (Wild type)	2020	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME005	2021	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCGACGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC

Plasmid	SEQ ID NO	Nucleic Acid Sequence (without the signal peptide)
		AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME006	2022	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAAATTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME007	2023	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCG AGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME008	2024	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTGCCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME009	2025	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCGACGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTGCCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME010	2026	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTGCCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAAATTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME011	2027	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTGCCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCG AGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME012	2028	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTACGGGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME013	2029	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA

Plasmid	SEQ ID NO	Nucleic Acid Sequence (without the signal peptide)
		CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG GCAGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME014	2030	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGCGAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME015	2031	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGGAGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME016	2032	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGCAGTCTGG GCAGGCCTGGCCCTGCTGTCGGCAGCTGTCCTGGCAGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME032	2033	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGCTGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME033	2034	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGCAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME034	2035	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGGCTGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME035	2036	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGCAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA

Plasmid	SEQ ID NO	Nucleic Acid Sequence (without the signal peptide)
IME036	2037	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTGCCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGCAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME037	2038	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGGCTCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME038	2039	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCGCTCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME039	2040	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCGCTTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME040	2041	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCGCCTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME041	2042	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACGCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME042	2043	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTGCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME043	2044	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTGCCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT

Plasmid	SEQ ID NO	Nucleic Acid Sequence (without the signal peptide)
		CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME044	2045	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG GCAGGCCTGGCCCTGCTGTCGCGAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCICGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTC CGGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME045	2046	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG GCAGGCCTGGCCCTGCTGTCGCGAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCGCCTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME046	2047	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCGCGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCGCAGTTAATTTCTATGCCTGGGCTAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME047	2048	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCGCACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAGCCCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME048	2049	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCGCACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAGCCCTGGCGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME049	2050	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCGCGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCGCAGTTAATTTCTATGCCTGGGCTAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCGCACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAGCCCTGGCGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME050	2051	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATGCAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGGCGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME051	2052	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCGCGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCGCAGTTAATTTCTATGCCTGGGCTAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC

Plasmid	SEQ ID NO	Nucleic Acid Sequence (without the signal peptide)
		AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATGCAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGGCGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCGCACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAGCCCTGGCGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME077	2053	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCGACGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTGCCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME085	2054	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATGCAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME086	2055	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGGCGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME087	2056	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCGCACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME088	2057	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAGCCCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME089	2058	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGGCTCAGGCCGTAGAAGTCTGG GCAGGCCTGGCCCTGCTGTCGCGAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME090	2059	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCGCGTTGGTCGCCGCTGCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME091	2060	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA

Plasmid	SEQ ID NO	Nucleic Acid Sequence (without the signal peptide)
		CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGGCTCAGGCCGTAGAAGTCTGG GCAGGCCTGGCCCTGCTGTCGCGAGCTGTCCTGCGGGGCCAGGCCGCGTTGGTCGCCGCTGCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME092	2061	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGGCTCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCGCTCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTGTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME093	2062	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGGCTCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCGCTTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME094	2063	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCGCTCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCGCTTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME095	2064	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAGGAGG CCGAGAATATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGAATATCACTGTCCCAGA CACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGGCTCAGGCCGTAGAAGTCTGG CAGGGCCTGGCCGCTCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCGCTTTGGTCAACTCTTCCC AGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGTGGCCTTCGCAGCCTCACCAC TCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCCCCTCCAGATGCGGCCTCAGCTGCT CCACTCCGAACAATCACTGCTGACACTTTCCGCAAACTCTTCCGAGTCTACTCCAATTTCCTCC GGGGAAAGCTGAAGCTGTACACAGGGGAGGCCTGCAGGACAGGGGACAGA
IME002	2065	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAG GAGGCCGAGCAGATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGCAGATCACT GTCCCAGACACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCC GTAGAAGTCTGGCAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTG TTGGTCCAGTCTTCCCAGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGT GGCCTTCGCAGCCTCACCACTCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCC CCTCCAGATGCGGCCTCAGCTGCTCCACTCCGAACAATCACTGCTGACACTTTCCGCAAA CTCTTCCGAGTCTACTCCAATTTCCTCCGGGGAAAGCTGAAGCTGTACACAGGGGAGGCC TGCAGGACAGGGGACAGA
IME028	2066	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAG GAGGCCGAGGCGATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGGCGATCACT GTCCCAGACACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCC GTAGAAGTCTGGCAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTG TTGGTCGCGTCTTCCCAGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGT GGCCTTCGCAGCCTCACCACTCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCC CCTCCAGATGCGGCCTCAGCTGCTCCACTCCGAACAATCACTGCTGACACTTTCCGCAAA CTCTTCCGAGTCTACTCCAATTTCCTCCGGGGAAAGCTGAAGCTGTACACAGGGGAGGCC TGCAGGACAGGGGACAGA
IME029	2067	GCCCCACCACGCCTCATCTGTGACAGCCGAGTCCTGGAGAGGTACCTCTTGGAGGCCAAG GAGGCCGAGTCGATCACGACGGGCTGTGCTGAACACTGCAGCTTGAATGAGTCGATCACT GTCCCAGACACCAAAGTTAATTTCTATGCCTGGAAGAGGATGGAGGTCGGGCAGCAGGCC GTAGAAGTCTGGCAGGGCCTGGCCCTGCTGTCGGAAGCTGTCCTGCGGGGCCAGGCCCTG TTGGTCTCGTCTTCCCAGCCGTGGGAGCCCCTGCAGCTGCATGTGGATAAAGCCGTCAGT GGCCTTCGCAGCCTCACCACTCTGCTTCGGGCTCTGGGAGCCCAGAAGGAAGCCATCTCC

Plasmid	SEQ ID NO	Nucleic Acid Sequence (without the signal peptide)
		CCTCCAGATGCGGCCTCAGCTGCTCCACTCCGAACAATCACTGCTGACACTTTCCGCAAA CTCTTCCGAGTCTACTCCAATTTCCTCCGGGGAAAGCTGAAGCTGTACACAGGGGAGGCC TGCAGGACAGGGGACAGA

[00655] Table 14. VH-CDR1, VH-CDR2, VL-CDR1, and VL-CDR2 Sequences for Anti-EPOR Antibodies

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype10	2068	GDSVSSNSA	2256	YYRSKWY	2444	TGTSSDVGGYNYVS	2632	EVSNRPS
clonotype13	2069	GDSVSSNSA	2257	YYRSKWY	2445	TGTSSDVGGYNYVS	2633	DVSKRPS
clonotype22	2070	GFTFDDY	2258	NWNGGS	2446	SGDKLGDKYAC	2634	QDSKRPS
clonotype31	2071	GGSISSSSY	2259	YYSGS	2447	SGDVLAKKYAR	2635	KDSERPS
clonotype33	2072	GFTFSSY	2260	SSSSSY	2448	QGDSLRSYYAS	2636	GKNNRPS
clonotype36	2073	GFTFNNY	2261	SSSSSY	2449	TGTSSDVGGYNYVS	2637	DVSKRPS
clonotype42	2074	GFTFSSY	2262	WYDGSN	2450	TGTSSDVGGYNYVS	2638	EVSKRPS
clonotype43	2075	GFTFSSY	2263	SGSGGS	2451	TGTSSDVGGYNYVS	2639	EVSNRPS
clonotype44	2076	GYTFTSY	2264	SPYNGN	2452	TGTSSDVGGYNYVS	2640	DVSKRPS
clonotype45	2077	GGSFSGY	2265	NHSGS	2453	QGDSLRSYYAS	2641	GKNNRPS
clonotype47	2078	GFTFSSY	2266	WYDGSN	2454	GGNNIGSKSVH	2642	YDSDRPS
clonotype56	2079	GFSFSGS	2267	RSKPNNYA	2455	TLRSGINVGTYRIY	2643	YKSDSDKQQGS
clonotype58	2080	GYTFTGY	2268	NPNSGG	2456	QGDSLRSYYAS	2644	GKNNRPS
clonotype62	2081	GYTFINY	2269	SAYSGN	2457	SGDALPKKYAY	2645	EDSKRPS
clonotype66	2082	GFTFSSY	2270	WYDGSN	2458	TGTSSDVGGYNYVS	2646	EVSNRPS
clonotype69	2083	GGSISSSN	2271	YHSGS	2459	TLRSGINVGTYRIY	2647	YKSDSDKQQGS
clonotype75	2084	GFSLSTSGV	2272	YWNDD	2460	SGDKLGDKYAC	2648	QDSKRPS
clonotype80	2085	GFTFSSY	2273	SGSGGS	2461	SGDALPKKYAY	2649	EDSKRPS
clonotype82	2086	GFTFSNA	2274	KSKTDGGT	2462	QGDSLRSYYAS	2650	GKNNRPS
clonotype95	2087	GFTFSSY	2275	SSSSST	2463	TGTSSDVGGYNYVS	2651	DVSKRPS
clonotype99	2088	GFTFDDY	2276	NWNGGS	2464	TGTSSDVGGYNYVS	2652	EVSNRPS
clonotype102	2089	GYSFTSY	2277	YPSDSD	2465	TGTSSDVGGYNYVS	2653	DVSKRPS
clonotype103	2090	GYTFTSY	2278	SVYNGN	2466	TGTSSDVGGYNYVS	2654	DVSKRPS
clonotype109	2091	GDSVSSNSA	2279	YYRSKWY	2467	TGTSSDVGGYNYVS	2655	DVSKRPS
clonotype110	2092	GGSFSGY	2280	NHSGS	2468	TLSSEHSTYTIE	2656	VKSDGSHSKGD

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype111	2093	GFTFSSY	2281	SSSSSY	2469	TLSSEHSTYTIE	2657	VKSDGSHSKGD
clonotype112	2094	GFTFSNA	2282	KSKTDGGT	2470	QGDSLRSYYAS	2658	GKNNRPS
clonotype397	2095	GGSISSGGY	2283	YYIGI	2471	GGNNVGSKSVH	2659	YDTDRPS
clonotype398	2096	GGSISSGGY	2284	YYSGS	2472	GGNTFGSKTVH	2660	YDSDRPS
clonotype399	2097	GFTFSNA	2285	KSKTDGGT	2473	SGDALPKKYAY	2661	EDSKRPS
clonotype400	2098	GYTFTSY	2286	NPNSGN	2474	TGTSSDVGGYNYVS	2662	EVSNRPS
clonotype401	2099	GYTFTTY	2287	SAYNGN	2475	TGTSSDVGGYNYVS	2663	EVIKRPS
clonotype402	2100	GFTFSSY	2288	SGSGGS	2476	SGSSSNIGSNTVN	2664	SNNQRPS
clonotype407	2101	GFTFSNA	2289	KSKSDGGT	2477	SADALPKQYAY	2665	KDSERPS
clonotype408	2102	GYTFTSY	2290	NPNSGN	2478	SGDALPKKYAY	2666	EDSKRPS
clonotype409	2103	GFTFSNA	2291	KSKTDGGT	2479	SADALPKQYAY	2667	KDSERPS
clonotype413	2104	GFTFSSY	2292	SSSSSY	2480	SGDKLGDKYAC	2668	QDSKRPS
clonotype414	2105	GYTFTSY	2293	NPNSGN	2481	SGDKLGDKYAC	2669	QDSKRPS
clonotype415	2106	GFTFSNA	2294	KSKTDGGT	2482	SGDKLGDKYAC	2670	QDSKRPS
clonotype418	2107	GFTFSSY	2295	SSSSSY	2483	QGDSLRSYYAS	2671	GKNNRPS
clonotype419	2108	GFTFSSY	2296	GTAGD	2484	TGTSSDVGGYNYVS	2672	DVSKRPS
clonotype420	2109	EFTFRNA	2297	RSEIDGGT	2485	QGDSLRSYYAS	2673	GKNNRPS
clonotype421	2110	GFTFSNA	2298	KSKTDGGT	2486	QGDSLRSYYAS	2674	GKNNRPS
clonotype423	2111	GFTFSNY	2299	WYDGSN	2487	SGSSSNIGNNAVN	2675	YDDLLPS
clonotype424	2112	GFTFSDY	2300	SSSGST	2488	TGTSSDVGGYNYVS	2676	DVSKRPS
clonotype426	2113	GYTFTNY	2301	NTYNDK	2489	SGDKLGDKHAC	2677	QDSKRPS
clonotype427	2114	GYTFTSY	2302	SAYNGN	2490	SGDVLAKKYAR	2678	KDSERPS
clonotype428	2115	GFTFSSY	2303	GTAGD	2491	SGDVLAKKYAR	2679	KDSERPS
clonotype429	2116	GFTFSNA	2304	KSKTDGGT	2492	SGDVLAKKYAR	2680	KDSERPS
clonotype430	2117	GFTFSNA	2305	KSKTDGGT	2493	SGDVLAKKYAR	2681	KDSERPS
clonotype431	2118	GFTFSSY	2306	SSSSSY	2494	QGDRLRSYYAS	2682	GKNNRPS
clonotype432	2119	GFTFSSY	2307	KQDGSE	2495	QGDSLRSYYAS	2683	GKNNRPS
clonotype434	2120	RYTFTSY	2308	NPSGGT	2496	GGNNIGSKSVH	2684	YDSDRPS
clonotype435	2121	GFTFSSY	2309	SSSSST	2497	SGDALPKKYAY	2685	EDSKRPS
clonotype436	2122	GLTVSTN	2310	YSGGG	2498	ASSTGAVTSGYYPN	2686	STSNKHS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype437	2123	GFTFDDY	2311	NWNGGS	2499	TGTSSDVGGYNYVS	2687	EVSKRPS
clonotype438	2124	GFTVSSN	2312	YSGGS	2500	TGTSSDVGGYNYVS	2688	DVSKRPS
clonotype439	2125	GFTFSSY	2313	SSSSSY	2501	TGTSSDVGGYNYVS	2689	DVSKRPS
clonotype442	2126	GFTFSSY	2314	NSDGSS	2502	SGDKLGDKYAC	2690	QDSKRPS
clonotype443	2127	GGSISSNN	2315	YHSGS	2503	SGDKLGDKYAC	2691	QDNKRPS
clonotype444	2128	GYTFTRN	2316	NTNIGN	2504	SGDKLGDKYAC	2692	QDSKRPS
clonotype445	2129	GFTFSSY	2317	SSSSSY	2505	QGDSLRSYYAS	2693	GKNNRPS
clonotype446	2130	GYTFTSY	2318	SAYNGN	2506	SGDALPKKYAY	2694	EDSKRPS
clonotype448	2131	GFTFSSY	2319	GTAGD	2507	QGDSLRSYYAS	2695	GKNNRPS
clonotype450	2132	GFTFSSY	2320	WYDGSN	2508	SGDALPKKYAY	2696	EDSKRPS
clonotype451	2133	GYSFTSY	2321	YPGDSD	2509	GGNNIGSKSVH	2697	YDSDRPS
clonotype452	2134	GFTFSNY	2322	KYDGRE	2510	SGSISNLGSNTVN	2698	SNNQRPS
clonotype453	2135	GFTFSSY	2323	KQDGSE	2511	TGTSSDVGGYNYVS	2699	EVSKRPS
clonotype454	2136	GYTFTSY	2324	SAYNGN	2512	TGTSSDVGGYNYVS	2700	EVSKRPS
clonotype455	2137	GFTFSSY	2325	NSDGSS	2513	TGTSSDVGGYNYVS	2701	DVSKRPS
clonotype456	2138	GFTVSSN	2326	YSGGS	2514	TGTSSDVGGYNYVS	2702	DVSKRPS
clonotype457	2139	GFTFDDY	2327	SWNSGS	2515	TGTSSDVGGYNYVS	2703	EVSKRPS
clonotype458	2140	GFTFSDY	2328	SSSGST	2516	TGSSSNIGAGYDVH	2704	GNSNRPS
clonotype459	2141	GFTVSRN	2329	YAGGN	2517	TGSSSNIGAGYDVH	2705	GNNNRPS
clonotype460	2142	GFTFSSY	2330	KQDGSE	2518	TLRSGINVGTYRIY	2706	YKSDSDKQQGS
clonotype461	2143	GFTFSSY	2331	KQDGSE	2519	TLRSGINVGTYRIY	2707	YKSDSDKQQGS
clonotype464	2144	GFTFSRY	2332	NIVGST	2520	RGNNIGSQNVH	2708	RNINRPS
clonotype465	2145	GFTFSSY	2333	SSSSSY	2521	SGDALPKKYAY	2709	EDSKRPS
clonotype466	2146	GFTFSIY	2334	KEDGSE	2522	QGDSLRSFYAS	2710	GKSNRPS
clonotype468	2147	GYTFTSY	2335	SAYNGN	2523	QGDSLRSYYAS	2711	GKNNRPS
clonotype469	2148	GYTFTSY	2336	NPNSGN	2524	SGDALPKKYAY	2712	EDSKRPS
clonotype470	2149	GYTFTSY	2337	NPSGGS	2525	QGDSLRSYYAS	2713	GKNNRPS
clonotype471	2150	GFTFSSY	2338	GTAGD	2526	SGDALPKKYAY	2714	EDSKRPS
clonotype474	2151	GFTFSNA	2339	KSKTDGGT	2527	ASSTGAVTSGYYPN	2715	STSNKHS
clonotype475	2152	GFTFSSH	2340	SSNGGN	2528	TGTSSDVGGYNYVS	2716	EVSNRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype476	2153	GFTFSSY	2341	SSSSSY	2529	SGSSSNIGSNTVN	2717	SNNQRPS
clonotype477	2154	GGSFSGY	2342	NHSGS	2530	TGTSSDVGGYNYVS	2718	EVSKRPS
clonotype478	2155	GYTFTSY	2343	NPSGGS	2531	TGTSSDVGGYNYVS	2719	DVSKRPS
clonotype479	2156	GFTFSDY	2344	SSSGST	2532	TGTSSDVGGYNYVS	2720	DVSKRPS
clonotype480	2157	GYSFTSY	2345	YPGDSD	2533	TGTSSDVGGYNYVS	2721	EVSKRPS
clonotype481	2158	GFTFSSY	2346	SSSSST	2534	TLRSGINVGTYRIY	2722	YKSDSDKQQGS
clonotype486	2159	GGSISSGGY	2347	FYSGS	2535	SGDKLGDKYAC	2723	QDSKRPS
clonotype487	2160	GFSLSTSGV	2348	YWNDD	2536	SADALPKQYAY	2724	KDSERPS
clonotype488	2161	GFTFSSY	2349	SYDGSN	2537	SGDKLGDKYAC	2725	QDTKRPS
clonotype490	2162	GFSLSTSGV	2350	YWSDD	2538	SADALPNQYAY	2726	KDSERPS
clonotype492	2163	GYPFTSY	2351	SAYNSN	2539	QGDSLRSYYAS	2727	GKNNRPS
clonotype493	2164	GYSFTGY	2352	SAYNGN	2540	SGDALPKKYAY	2728	EDSKRPS
clonotype494	2165	GYTFSSY	2353	NTNTGN	2541	QGDSLRSYYAS	2729	GKNNRPS
clonotype495	2166	GYTFTGY	2354	NPNSGG	2542	SGDALPKKYAY	2730	EDSKRPS
clonotype496	2167	GYTFTSY	2355	NPNSGN	2543	SGDALPKKYAY	2731	EDSKRPS
clonotype497	2168	GYTFTSY	2356	NPNSGN	2544	SGDALPKKYAY	2732	EDSKRPS
clonotype498	2169	GDTFSNF	2357	IPIFAT	2545	GGNNIGSKSVH	2733	YDSDRPS
clonotype499	2170	GFTFSNA	2358	KRKTDGGT	2546	SADALPKQYAY	2734	KDSERPS
clonotype501	2171	GDSVSSNSA	2359	YYRSKWY	2547	QGDSLRSYYAS	2735	GKNNRPS
clonotype502	2172	GFTFNNA	2360	KSKTDGGT	2548	GSSTGAVTSGHYPY	2736	DTSNKHS
clonotype504	2173	GFTFSNA	2361	KSKTDGGT	2549	TGTSSDVGGYNYVS	2737	EVSKRPS
clonotype505	2174	GFTFSSY	2362	SYDGSN	2550	TGTSSDVGGYNYVS	2738	DVSKRPS
clonotype506	2175	GFTFDDY	2363	NWNGGS	2551	TGTSSDVGGYNYVS	2739	EVSNRPS
clonotype507	2176	GDSVSSNSA	2364	YYRSKWY	2552	TGTSSDVGGYNYVS	2740	DVSKRPS
clonotype508	2177	GFTFDDY	2365	SWNSGS	2553	TGTSSDVGGYNYVS	2741	DVSKRPS
clonotype509	2178	GFTFSSY	2366	SSSSNT	2554	TGTSSDVGGYNYVS	2742	EVSKRPS
clonotype511	2179	GYTFTSY	2367	NPSGGS	2555	SGDKLGDKYAC	2743	QDSKRPS
clonotype512	2180	GFNFSSY	2368	SNTGNT	2556	SGDVLAKKYAR	2744	KDSERPS
clonotype513	2181	GFTFSNA	2369	KRKTDGGT	2557	SGDKLGDKYAC	2745	QDSKRPS
clonotype514	2182	GFTFSSY	2370	NSDGSS	2558	SGDKLGDKYAC	2746	QDSKRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype515	2183	GFTFSSY	2371	SGSGGS	2559	SGDALPKKYAY	2747	EDSKRPS
clonotype517	2184	GGSISSNN	2372	YHSGS	2560	SGDALPKKYAY	2748	EDSKRPS
clonotype518	2185	GGSISSSN	2373	YHSGS	2561	TGTSSDVGGYNYVS	2749	DVSKRPS
clonotype519	2186	GGSIISSN	2374	YHSGS	2562	QGDSLRSYYAS	2750	GKNNRPS
clonotype520	2187	GFTFSSY	2375	SSSSSY	2563	QGDSLRSYYAS	2751	GKNNRPS
clonotype522	2188	GFTFSSY	2376	KQDGSE	2564	QGDSLRSYYAS	2752	GKNNRPS
clonotype523	2189	GFSLNSSGV	2377	YWNGD	2565	GGNNIGSKSVH	2753	YDSDRPS
clonotype524	2190	GYIFMNY	2378	SAYNGN	2566	QGDSLRSYYAS	2754	GKNNRPS
clonotype526	2191	GYTFTNY	2379	NTNTGK	2567	QGDSLRSYYAS	2755	GKNNRPS
clonotype527	2192	GYTFTDN	2380	NPNSGG	2568	QGDSLRSYYAS	2756	GKNNRPS
clonotype528	2193	GYTFTSY	2381	NPSGGS	2569	QGDSLRSYYAS	2757	GKKNRPS
clonotype529	2194	GFTFSSY	2382	SSSSST	2570	SGDALPKKYAY	2758	EDSKRPS
clonotype530	2195	GFTFSNY	2383	SGSGGR	2571	QGDSFRNYYAS	2759	GKNNRPS
clonotype531	2196	GFTFSSY	2384	SYDGSN	2572	QGDSLRSYYAS	2760	GKNNRPS
clonotype532	2197	GYRFSNY	2385	YPGDSD	2573	QGDSLRSYYAS	2761	GKNNRPS
clonotype534	2198	GYTFTSY	2386	NTNTGN	2574	ASSTGAVTSGYYPN	2762	STSNKHS
clonotype537	2199	GFTFSSY	2387	WYDGSN	2575	TGTSSDVGVYNFVS	2763	DVTKRPS
clonotype538	2200	GYTFTGY	2388	NPNSGG	2576	TGSSSNIGAGYDVH	2764	VNNNRPS
clonotype539	2201	GDSVSSNSA	2389	YYRSKWY	2577	TGTSSDVGGYNYVS	2765	DVSKRPS
clonotype540	2202	GYTFTSY	2390	SAYNGN	2578	TGSSSNIGAGYDVH	2766	GNSNRPS
clonotype541	2203	GFSITTSGV	2391	YWNDD	2579	TLRSGIHVDTSRIY	2767	YKSDSDKHQDS
clonotype542	2204	GFSLSTSGV	2392	YWNDD	2580	TLRSGINVGSYRIY	2768	YKSDSDKQQGS
clonotype543	2205	GYTFTSY	2393	NPNSGN	2581	TLRSGINVGTYRIY	2769	YKSDSDKQQGS
clonotype548	2206	GFSLSTSGM	2394	DWDDD	2582	QGDSLRSYYAS	2770	GKNNRPS
clonotype549	2207	GYTFTSY	2395	SGYKGN	2583	QGDSLRSYYAS	2771	GKNNRPS
clonotype550	2208	GDTFTNC	2396	SAYNGN	2584	QGDSLRSYYAS	2772	GKNNRPS
clonotype552	2209	GFTFDDY	2397	SKNSGS	2585	QGDSLRSYYAS	2773	GKNNRPS
clonotype553	2210	GFTFSSY	2398	SSSSST	2586	QGDSLRSYYAS	2774	HKNNRPS
clonotype554	2211	GFTFSSY	2399	SGSGGS	2587	QGDSLRSYYAS	2775	GKNNRPS
clonotype555	2212	GFTFSSY	2400	WYDGSN	2588	SGDALPKKYAY	2776	EDSKRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype559	2213	GYTFTGY	2401	NPNSGG	2589	TGTSSDVGGYNYVS	2777	EVSKRPS
clonotype560	2214	GFTFSSY	2402	SSSSST	2590	TGTSSDVGGYNYVS	2778	EVSKRPS
clonotype561	2215	GFTFSDY	2403	SSSGST	2591	ASSTGAVTSGYYPN	2779	STSNKHS
clonotype562	2216	GYTFNSY	2404	NTNTGN	2592	TGSNSNIGAGYDIH	2780	GNSNRPS
clonotype568	2217	GGSISRSSY	2405	YYSGS	2593	SGDVLAKKFAR	2781	KDSERPS
clonotype569	2218	GGSISSSF	2406	YHSGS	2594	SGDALPKKYAY	2782	EDSKRPS
clonotype573	2219	GFTFSNA	2407	KSKSDGET	2595	GGNNFGSKSVH	2783	YDSDRPS
clonotype576	2220	GGSISSY	2408	YYSGS	2596	TGTSSDVGAYNYVS	2784	AVSKRPS
clonotype577	2221	GFTFSSY	2409	SGSGGS	2597	TGTSSDVGGYNYVS	2785	DVSKRPS
clonotype578	2222	GFTFGDF	2410	NWNGGS	2598	TGTSSDVGGYNYVS	2786	EVNKRPS
clonotype579	2223	GDSVSSNSA	2411	YYRSKWY	2599	TGTSSDVGGYNYVS	2787	DVSKRPS
clonotype581	2224	GFTFSSY	2412	SSSSST	2600	TGSSSNIGAGYDVH	2788	GNSNRPS
clonotype582	2225	GDSVSSNSA	2413	YYMSKWY	2601	TGTSSDVGSYNRVS	2789	DVSNRPS
clonotype583	2226	GYTFTTY	2414	SAYNGN	2602	TGSDSNIGAGYDVH	2790	DNIIRPS
clonotype586	2227	GFTFDDY	2415	NWNGGS	2603	SGDKLGDKYAC	2791	QDSKRPS
clonotype587	2228	GDSVSSNSA	2416	YYRSKWY	2604	SGDGLSKKYAY	2792	EDSKRPS
clonotype588	2229	AFTFSNY	2417	SSSTSY	2605	QGDSLRSYYAS	2793	GKNNRPS
clonotype589	2230	GFTFSSY	2418	SSSSSY	2606	QGDSLRSYYAS	2794	GKNNRPS
clonotype596	2231	GFTFSNA	2419	KSKTDGGT	2607	SGDALPKKYAY	2795	EDSKRPS
clonotype598	2232	GFTFSSH	2420	SGSESS	2608	QGDSLRSYYAS	2796	GKNNRPS
clonotype599	2233	GFTFSSY	2421	WYDGSN	2609	QGDSLRSYYAS	2797	GKNNRPS
clonotype600	2234	GGSISSSSY	2422	HYSGS	2610	QGDSLRSYYAS	2798	GKNNRPS
clonotype601	2235	GYSFSSY	2423	SGYNGN	2611	TGTSSDVGGYNYVS	2799	EVSNRPS
clonotype602	2236	GFTFSNA	2424	KSKTDGGT	2612	TGTSSDVGGYNYVS	2800	DVSKRPS
clonotype607	2237	GFTFSTY	2425	SSGSST	2613	QGDSLRSYYAT	2801	GRNNRPS
clonotype608	2238	GFTFSNA	2426	KSKTDGGT	2614	GGNNIGSKSVH	2802	YDSDRPS
clonotype610	2239	GGSITTRSY	2427	YYSGN	2615	QGDSLRSYYAS	2803	GKNNRPS
clonotype611	2240	GDSVSSNSA	2428	YYRSKWY	2616	QGDSLRSYYAS	2804	GKNKRPS
clonotype612	2241	GFTFDDY	2429	NWNGGS	2617	TGTSSDVGGYNYVS	2805	DVSKRPS
clonotype613	2242	GYTFTGN	2430	NPTSGV	2618	TGSSSNIGARYDVH	2806	GNSNRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype616	2243	GYTFTDY	2431	NPNSGG	2619	QGDSLRSYYAS	2807	GKNNRPS
clonotype617	2244	GGSISSRSY	2432	FYSGS	2620	TGTSSDVGGYNYVS	2808	DVSKRPS
clonotype622	2245	GFTFSGS	2433	RSKANSYA	2621	SGDKLGDKYAC	2809	QDSKRPS
clonotype625	2246	GGSFSGY	2434	NHSGS	2622	SGDALPKKYAY	2810	EDNKRPS
clonotype626	2247	GGSFSGY	2435	NRSGS	2623	QGDSLRNYYAS	2811	GKNNRPS
clonotype629	2248	GGSISSSSY	2436	YYSGS	2624	TGTSSDVGGYNYVS	2812	EVSKRPS
clonotype630	2249	GGSISSSSY	2437	YYSGS	2625	QGDSLRTYYAS	2813	GKNKRPS
clonotype634	2250	GFTFRSY	2438	NQDGSE	2626	GGDNIGIKNVH	2814	DDSDRPS
clonotype638	2251	GGSINSSNF	2439	FYSGF	2627	SGDKLGDKYTC	2815	QDIKRPS
clonotype641	2252	GGSISSSSY	2440	YYSGS	2628	QGDSLRSYYAS	2816	GKNNRPS
clonotype644	2253	GGSFSGY	2441	NRGGS	2629	TGTSSDVGGYNYVS	2817	EVSKRPS
clonotype646	2254	GGSISSSGY	2442	YYSGS	2630	TGTSSDVGGYNYVS	2818	EVSNRPS
clonotype647	2255	GGSFSGY	2443	NHSGS	2631	GSSTGAVTSGHYPY	2819	DTSNKHS

[00656] Table 15: VH-CDR1, VH-CDR2, VL-CDR1, and VL-CDR2 Sequences for Anti-CD131 Antibodies

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype8	2820	GGSISSSSY	2949	YYSGS	3078	TGTSSDVGGYNYVS	3207	EVSNRPS
clonotype11	2821	GFTFSNA	2950	KSKTDGGT	3079	SGDALPKKYAY	3208	EDSKRPS
clonotype14	2822	GFTFDDY	2951	NWNGGS	3080	TGSSSNIGAGYDVH	3209	GNSNRPS
clonotype15	2823	GFTFSSY	2952	SSSSST	3081	SGDVLAKKYAR	3210	KDSERPS
clonotype16	2824	GFTFSSS	2953	YTTGD	3082	SGDALPKKYAY	3211	EDSKRPS
clonotype17	2825	GFTFSSY	2954	SGSGGS	3083	TGSSSNIGAGYDVH	3212	GNSNRPS
clonotype25	2826	GYTFTSY	2955	SAYNGN	3084	TGTSSDVGGYNYVS	3213	EVSKRPS
clonotype27	2827	GFTFSSY	2956	SGSGGS	3085	TGTSSDVGGYNYVS	3214	DVSKRPS
clonotype36	2828	GGSFSGY	2957	NHSGS	3086	QGDSLRSYYAS	3215	GKNNRPS
clonotype37	2829	GFTFSSY	2958	WYDGSN	3087	GGNNIGSKSVH	3216	YDSDRPS
clonotype44	2830	GYTFTSY	2959	SAYNGN	3088	SGSSSNIGSNTVN	3217	SNNQRPS
clonotype45	2831	GGSFSGY	2960	NHSGS	3089	TGTSSDVGGYNYVS	3218	EVSKRPS
clonotype47	2832	GFTVSSN	2961	YSGGS	3090	SGSSSNIGNNAVN	3219	YDDLLPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype52	2833	GFTFSTY	2962	SGSSSY	3091	GGNNIGSKNVH	3220	RDSNRPS
clonotype115	2834	GFTFSSY	2963	GTAGD	3092	SGDALPKKYAY	3221	EDSKRPS
clonotype116	2835	GYTFTTY	2964	SAYNGN	3093	TGTSSDVGGYNYVS	3222	EVIKRPS
clonotype118	2836	GFTFSVS	2965	RSKANSYA	3094	SGDKLGDKYAC	3223	QDSKRPS
clonotype119	2837	GFTFSNA	2966	KSKTDGGT	3095	SADALPNQYAY	3224	KDSERPS
clonotype122	2838	GFTFDDY	2967	SWNSGS	3096	SGDALPKKYAY	3225	EDSKRPS
clonotype123	2839	GFTFSDA	2968	KSKTDGGT	3097	SGDALPKKYAY	3226	EDSKRPS
clonotype124	2840	GFTFDDY	2969	NWNGGS	3098	SGDALPKKYAY	3227	EDSKRPS
clonotype125	2841	GFTVSSN	2970	YSGGS	3099	SGDALPKKYAY	3228	EDSKRPS
clonotype126	2842	GYTFTSF	2971	SAYNDN	3100	TGTSSDVGGYNYVS	3229	EVSDRPS
clonotype127	2843	GFTFSGS	2972	RSKANSYA	3101	TGTSSDVGGYNYVS	3230	EVSNRPS
clonotype128	2844	GFTVSSN	2973	YSGGS	3102	TGTSSDVGGYNYVS	3231	DVSKRPS
clonotype130	2845	GFTFSSY	2974	SSSSSY	3103	SGDVLAKKYAR	3232	KDSERPS
clonotype132	2846	GFTFSSY	2975	GTAGD	3104	SADALPKQYAY	3233	KDSERPS
clonotype133	2847	GFTFSSY	2976	SSSSSY	3105	SGDALPKKYAY	3234	EDSKRPS
clonotype134	2848	GFTFSSY	2977	KQDGSE	3106	SGDALPKKYAY	3235	EDSKRPS
clonotype135	2849	GFTFSSY	2978	SGSGGS	3107	SGDALPKKYAY	3236	EDSKRPS
clonotype136	2850	GFTFSSY	2979	SGSGGS	3108	SGDALPKKYAY	3237	EDSKRPS
clonotype137	2851	GFTFSSY	2980	SGSGGS	3109	SGDALPKKYAY	3238	EDSKRPS
clonotype138	2852	GFTFSSY	2981	WYDGSN	3110	GGNNIGSKNVH	3239	RDSNRPS
clonotype140	2853	GFPFSNS	2982	SYDGNS	3111	QGDSLRSYYAS	3240	GKNNRPS
clonotype141	2854	GYTFTGY	2983	NPNSGG	3112	ASSTGAVTSGYYPN	3241	STSNKHS
clonotype143	2855	GFTFSNA	2984	KSKTDGGT	3113	SGSSSNIGSNTVN	3242	SNNQRPS
clonotype145	2856	GYTFTSY	2985	NPNSGN	3114	SGDKLGDKYAC	3243	QDSKRPS
clonotype146	2857	GFTFSSY	2986	SYDGSN	3115	SGDKLGDKYAC	3244	QDSKRPS
clonotype147	2858	GYSFTSY	2987	YPGDSD	3116	SGDKLGDKYAC	3245	QDSKRPS
clonotype148	2859	GFTFSSY	2988	SSSSSY	3117	SGDALPKKYAY	3246	EDSKRPS
clonotype150	2860	GYTFTGY	2989	NPNSGG	3118	SGDALPKKYAY	3247	EDSKRPS
clonotype151	2861	GFTFSSY	2990	GTAGD	3119	SGDALPKKYAY	3248	EDSKRPS
clonotype152	2862	GFTFSNA	2991	KSKTDGGT	3120	SGDALPKKYAY	3249	EDSKRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype153	2863	GFTFSSY	2992	SGSGGS	3121	SGDALPKKYAY	3250	EDSKRPS
clonotype154	2864	GFTFSSY	2993	SGSGGS	3122	SGDALPKKYAY	3251	EDSKRPS
clonotype156	2865	GFTFSSY	2994	SGSGGS	3123	SGDALPKKYAY	3252	EDSKRPS
clonotype157	2866	GFTFSSY	2995	WYDGSN	3124	QGDSLRSYYAS	3253	GKNNRPS
clonotype158	2867	GFTFDDY	2996	NWNGGS	3125	QGDSLRSYYAS	3254	GKNNRPS
clonotype159	2868	GYSFTSY	2997	YPGDSD	3126	SGDALPKKYAY	3255	EDSKRPS
clonotype160	2869	GYTFTGY	2998	NPNSGG	3127	TGTSSDVGGYNYVS	3256	DVSNRPS
clonotype161	2870	GFTFDDH	2999	TWNSNI	3128	TGTSSDVGGYNYVS	3257	EVSNRPS
clonotype162	2871	GFTFDDY	3000	SWNSGS	3129	TGTSSDVGGYNYVS	3258	EVSNRPS
clonotype164	2872	GFTFSSY	3001	NSDGGN	3130	TLRSGIYVGTYRIY	3259	YKSDSDKQQGS
clonotype165	2873	GFTFSSY	3002	KQDGSE	3131	SGDKLGDKYAC	3260	QDSKRPS
clonotype166	2874	GYTFTSY	3003	NPNSGN	3132	SGDKLGDKYAC	3261	QDSKRPS
clonotype167	2875	GFTFSSY	3004	WYDGSN	3133	SGDVLAKKYAR	3262	KDSERPS
clonotype168	2876	GFTFSGS	3005	RSKANSYA	3134	SGDVLAKKYAR	3263	KDSERPS
clonotype169	2877	GFTFSSY	3006	SSSSSY	3135	SGDALPKKYAY	3264	EDSKRPS
clonotype170	2878	GYTLTEL	3007	DPEDGE	3136	SGDALPKKYAY	3265	EDSKRPS
clonotype171	2879	GYTLTEL	3008	DPEDGE	3137	QGDSLRSYYAS	3266	GKNNRPS
clonotype172	2880	GFTFSSY	3009	SSSSST	3138	SGDALPKKYAY	3267	EDSKRPS
clonotype173	2881	GFTFSNA	3010	KSKTDGGT	3139	SGDALPKKYAY	3268	EDSKRPS
clonotype174	2882	GFTFSSY	3011	SSSSSY	3140	ASSTGAVTSGYYPN	3269	STSNKHS
clonotype175	2883	GFTFSSY	3012	SGSGGS	3141	TGTSSDVGGYNYVS	3270	EVSKRPS
clonotype176	2884	GGSISSSD	3013	NHSGT	3142	TGSSSNIGAGYDVH	3271	DNNNRPS
clonotype178	2885	GGSFSGY	3014	NHSGS	3143	QGDSLRNYYAS	3272	GKNNRPS
clonotype179	2886	GFTFSSY	3015	KQDGSE	3144	QGDSLRSYYAS	3273	GKNNRPS
clonotype180	2887	GFSLSTSGV	3016	YWNDD	3145	QGDSLRSYYAS	3274	GKNNRPS
clonotype181	2888	GYTFTSY	3017	SAYNGN	3146	SGDALPKKYAY	3275	EDSKRPS
clonotype182	2889	GFTFSRY	3018	NTAGD	3147	QGDNLRNYSVS	3276	GKNNRPS
clonotype183	2890	GFTFSSS	3019	YTTGD	3148	SGDALPKKYAY	3277	EDSKRPS
clonotype184	2891	GFTFSSY	3020	SSSSST	3149	SGDALPKKYAY	3278	EDSKRPS
clonotype185	2892	GFTFSSY	3021	SGSGGS	3150	SGDALPKKYAY	3279	EDSKRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype186	2893	GFTFSSY	3022	SYDGSN	3151	QGDSLRSYYAS	3280	GKNNRPS
clonotype187	2894	GFTFSDY	3023	SSSGST	3152	GGNNIGSKSVH	3281	YDSDRPS
clonotype188	2895	GFTFSEY	3024	NSDGSR	3153	QGDSLRSYYAN	3282	GKNNRPS
clonotype189	2896	GFTFSSY	3025	NSDGSG	3154	QGDSLRTYYAS	3283	GKNNRPS
clonotype190	2897	GFTFDDY	3026	SWNSGS	3155	SGDALPKKYAY	3284	EDSKRPS
clonotype191	2898	GFTFSDY	3027	SHSGTT	3156	ASSTGAVTSGYYPN	3285	STSNKHS
clonotype192	2899	GFTFSSY	3028	NDSGYS	3157	TGTSSDVGGYNYVS	3286	EVIIRPS
clonotype193	2900	GFTFSSY	3029	GTAGD	3158	TGTSSDVGGYNYVS	3287	EVSNRPS
clonotype194	2901	GFTFSSY	3030	SSSSST	3159	TGTSSDVGGYNYVS	3288	EVSNRPS
clonotype195	2902	GYTLTEL	3031	DPEDGE	3160	SGDKLGDKYAC	3289	QDSKRPS
clonotype196	2903	GFTFSSY	3032	SSSSSY	3161	SGDALPKKYAY	3290	EDSKRPS
clonotype198	2904	GFTFSNY	3033	WSDGSN	3162	GGNNIGSKSVH	3291	YDSDRPS
clonotype199	2905	GFTFSNA	3034	KSKTDGGT	3163	SGDALPKKYAY	3292	EDSKRPS
clonotype200	2906	GYSFTSY	3035	YPGDSD	3164	SGDALPKKYAY	3293	EDSKRPS
clonotype201	2907	GFTFSSY	3036	KQDGSE	3165	ASSTGAVTSGYYPN	3294	STSNKHS
clonotype202	2908	GFSLSTSGV	3037	YWNDD	3166	TGTSSDVGGYNYVS	3295	DVSKRPS
clonotype203	2909	GYTFSSY	3038	SAYNGN	3167	SGSSSNIGNNAVN	3296	HDVLLSS
clonotype204	2910	YMHWVRQ	3039	NYAQKF	3168	SGSSSNIGSNTVN	3297	SNNQRPS
clonotype205	2911	GYTFTDH	3040	NPNSGG	3169	SGSISNIGNNAVS	3298	YDDLLPS
clonotype206	2912	GFTFDDY	3041	SWNSGS	3170	TGTSSDVGGYNYVS	3299	EVSKRPS
clonotype207	2913	GGSITSSN	3042	YHSGN	3171	SGSSSNIGAGYDVH	3300	GNRNRPS
clonotype209	2914	GFTFSSY	3043	SSSSSY	3172	SGDVLAKKYAR	3301	KDSERPS
clonotype210	2915	GYTFTSY	3044	NTNTGN	3173	SGDKLGDKYAC	3302	QDSKRPS
clonotype211	2916	GFTFSSY	3045	SSSSSY	3174	QGDSLRSYYAS	3303	GKNNRPS
clonotype212	2917	GYTLTEL	3046	DPEDGE	3175	GGNNIGSKSVH	3304	YDSDRPS
clonotype213	2918	GYTVTRH	3047	NTNTGT	3176	QGDSLRSYYAS	3305	GKNNRPS
clonotype214	2919	GYAFRGQ	3048	RPNSGD	3177	QGDSLRSYYAS	3306	GKNNRPS
clonotype215	2920	GFTFSDS	3049	RGKPNTYA	3178	TGTSSDVGAYNYVS	3307	DVSKRPS
clonotype217	2921	GFSLSTSGV	3050	YWNDD	3179	SGDKLGDKYAC	3308	QDSKRPS
clonotype218	2922	GYTFTSY	3051	SAYNGN	3180	SGDKLGDKYAC	3309	QDSKRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR2 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype219	2923	GFTFDDY	3052	SWNSGS	3181	SGDKLGDKYAC	3310	QDSKRPS
clonotype220	2924	GFTFDDY	3053	SRNSGS	3182	GENNIVNKNVH	3311	RDGNRPS
clonotype223	2925	GFTFSNA	3054	KSKTDGGT	3183	SGDALPKKYAY	3312	EDSKRPS
clonotype225	2926	GDSVSSNSA	3055	YYRSKWY	3184	SGDALPKKYAY	3313	EDSKRPS
clonotype226	2927	GYTFTRN	3056	DTHTGN	3185	SGSSSNIERTAVN	3314	SNDQRPL
clonotype228	2928	GYTFTTY	3057	SAYNGN	3186	TGNSSNIGADYDVQ	3315	ANIIRPS
clonotype230	2929	GFTFSSY	3058	KQDGSE	3187	SGDALPKKYAY	3316	EDSKRPS
clonotype232	2930	GYTFTSY	3059	SAYNGN	3188	SGDALPKKYAY	3317	EDSKRPS
clonotype234	2931	GFTFSNA	3060	KSKTDGGT	3189	QGDSLRSYYAS	3318	GKNNRPS
clonotype236	2932	GDSVSSNSA	3061	YYRSKWY	3190	SGDALPKKYAY	3319	EDSKRPS
clonotype242	2933	GFTFSTY	3062	SSRSSY	3191	SGDALPKKYAY	3320	EDSKRPS
clonotype245	2934	GYSFTGY	3063	NPNSGG	3192	QGDSLRSYYAS	3321	GKNNRPS
clonotype247	2935	GGSISSSSY	3064	YYSGS	3193	SGDALPKKYAY	3322	EDSKRPS
clonotype248	2936	GDSVSSNSA	3065	YYRSKWY	3194	GGNNIGSKSVH	3323	YDSDRPS
clonotype249	2937	GDSVSSNSA	3066	YYRSKWY	3195	SGDALPKKYAY	3324	EDSKRPS
clonotype251	2938	GGSFSGH	3067	NHSGF	3196	TGTSSDVGVYNYVS	3325	EVSNRPS
clonotype252	2939	GDSVSSNSA	3068	YYRSKWY	3197	TGTSSDVGGYNYVS	3326	EVSNRPS
clonotype255	2940	GFIFSSY	3069	SGSSSF	3198	QGDSLRSYYAS	3327	GKNNRPS
clonotype261	2941	GFDFTNA	3070	KSKTDGGS	3199	TGSSSNIGAGYAVH	3328	GNINRPS
clonotype262	2942	RFTFSSA	3071	KTKTEGGT	3200	SCSGSSSNIGAGYA	3329	IYGNLNR
clonotype263	2943	GGSISSSSY	3072	YYSGS	3201	TLRSGINVGTYRIY	3330	YKSDSDKQQGS
clonotype264	2944	GGSISSSSY	3073	YYSGS	3202	SGDKLGDKYAC	3331	QDSKRPS
clonotype266	2945	GGSFSGY	3074	NHSGS	3203	GGNNIGSKSVH	3332	YDSDRPS
clonotype269	2946	GGSISSSSY	3075	YYSGS	3204	SGDALPKKYAY	3333	EDSKRPS
clonotype270	2947	GGSFSGY	3076	NHSGS	3205	SGDKLGDKYAC	3334	QDSKRPS
clonotype272	2948	GYTFTSY	3077	NPKNGY	3206	TGSSSNIGAGYDVH	3335	GNSNRPS

[00657] Table 16: VH-CDR1, VH-CDR2, VL-CDR1, and VL-CDR2 Sequences for EPOR/CD131 Binders

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR1 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype7	3336	GYTFTSY	3472	NPNSGN	3608	SGDKLGDKYAC	3744	QDSKRPS
clonotype9	3337	GGTFSSY	3473	IPIFGT	3609	TGTSSDVGGYNYVS	3745	DVSKRPS
clonotype14	3338	GGSISSSSY	3474	YYSGS	3610	TGTSSDVGGYNYVS	3746	DVSKRPS
clonotype15	3339	GFTFSSY	3475	SSSSTY	3611	TGTSSDVGGYNYVS	3747	EVSNRPS
clonotype17	3340	GFTFSSY	3476	GTAGD	3612	GGNNIGSKNVH	3748	RDSNRPS
clonotype19	3341	GFTFSDY	3477	SSSGST	3613	TGTSSDVGGYNYVS	3749	EVSNRPS
clonotype22	3342	GFTFSTD	3478	SGSSSY	3614	SGDALPKKYAY	3750	EDSKRPS
clonotype29	3343	GFTVSSN	3479	YSGGS	3615	TGTSSDVGGYNYVS	3751	EVSKRPS
clonotype32	3344	GGSISSSSY	3480	YYSGS	3616	TLSSEHSTYTIE	3752	VKSDGSHSKGD
clonotype38	3345	GYTFTSY	3481	SAYNGN	3617	GGNNIGSKSVH	3753	YDSDRPS
clonotype42	3346	GFTFSSY	3482	KQDGSE	3618	SGDKLGDKYAC	3754	QDSKRPS
clonotype43	3347	GYTFTSY	3483	NPNSGN	3619	SGDKLGDKYAC	3755	QDSKRPS
clonotype44	3348	GFTFSSY	3484	GTAGD	3620	GGNNIGSKNVH	3756	RDSNRPS
clonotype45	3349	GFTFSSY	3485	SSSSSY	3621	SGDVLAKKYAR	3757	KDSERPS
clonotype56	3350	GFTFSSY	3486	SSSSSY	3622	SGDALPKKYAY	3758	EDSKRPS
clonotype57	3351	GYTFISY	3487	NTNTGN	3623	GSSTGAVTSGHYPY	3759	DTSNKHS
clonotype65	3352	GFTVSSN	3488	YSGGS	3624	TGTSSDVGGYNYVS	3760	EVSNRPS
clonotype68	3353	GFTFSSY	3489	SSSSSY	3625	TGTSSDVGGYNYVS	3761	EVSKRPS
clonotype70	3354	GFTVSSN	3490	YSGGS	3626	TGSSSNIGAGYDVH	3762	GNSNRPS
clonotype72	3355	GDSVSSNSA	3491	YYRSKWY	3627	TGTSSDVGGYNYVS	3763	DVSKRPS
clonotype74	3356	GYSFSSY	3492	YPGDSD	3628	EGDNIGSESVH	3764	FDSDRPS
clonotype215	3357	GFTFSSY	3493	NSDGSS	3629	TGTSSDVGGYNYVS	3765	EVSNRPS
clonotype216	3358	GFTFSSY	3494	KQDGSE	3630	SGDALPKKYAY	3766	EDSKRPS
clonotype219	3359	GGSISSY	3495	YYSGS	3631	SGDVLAKKYAR	3767	KDSERPS
clonotype221	3360	GFTFINA	3496	KSKTDGGT	3632	SADALPNQYAY	3768	KDSERPS
clonotype223	3361	GFTFSNA	3497	KSKTDGGT	3633	SADALSKQYAY	3769	KDSERPS
clonotype224	3362	GFTFSNA	3498	KSKTDGGT	3634	SGDALPKKYAY	3770	EDSKRPS
clonotype225	3363	GYTFTSY	3499	SAYNGN	3635	TGTSSDVGGYNYVS	3771	EVSNRPS
clonotype226	3364	GFTFSTY	3500	SGGGGS	3636	TGTSSDVGGYNYVS	3772	EVSNRPS
clonotype228	3365	GFTFSSY	3501	GTAGD	3637	SGDALPKKYAY	3773	EDSKRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR1 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype229	3366	GFTFSRY	3502	NQDGSE	3638	TGTSSDVGGYDYVS	3774	GVSNRPS
clonotype230	3367	GFTFSRC	3503	GAAGD	3639	TLRSGINVGTYRIY	3775	YKSDSDKQQGS
clonotype231	3368	GFTFINY	3504	WYDGSN	3640	SGDVLAKKYAR	3776	KDSERPS
clonotype232	3369	GFTFSSY	3505	NSDGSS	3641	SGDVLAKKYAR	3777	KDSERPS
clonotype233	3370	GFTFDDY	3506	SWNSGS	3642	SGDALPKKYAY	3778	EDSKRPS
clonotype234	3371	GYTFTSY	3507	SAYNGN	3643	SGDALPKKYAY	3779	EDSKRPS
clonotype235	3372	GYTFTSY	3508	NPSGGS	3644	QGDSLRSYYAS	3780	GKNNRPS
clonotype236	3373	GFTFSSY	3509	GTAGD	3645	QGDSLRSYYAS	3781	GKNNRPS
clonotype237	3374	GFTFSSY	3510	SGSGGS	3646	SGDALPKKYAY	3782	EDSKRPS
clonotype238	3375	GFTFSSY	3511	WYDGSN	3647	SGDALPKKYAY	3783	EDSKRPS
clonotype239	3376	GFSFSSH	3512	SGISNY	3648	TGTNNDVGYYNYVS	3784	DVIKRPS
clonotype240	3377	GFTFSSY	3513	SGSGGN	3649	TGTSSDVGGYNYVS	3785	EVSKRPS
clonotype241	3378	GYTFTSY	3514	NPSGGT	3650	TGTSSDVGNYNYVS	3786	EVIYRPS
clonotype242	3379	GFTFSSY	3515	KQDGSE	3651	TGSSSNIGAGYDVH	3787	GNSNRPS
clonotype243	3380	GYTFTSY	3516	SAYNGN	3652	TGTSSDVGGYNYVS	3788	DVSKRPS
clonotype244	3381	GYTFTNY	3517	SAYNGN	3653	TGTSSDVGGYNYVS	3789	DVSKRPS
clonotype246	3382	GFTFSSY	3518	SSSSST	3654	QGDSLRSYYAS	3790	GKNNRPS
clonotype247	3383	GFTFSSY	3519	GTAGD	3655	SGEALPKKYAY	3791	KDSERPS
clonotype249	3384	GYTFTSY	3520	IPNSGN	3656	TGTSSDVGGYNYVS	3792	EVSHRPS
clonotype250	3385	GYTFTSY	3521	NPSGGS	3657	TGTSSDVGGYNYVS	3793	EVSNRPS
clonotype251	3386	GFTFSNA	3522	KSKTDGGT	3658	TGTSSDVGGYNYVS	3794	DVTTRPS
clonotype252	3387	GFTFSNY	3523	WYDGNN	3659	TGTSSDVGGYNYVS	3795	EVSNRPS
clonotype253	3388	GFTFSSY	3524	WYDGSN	3660	TGTSSDVGGYNYVS	3796	EVSNRPS
clonotype254	3389	GFTFDDY	3525	NWNGGS	3661	TGTSSDVGGYNYVS	3797	EVSKRPS
clonotype255	3390	GFTFSSY	3526	SSSSSY	3662	TGTSSDVGGYNYVS	3798	EVSKRPS
clonotype256	3391	GFTFSSY	3527	SGSGGS	3663	TGTSSDVGGYNYVS	3799	EVSNRPS
clonotype259	3392	GFTFSSY	3528	GTAGD	3664	SGDKLGDKYAC	3800	QDSKRPS
clonotype260	3393	GFPFDDF	3529	NWNGGT	3665	SGDVLAKKYAR	3801	KDSERPS
clonotype262	3394	GFSISIN	3530	SSSSTY	3666	SGDALPKKYAY	3802	EDSKRPS
clonotype264	3395	GFTFSSY	3531	NSDGSS	3667	QGDSLRSYYAS	3803	GKNNRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR1 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype265	3396	GFTFSTY	3532	SSSSTY	3668	TGTSSDVGGYNYVS	3804	EVSNRPS
clonotype266	3397	GFTFSSY	3533	SGSGGS	3669	TGSSSNIGAGYDVH	3805	GNSNRPS
clonotype270	3398	GYTFTTY	3534	SGYSGY	3670	SRDKLGDKYAC	3806	QDSKRPS
clonotype271	3399	GFTFSSY	3535	SRSSGT	3671	SGDKLGDRYAC	3807	QGSKRPS
clonotype272	3400	GFTFNRY	3536	SSSSDT	3672	QGDSLRSYYAS	3808	GKNNRPS
clonotype273	3401	GGSISSSN	3537	YHSGS	3673	SGDKLENKYTC	3809	QDNKRPS
clonotype274	3402	GFTFSIY	3538	NLDGSE	3674	QGDNIRNYYAS	3810	GKNNRPS
clonotype275	3403	GFTFSGY	3539	KHDGSE	3675	QGDSLRRYYAS	3811	GKDNRPS
clonotype276	3404	GYTFTTY	3540	SAFNGN	3676	QGDSLRSYYAS	3812	GKNNRPS
clonotype277	3405	GFTFSSY	3541	GTAGD	3677	SGDALPKKYAY	3813	EDSKRPS
clonotype278	3406	GFTFSNA	3542	KSKTDGGT	3678	SGDALPKKYAY	3814	EDSKRPS
clonotype279	3407	GFTFSSY	3543	SGGGGS	3679	SGDALPKKYAY	3815	EDSKRPS
clonotype280	3408	GFTFSSY	3544	WYDGSN	3680	SGDALPKKYAY	3816	EDIKRPS
clonotype281	3409	GFTFSSY	3545	SSSSSY	3681	TGTSSDVGGYNYVS	3817	DVSKRPS
clonotype282	3410	GFTFSSY	3546	SSSSSY	3682	TGTSSDVGGYNYVS	3818	DVSKRPS
clonotype283	3411	GYTFTGY	3547	NPNSGG	3683	TGTSSDVGGYNYVS	3819	EVSKRPS
clonotype284	3412	GFTFSNA	3548	KSKTDGGT	3684	TGTSSDVGGYNYVS	3820	EVSNRPS
clonotype286	3413	GYTFTGY	3549	NPNSGG	3685	SGDKLGDKYAC	3821	QDSKRPS
clonotype287	3414	GYTFTSY	3550	NPNSGN	3686	SGDKLGDKYAC	3822	QDSKRPS
clonotype288	3415	GFTFSNA	3551	KSKTDGGT	3687	SGDVLAKKYAR	3823	KDSERPS
clonotype289	3416	GFTFSGY	3552	KQDGSD	3688	SGDALPQKYAF	3824	EDSERPS
clonotype290	3417	GYTFTSY	3553	NPNSGN	3689	SGDALPKKYAY	3825	EDSKRPS
clonotype291	3418	GFTFSSY	3554	WYDGSN	3690	SGDALPKKYAY	3826	EDSKRPS
clonotype292	3419	GGSISDY	3555	SSRGR	3691	QGDSLRSYYAS	3827	GKNNRPS
clonotype293	3420	GFTFSSD	3556	GSSSSY	3692	QGDSLRNYYAS	3828	GKNNRPS
clonotype294	3421	GFTFSSY	3557	SSSSSY	3693	QGDSLRSYYAS	3829	GKNNRPS
clonotype295	3422	GFTFSSY	3558	SSSSSY	3694	SGDALPKKYAY	3830	EDSKRPS
clonotype296	3423	GYTFTSY	3559	SAYNGN	3695	QGDSLRSYYAS	3831	GKNNRPS
clonotype297	3424	GYTFTDH	3560	NPNSGG	3696	QGDSLRSYYAS	3832	GKNNRPS
clonotype298	3425	GYTFTGY	3561	NPNSGG	3697	QGDSLRSYYAS	3833	GKNNRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR1 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype300	3426	GFTFSSY	3562	NSDGSN	3698	QGDSLRSYYAS	3834	GQNNRPS
clonotype301	3427	GDNVSSNSA	3563	YYRSKWY	3699	QGDSLRSYYAS	3835	GKNNRPS
clonotype302	3428	GYTFTSY	3564	SAYNGN	3700	SGSSSNIGYNAVN	3836	HDDLLPS
clonotype303	3429	GYTFTGY	3565	NPNSGG	3701	TGTSSDVGGYNYVS	3837	DVSKRPS
clonotype304	3430	GFTFSRY	3566	ISSTSY	3702	TGSSSNIGARYDVH	3838	DNSDRPS
clonotype305	3431	GFTFDEY	3567	SWNSGS	3703	TGSSSNIGAGYDVH	3839	GNSNRPS
clonotype306	3432	GFTFSSY	3568	WYDGSN	3704	TGSSSNIGAGYDVH	3840	GNSNRPS
clonotype307	3433	GFSISTSGV	3569	FWNDD	3705	TLRSGINVGTSRIY	3841	YKSDSDKHQDS
clonotype308	3434	GFTFDDY	3570	NWNGGS	3706	TLRSGINVGTYRIY	3842	YKSDSDKQQGS
clonotype309	3435	GYTFTSY	3571	NPNSGN	3707	SGAKLGDKYAC	3843	QDRKRPS
clonotype310	3436	GFTFSSY	3572	SSSSSY	3708	SGDALPKKYAY	3844	EDSKRPS
clonotype316	3437	GFTFSSY	3573	KQDGSE	3709	QGDSLRSYYAS	3845	GKNNRPS
clonotype318	3438	GDSVSSNSA	3574	YYRSKWY	3710	SGDKLGDKYAC	3846	QDSKRPS
clonotype319	3439	GFTFSTY	3575	SSSSTY	3711	QGDSLRSYYAS	3847	GKNNRPS
clonotype320	3440	GFSLSTSGM	3576	DWDDD	3712	SGDALPKKYAY	3848	EDSKRPS
clonotype322	3441	EFIFRSY	3577	SISSRT	3713	SGDALPKKYAY	3849	EDSKRPS
clonotype323	3442	GFTFSDY	3578	SSSGST	3714	SGDALPKKYAY	3850	EDSKRPS
clonotype326	3443	GFTFSSY	3579	SSSSST	3715	TGSSSNIGAGYDVH	3851	GNSNRPS
clonotype327	3444	GYTFTSY	3580	NPNSGN	3716	TLRSGINVGTYRIY	3852	YKSDSDKQQGS
clonotype328	3445	GGSISSGGY	3581	YYSGS	3717	SGDKLGDKYAC	3853	QDSKRPS
clonotype333	3446	GFTFSSY	3582	KQDGSE	3718	QGDSLRRYYAS	3854	GKNNRPS
clonotype339	3447	GFTFSSY	3583	SSSSST	3719	SGDALPKKYAY	3855	EDSKRPS
clonotype340	3448	GFTFSSY	3584	SGSGGS	3720	SGDALPKKYAY	3856	EDSKRPS
clonotype341	3449	GFTFSSY	3585	WYDGSN	3721	GGNNIGGKSVH	3857	YNRDRPS
clonotype342	3450	GFTFRNA	3586	KTKTDGGA	3722	SGSNSNIGFNTVN	3858	SNNQRPS
clonotype343	3451	GYTFTSY	3587	SAYNGN	3723	TGTSSDVGGYNYVS	3859	EVSKRPS
clonotype345	3452	GDSVSSNSA	3588	YYRSKWY	3724	TGTSSDVGGYNYVS	3860	EVSKRPS
clonotype349	3453	GFTFSSY	3589	SSSSSY	3725	SGDKLGNKYAC	3861	QDNKRPS
clonotype350	3454	GFTFSSY	3590	SSSTST	3726	SGDKLGDKYAC	3862	QDIKRPS
clonotype351	3455	GFTFSNA	3591	KSKTDGGT	3727	SGDKLGDKYAC	3863	QDSMRPS

clonotype_id	SEQ ID NO	HCDR1 AA	SEQ ID NO	HCDR1 AA	SEQ ID NO	LCDR1 AA	SEQ ID NO	LCDR2 AA
clonotype352	3456	GDSVSSNSA	3592	YYRSKWY	3728	SGDKLGDKYAC	3864	QDSKRPS
clonotype356	3457	GFTFSSY	3593	KQDGSE	3729	SGDALPKKYAY	3865	EDSKRPS
clonotype358	3458	GGSITTRSY	3594	YYSGN	3730	SGDALPKKYAY	3866	EDSKRPS
clonotype359	3459	GGSISTRSY	3595	YYSGS	3731	SGSSSNIGINTVN	3867	FNNQRPS
clonotype360	3460	GGSFSGH	3596	NHSGF	3732	ASSTGAVTSGYYPN	3868	STSNKHS
clonotype361	3461	GGFLRGY	3597	NHSGS	3733	TGTSSDVGGYNYVS	3869	DVSKRPS
clonotype363	3462	GYIFSNY	3598	NPYNVN	3734	SGNLLAKKYPR	3870	TDCERPS
clonotype364	3463	GFTFSSY	3599	SSSSSY	3735	QGDSLRSYYAS	3871	GKNNRPS
clonotype365	3464	GFTFTSY	3600	TPSGGT	3736	SGDALPKKYAY	3872	EDSKRPS
clonotype366	3465	GGSISTRSY	3601	FYSGS	3737	TGTSSDVGGYNYVS	3873	EVSKRPS
clonotype367	3466	GGSFSVY	3602	NHSGS	3738	SGSSSNIGSKTVN	3874	SSNQRPS
clonotype368	3467	GGSISSIIY	3603	YYSGS	3739	GENNIGSRNVH	3875	RDSDRPS
clonotype369	3468	GGSFSGY	3604	NHSGN	3740	QGDSLRSYYAS	3876	GKNNRPS
clonotype370	3469	GGSFSGY	3605	NHSGS	3741	SGDALPKKYAY	3877	EDSKRPS
clonotype379	3470	GYTFITY	3606	SAYNGN	3742	TGTSSDVGGYNYVS	3878	DVSKRPS
clonotype380	3471	GYTFITY	3607	SSYNGN	3743	TGTSSDVGGYNHVS	3879	DVSKRPS

[00658] It is understood that, while particular embodiments have been illustrated and described, various modifications may be made thereto and are contemplated herein. It is also understood that the disclosure is not limited by the specific examples provided herein. The description and illustration of embodiments and examples of the disclosure herein are not intended to be construed in a limiting sense. It is further understood that all aspects of the disclosure are not limited to the specific depictions, configurations or relative proportions set forth herein, which may depend upon a variety of conditions and variables. Various modifications and variations in form and detail of the embodiments and examples of the disclosure will be apparent to a person skilled in the art. It is therefore contemplated that the disclosure also covers any and all such modifications, variations and equivalents.

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising an antibody or a functional fragment thereof, wherein:
(i) said antibody or said functional fragment thereof selectively binds to a target comprising an erythropoietin (EPO) protein, an EPO receptor subunit, a CD131 subunit, or a combination thereof;
(ii) binding of said antibody or said functional fragment thereof to said target prevents (a) formation of an EPO protein-hetero-EPO receptor complex, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit, (b) formation of a hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit or (c) activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit; and
(iii) said antibody or said functional fragment thereof comprises an antigen binding domain.

2. The composition of claim 1, wherein said antigen binding domain comprises:
a heavy chain variable region (VH) comprising a VH complementarity determining region 1 (VH-CDR1) sequence, a VH-CDR2 sequence, and a VH-CDR3 sequence; and a light chain variable region (VL) comprising a VL-CDR1 sequence, a VL-CDR2 sequence, and a VL-CDR3 sequence;
a VH and a kappa chain variable regions (VK);
or a VH and a lambda chain variable regions.

3. The composition of claim 1 or 2, wherein said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit inhibits immune tolerance.

4. The composition of claim 3, wherein said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit promotes differentiation of a plurality of naïve T cells into a plurality of effector T cells.

5. The composition of claim 4, wherein said plurality of effector T cells expresses Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα).

6. The composition of claim 3, wherein said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit inhibits differentiation of a plurality of naïve T cells into a plurality of regulatory T cells.

7. The composition of claim 6, wherein said plurality of regulatory T cells expresses Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4).

8. The composition of claim 1 or 2, wherein said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit increases a plurality of progenitor exhausted T cells.

9. The composition of claim 8, wherein said plurality of progenitor exhausted T cells expresses Cluster of Differentiation 44 (CD44), Signaling lymphocyte activation molecule family member 6 (SLAMF6) or T cell factor 1 (TCF1).

10. The composition of claim 1 or 2, wherein said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit stimulates immune response in cancer.

11. The composition of claim 1 or 2, wherein said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit renders cancer cells sensitive to an immune checkpoint inhibitor.

12. The composition of claim 11, wherein said immune checkpoint inhibitor comprises a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) inhibitor, a Programmed Death 1 (PD-1) inhibitor, or a Programmed Death Ligand 1 (PD-L1) inhibitor.

13. The composition of claim 12, wherein said CTLA-4 inhibitor comprises an anti-CTLA-4 antibody.

14. The composition of claim 12, wherein said PD-1 inhibitor comprises an anti-PD-1 antibody.

15. The composition of claim 12, wherein said PD-L1 inhibitor comprises an anti-PD-L1 antibody.

16. The composition of claim 1 or 2, wherein said preventing formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit attenuates tumor growth.

17. The composition of any one of claims 1-16, wherein said antibody or said functional fragment thereof is an IgG, an IgM, an IgE, an IgA, an IgD, is derived therefrom, or a combination thereof.

18. The composition of any one of claims 1-17, wherein said antibody or said functional fragment thereof comprises a monoclonal antibody, a grafted antibody, a chimeric antibody, a human antibody, a humanized antibody, or a combination thereof.

19. The composition of any one of claims 1-18, wherein said antigen binding domain comprises a Fab, a Fab', a $(Fab')_2$, a variable fragment (Fv), a single chain variable fragment (scFv), a scFv-Fc, a Fab-Fc, a VHH, a non-antibody scaffold, or a combination thereof.

20. The composition of any one of claims 1-19, wherein said antigen binding domain is isolated, recombinant, synthetic, or a combination thereof.

21. The composition of any one of claims 2-20, wherein said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 63-250.

22. The composition of any one of claims 2-20, wherein said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 815-943.

23. The composition of any one of claims 2-20, wherein said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1331-1466.

24. The composition of any one of claims 2-20, wherein said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 251-438.

25. The composition of any one of claims 2-20, wherein said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 944-1072.

26. The composition of any one of claims 2-20, wherein said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1467-1602.

27. The composition of any one of claims 2-20, wherein said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 439-626.

28. The composition of any one of claims 2-20, wherein said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1073-1201.

29. The composition of any one of claims 2-20, wherein said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1603-1738.

30. The composition of any one of claims 2-20, wherein said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 627-814.

31. The composition of any one of claims 2-20, wherein said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1202-1330.

32. The composition of any one of claims 2-20, wherein said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1739-1874.

33. The composition of any one of claims 2-20, wherein said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1739-1955.

34. The composition of any one of claims 2-20, wherein said VK comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1956-1972.

35. A composition comprising a nucleic acid sequence encoding said antibody or said functional fragment thereof of the composition of any one of claims 1-34.

36. A cell comprising the composition of any one of claims 1-35.

37. A method of treating a disease or a condition in a subject in need thereof, said method comprising administering to said subject the composition of any one of claims 1-35.

38. The method of claim 37, further comprising inhibiting immune tolerance in said subject.

39. The method of claim 38, wherein said inhibiting immune tolerance comprises increasing immune response to a vaccine, when said vaccine is administered to said subject.

40. The method of claim 38, wherein said inhibiting immune tolerance comprises increasing immune response to a viral or bacterial infection in said subject.

41. The method of claim 38, wherein said inhibiting immune tolerance comprises increasing immune response to an antigen produced by cancer.

42. The method of claim 37, wherein said disease or said condition comprises a cancer or an infection.

43. The method of claim 42, wherein said cancer comprises a lung cancer, a breast cancer, a colon cancer, a brain cancer, a melanoma, hepatocarcinoma, or a liver cancer.

44. The method of claim 42, wherein said cancer is a melanoma.

45. The method of claim 42, wherein said cancer is a liver cancer.

46. The method of claim 42, wherein said cancer is a colon cancer.

47. The method of claim 42, wherein said cancer is a breast cancer.

48. A method for treating cancer, wherein said method comprises administering a composition or a derivative thereof to a subject having cancer or at risk of having cancer, wherein said composition or said derivative thereof inhibits a hetero-erythropoietin (EPO) receptor activity in said subject.

49. The method of claim 48, wherein said hetero-EPO receptor is expressed on a myeloid cell.

50. A composition comprising an antibody or a functional fragment thereof, wherein:
(i) said antibody or said functional fragment thereof selectively binds to a target comprising an erythropoietin (EPO) protein, an EPO receptor subunit, a CD131 subunit, or a combination thereof;
(ii) binding of said antibody or said functional fragment thereof to said target promotes (a) formation of an EPO protein-hetero-EPO receptor complex, wherein said hetero-EPO

receptor comprises said EPO receptor subunit and said CD131 subunit, (b) formation of a hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or (c) activation of a hetero-EPO receptor, wherein said hetero-EPO receptor comprises said EPO receptor subunit and said CD131 subunit; and

(iii) said antibody or said functional fragment thereof comprises an antigen binding domain.

51. The composition of claim 50, wherein said antigen binding domain comprises:
a heavy chain variable region (VH) comprising a VH complementarity determining region 1 (VH-CDR1) sequence, a VH-CDR2 sequence, and a VH-CDR3 sequence; and a light chain variable region (VL) comprising a VL-CDR1 sequence, a VL-CDR2 sequence, and a VL-CDR3 sequence, or
a VH and a kappa chain variable regions (VK),
or a VH and a lamda chain variable regions.

52. The composition of claim 50 or claim 51, wherein said hetero-EPO receptor is expressed on a myeloid cell.

53. The composition of any one of claims 50-52, wherein said promoting formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit induces antigen-specific immune tolerance.

54. The composition of claim 52, wherein said promoting formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit inhibits differentiation of a plurality of naïve T cells into a plurality of effector T cells.

55. The composition of claim 54, wherein said plurality of effector T cells expresses Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα).

56. The composition of claim 52, wherein said promoting formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit promotes differentiation of a plurality of naïve T cells into a plurality of regulatory T cells.

57. The composition of claim 56, wherein said plurality of regulatory T cells expresses Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4).

58. The composition of any one of claims 50-57, wherein said antibody or said functional fragment thereof does not affect a homo-EPO receptor activity.

59. The composition of any one of claims 50-57, wherein said antibody or said functional fragment thereof does not bind a homo-EPO receptor comprising at least two EPO receptor subunits.

60. The composition of any one of claims 50-59, wherein said promoting formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit reduces immune reaction when administered to a subject having an autoimmune disease or a subject with a transplanted organ.

61. The composition of claim 60, wherein said transplanted organ comprises bone marrow, kidney, liver, lung, or heart.

62. The composition of claim 60, wherein said autoimmune disease comprises a rheumatoid arthritis, a systemic lupus erythematosus, or a multiple sclerosis.

63. The composition of any one of claims 50-59, wherein said promoting formation of said EPO protein-hetero-EPO receptor complex, formation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit, or activation of said hetero-EPO receptor between said EPO receptor subunit and said CD131 subunit reduces systemic chronic inflammation when administered to a subject suffering from a systemic chronic inflammation.

64. The composition of any one of claims 50-63, wherein said antibody or said functional fragment thereof is an IgG, an IgM, an IgE, an IgA, an IgD, is derived therefrom, or a combination thereof.

65. The composition of any one of claims 50-64, wherein said antibody or said functional fragment thereof comprises a monoclonal antibody, a grafted antibody, a chimeric antibody, a human antibody, a humanized antibody, or a combination thereof.

66. The composition of any one of claims 50-65, wherein said antigen binding domain comprises a Fab, a Fab', a $(Fab')_2$, a variable fragment (Fv), a single chain variable fragment (scFv), a scFv-Fc, a Fab-Fc, a VHH, a non-antibody scaffold, or a combination thereof.

67. The composition of any one of claims 50-66, wherein said antigen binding domain is isolated, recombinant, synthetic, or a combination thereof.

68. The composition of any one of claims 51-67, wherein said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 63-250.

69. The composition of any one of claims 51-67, wherein said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 815-943.

70. The composition of any one of claims 51-67, wherein said VH-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1331-1466.

71. The composition of any one of claims 51-67, wherein said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 251-438.

72. The composition of any one of claims 51-67, wherein said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 944-1072.

73. The composition of any one of claims 51-67, wherein said VL-CDR3 comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1467-1602.

74. The composition of any one of claims 51-67, wherein said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NO: 439-626.

75. The composition of any one of claims 50-67, wherein said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1073-1201.

76. The composition of any one of claims 50-67, wherein said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NO: 1603-1738.

77. The composition of any one of claims 50-67, wherein said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 627-814.

78. The composition of any one of claims 50-67, wherein said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1202-1330.

79. The composition of any one of claims 50-67, wherein said VL comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1739-1874.

80. The composition of any one of claims 50-67, wherein said VH comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1739-1955.

81. The composition of any one of claims 50-67, wherein said VK comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1956-1972.

82. The composition of any one of preceding claims, wherein said antibody further comprises a binding domain that selectively binds to an antigen associated with tumor, a cell surface marker associated with immune cells, or a signaling molecule associated with immune cells.

83. The composition of claim 82, wherein said antigen associated with tumor is selected from the group consisting of PD1, HER2, EpCAM, CEA, CEACAM5, EGFR, CD33, CD19, CD20, CD22, and any combinations thereof.

84. The composition of claim 82, wherein said cell surface marker is DEC205, XCR1, or XCL1.

85. The composition of claim 82, wherein said signaling molecule is PD-L1, Tim3, or TREM2.

86. A composition comprising a nucleic acid sequence encoding said antibody or said functional fragment thereof of the composition of any one of claims 50-85.

87. A cell comprising the composition of any one of claims 50-86.

88. A method of treating a disease or a condition in a subject in need thereof, said method comprising administering to said subject the composition of any one of claims 50-86.

89. The method of claim 88, wherein said disease or said condition comprises an autoimmune disease.

90. The method of claim 88, wherein said subject has received or is to receive an organ transplant or a foreign therapeutics protein.

91. A composition for administering to a subject having cancer or chronic infection condition, wherein said composition or derivative thereof inhibits erythropoietin (EPO) receptor activity in a myeloid cell in said subject.

92. The composition of claim 91, wherein said composition is an antibody or a functional fragment thereof.

93. The composition of claim 91, wherein said myeloid cell is selected from the group consisting of a macrophage, a monocyte, a dendritic cell, a basophil, a neutrophil, and an eosinophil.

94. The composition of claim 91, wherein said EPO receptor comprises a homo-EPO receptor comprising at least two EPO receptor subunits or a hetero-EPO receptor comprising an EPO receptor subunit and a CD131 subunit.

95. The composition of claim 91, wherein said EPO receptor is a hetero-EPO receptor comprising a EPO receptor subunit and a CD131 subunit.

96. The composition of claim 91, wherein said composition is an antibody or a functional fragment thereof.

97. The composition of any one of claims 91-96, wherein said composition is a soluble fragment of a EPO receptor.

98. The composition of claim 97, wherein said soluble fragment is capable of binding to EPO to form a complex.

99. The composition of claim 98, wherein said complex is capable of preventing a EPO receptor activity.

100. The composition of claim 91, wherein said composition or derivative thereof comprises an engineered erythropoietin (EPO) protein, wherein said engineered EPO protein inhibits a hetero-erythropoietin (EPO) receptor activity in a myeloid cell.

101. A composition comprising an engineered erythropoietin (EPO) protein, wherein said engineered EPO protein inhibits a hetero-erythropoietin (EPO) receptor activity in a myeloid cell.

102. The composition of claim 100 or 101, wherein said engineered EPO protein comprises at least one amino acid substitution comprising:
K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A, R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A.

103. The composition of claim 101 or 102, wherein said composition or derivative thereof inhibits immune tolerance.

104. The composition of claim 101 or 102, wherein said composition or derivative thereof promotes immune response.

105. The composition of claim 101 or 102, wherein said composition or derivative thereof promotes differentiation of a plurality of naïve T cells into a plurality of effector T cells.

106. The composition of claim 105, wherein said plurality of effector T cells expresses Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα).

107. The composition of claim 101 or 102, wherein said composition or derivative thereof inhibits differentiation of a plurality of naïve T cells into a plurality of regulatory T cells.

108. The composition of claim 107, wherein said plurality of regulatory T cells expresses Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4).

109. The composition of claim 101 or 102, wherein said composition or derivative thereof increases a plurality of progenitor exhausted T cells.

110. The composition of claim 109, wherein said plurality of progenitor exhausted T cells expresses Cluster of Differentiation 44 (CD44), Signaling lymphocyte activation molecule family member 6 (SLAMF6) or T cell factor 1 (TCF1).

111. The composition of claim 101 or 102, wherein said composition or derivative thereof stimulates immune response in cancer.

112. The composition of claim 101 or 102, wherein said composition or derivative thereof renders cancer cells sensitive to an immune checkpoint inhibitor.

113. The composition of claim 112, wherein said immune checkpoint inhibitor comprises a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) inhibitor, a Programmed Death 1 (PD-1) inhibitor, or a Programmed Death Ligand 1 (PD-L1) inhibitor.

114. The composition of claim 113, wherein said CTLA-4 inhibitor comprises an anti-CTLA-4 antibody.

115. The composition of claim 113, wherein said PD-1 inhibitor comprises an anti-PD-1 antibody.

116. The composition of claim 113, wherein said PD-L1 inhibitor comprises an anti-PD-L1 antibody.

117. The composition of claim 101 or 102, wherein said composition or derivative thereof reduces a size of said cancer or attenuates the growth of said cancer.

118. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises R103A.

119. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises E72A.

120. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises Q58A.

121. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises L69A.

122. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises L80A.

123. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises N147K or R103A.

124. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises R150E or R103A.

125. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises Q65A or E72R.

126. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises Q65A, E72R, or N83A.

127. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises K20A, K45A, or K52A.

128. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises K140A or K152A.

129. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises K140A, K152A, or K154A.

130. The composition of any one of claims 102-117, wherein said at least one amino acid substitution comprises K20A, K45A, K52A, K140A, K152A, or K154A.

131. The composition of any one of claims 102-130, wherein the position is determined by alignment with SEQ ID NO: 1.

132. The composition of any one of claims 101-131, wherein said engineered EPO further comprises an amino acid modification comprising carbamylation or PEGylation.

133. The composition of claim 132, wherein said amino acid modification comprises carbamylation of one or more lysine residues.

134. The composition of any one of claims 101-133, wherein said engineered EPO protein has a lower binding affinity to a hetero-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

135. The composition of any one of claims 101-134, wherein said hetero-EPO receptor activity comprises phosphorylation of an intracellular domain of said hetero-EPO receptor or activation of Janus tyrosine kinase 2 (Jak2), Signal transducer and activator of transcription 5 (Stat5), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), or Mammalian target of rapamycin (mTOR).

136. The composition of any one of claims 101-135, wherein said hetero-EPO receptor activity is measured by a western blotting, an enzyme-linked immunosorbant assay (ELISA), a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or a combination thereof.

137. The composition of any one of claims 101-136, wherein said engineered EPO protein has a higher binding affinity to a homo-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

138. The composition of any one of claims 101-136, wherein said engineered EPO protein has the same level of binding affinity to a homo-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

139. The composition of any one of claims 101-136, wherein said engineered EPO protein binds to a homo-EPO receptor with a binding affinity that is lower than a binding affinity to a hetero-EPO receptor.

140. The composition of any one of claims 101-136, wherein said engineered EPO protein does not affect or inhibit a homo-EPO receptor activity.

141. The composition of any one of claims 101-140, wherein said engineered EPO has a half-life of at least 5 hours.

142. The composition of any one of claims 101-141, wherein said engineered EPO protein comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1973-2019.

143. The composition of any one of claims 101-142, wherein said myeloid cell comprises a granulocyte, a monocyte, a macrophage, or a dendritic cell.

144. A composition comprising a nucleic acid sequence encoding said engineered EPO protein of the composition of any one of claims 101-143.

145. A cell comprising the composition of any one of claims 101-144.

146. A method of treating a disease or a condition in a subject in need thereof, said method comprising administering to said subject the composition of any one of claims 101-144 or the cell of claim 145.

147. A method of treating anemia in a subject in need thereof, said method comprising administering to said subject the composition of any one of claims 101-144 or the cell of claim 145, wherein said subject has a cancer.

148. The method of any one of claims 101-147, wherein said cancer comprises a lung cancer, a breast cancer, a colon cancer, a brain cancer, a melanoma, hepatocarcinoma, or a liver cancer.

149. The method of any one of claims 101-147, wherein said cancer is a melanoma.

150. The method of any one of claims 101-147, wherein said cancer is a liver cancer.

151. The method of any one of claims 101-147, wherein said cancer is a colon cancer.

152. The method of any one of claims 101-147, wherein said cancer is a breast cancer.

153. A composition comprising an engineered erythropoietin (EPO) protein, wherein said engineered EPO protein promotes a hetero-erythropoietin (EPO) receptor activity to reduce immune response, wherein said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit.

154. The composition of claim 153, wherein said engineered EPO protein comprises at least one amino acid modification and/or at least one amino acid substitution comprising: K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A, R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A.

155. The composition of claim 153 or 154, wherein said promoting said hetero-EPO receptor activity reduces immune reaction when administered to a subject having an autoimmune disease or a subject with a transplanted organ.

156. The composition of claim 155, wherein said transplanted organ comprises bone marrow, kidney, liver, lung, or heart.

157. The composition of claim 155, wherein said autoimmune disease comprises a rheumatoid arthritis, a systemic lupus erythematosus, or a multiple sclerosis.

158. The composition of claim 153 or 154, wherein said promoting said hetero-EPO receptor activity reduces systemic chronic inflammation when administered to a subject suffering from a systemic chronic inflammation.

159. The composition of any one of claims 153-158, wherein said promoting said hetero-EPO receptor activity induces antigen-specific immune tolerance.

160. The composition of any one of claims 153-158, wherein said promoting said hetero-EPO receptor activity inhibits differentiation of a plurality of naïve T cells into a plurality of effector T cells.

161. The composition of claim 160, wherein said plurality of effector T cells expresses Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα).

162. The composition of any one of claims 153-158, wherein said promoting said hetero-EPO receptor activity promotes differentiation of a plurality of naïve T cells into a plurality of regulatory T cells.

163. The composition of claim 162, wherein said plurality of regulatory T cells expresses Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4).

164. The composition of any one of claims 153-163, wherein said at least one amino acid substitution comprises Q65A.

165. The composition of any one of claims 153-163, wherein said at least one amino acid substitution comprises N83A.

166. The composition of any one of claims 153-166, wherein the amino acid residue position is determined by alignment with SEQ ID NO: 1.

167. The composition of any one of claims 153-166, wherein said at least one amino acid modification comprises a chemical modification comprising carbamylation or PEGylation.

168. The composition of claim 167, wherein said at least one amino acid modification comprises carbamylation of one or more lysine residues.

169. The composition of claim 168, wherein said at least one amino acid modification comprises carbamylation of all lysine residues.

170. The composition of any one of claims 153-169, wherein said engineered EPO protein has higher binding affinity to said hetero-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

171. The composition of any one of claims 153-170, wherein said hetero-EPO receptor activity comprises phosphorylation of an intracellular domain of said hetero-EPO receptor, or activation of Janus tyrosine kinase 2 (Jak2), Signal transducer and activator of transcription 5 (Stat5), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), or Mammalian target of rapamycin (mTOR).

172. The composition of any one of claims 153-171, wherein said hetero-EPO receptor activity is measured by a western blotting, an enzyme-linked immunosorbant assay (ELISA), a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or a combination thereof.

173. The composition of any one of claims 153-172, wherein said engineered EPO protein has a lower binding affinity to a homo-EPO receptor comprising at least two EPO receptor subunits, compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

174. The composition of any one of claims 153-172, wherein said engineered EPO protein has the same level of binding affinity to a homo-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

175. The composition of any one of claims 153-174, wherein said engineered EPO protein does not affect or inhibits said homo-EPO receptor activity.

176. The composition of any one of claims 153-175, wherein said homo-EPO receptor activity comprises phosphorylation of an intracellular domain of said homo-EPO receptor, or activation of Janus tyrosine kinase 2 (Jak2), Signal transducer and activator of transcription 5 (Stat5), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), or Mammalian target of rapamycin (mTOR).

177. The composition of claim 176, wherein said homo-EPO receptor activity is measured by a western blotting, an enzyme-linked immunosorbant assay (ELISA), a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or a combination thereof.

178. The composition of any one of claims 153-177, wherein said engineered EPO has a half-life of at least 5 hours.

179. The composition of any one of claims 153-178, wherein said engineered EPO protein comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1973-2019.

180. The composition of any one of claims 153-179, wherein said hetero-EPOR is on an immune cell.

181. The composition of claim 180, wherein said immune cell comprises a macrophage, a dendritic cell, a T-cell, a natural killer cell, or a B cell.

182. The composition of claim 181, wherein said T-cell comprises a cytotoxic T-cell.

183. The composition of any one of claims 153-179, wherein said hetero-EPOR is on an endothelial cell.

184. A composition comprising a nucleic acid sequence encoding said EPO protein of the composition of any one of claims 153-183.

185. A cell comprising the composition of any one of claims 153-184.

186. A method of treating a disease or a condition in a subject in need thereof, said method comprising administering to said subject the composition of any one of claims 153-184 or the cell of claim 185.

187. The method of claim 186, wherein said disease or said condition comprises an autoimmune disease.

188. The method of claim 186, wherein said subject has received or is to receive an organ transplant or a foreign therapeutics protein.

189. A composition comprising an engineered erythropoietin (EPO) protein, said engineered EPO protein promotes a homo-erythropoietin (EPO) receptor activity and has reduced effect on a hetero-EPO receptor activity, wherein said homo-EPO receptor comprises at least two EPO receptor subunits and said hetero-EPO receptor comprises an EPO receptor subunit and a CD131 subunit.

190. The composition of claim 189, wherein said engineered EPO protein comprises at least one amino acid substitution comprising:
K20A, N24Q, N24A, N24S, N38Q, N38A, N38S, K45A, K52A, Q58A, E62R, E62A, Q65A, L69A, E72A, R76E, R76A, L80A, N83Q, N83A, N83S, S84A, S85A, K97A, K116A, G151A, R103A, K45D, N147K, R150E, Q65A, E72R, N83A, K140A, K152A, or K154A.

191. The composition of claim 189 or 190, wherein said engineered EPO has no substantial effect on said hetero-EPO receptor activity.

192. The composition of claim 189 or 190, wherein said engineered EPO inhibits said hetero-EPO receptor activity.

193. The composition of claim 190, wherein said engineered EPO protein comprises at least one amino acid substitution comprising E72A, Q 58A, L69A, or L80A.

194. The composition of claim 190, wherein said engineered EPO protein comprises Q65A, E72R, and N83A amino acid substitutions.

195. The composition of claim 190, wherein said engineered EPO protein comprises K20A, K45A, and K52A amino acid substitutions.

196. The composition of any one of claims 189-192, wherein the position is determined by alignment with SEQ ID NO: 1.

197. The composition of any one of claims 189-193, wherein said engineered EPO further comprises an amino acid modification comprising carbamylation or PEGylation.

198. The composition of claim 197, wherein said amino acid modification comprises carbamylation of one or more lysine residue.

199. The composition of any one of claims 189-198, wherein said engineered EPO protein has higher binding affinity to said homo-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

200. The composition of any one of claims 189-199, wherein said homo-EPO receptor activity comprises phosphorylation of an intracellular domain of said homo-EPO receptor, or activation of Janus tyrosine kinase 2 (Jak2), Signal transducer and activator of transcription 5 (Stat5), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), or Mammalian target of rapamycin (mTOR).

201. The composition of any one of claims 189-200, wherein said homo-EPO receptor activity is measured by a western blotting, an enzyme-linked immunosorbant assay (ELISA), a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or a combination thereof.

202. The composition of any one of claims 189-201, wherein said engineered EPO protein has the same level of binding affinity to said hetero-EPO receptor compared to a corresponding wild type EPO protein without said at least one amino acid substitution.

203. The composition of any one of claims 189-202, wherein said hetero-EPOR activity comprises phosphorylation of an intracellular domain of said homo-EPO receptor, or activation of Janus tyrosine kinase 2 (Jak2), Signal transducer and activator of transcription 5 (Stat5), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), phosphatidylinositol 3-kinase (PI3K), v-Akt Murine Thymoma Viral Oncogene/Protein Kinase-B (Akt/PKB), or Mammalian target of rapamycin (mTOR).

204. The composition of any one of claims 189-203, wherein said hetero-EPO receptor activity is measured by a western blotting, an enzyme-linked immunosorbant assay (ELISA), a flow cytometry assay, a cell proliferation assay, an apoptosis assay, or a combination thereof.

205. The composition of any one of claims 202-204, wherein said engineered EPO protein does not affect immune tolerance.

206. The composition of claim 205, wherein said engineered EPO protein does not affect differentiation of a plurality of naïve T cells into a plurality of effector T cells.

207. The composition of claim 206, wherein said plurality of effector T cells expresses Cluster of Differentiation 45 (CD45), CD3, CD8, Perforin, Interferon gamma (IFNγ), Granzyme B, or tumor necrosis factor alpha (TNFα).

208. The composition of claim 205, wherein said engineered EPO protein does not affect differentiation of a plurality of naïve T cells into a plurality of regulatory T cells.

209. The composition of claim 208, wherein said plurality of regulatory T cells expresses Cluster of Differentiation 4 (CD4), CD25, CD127, Forkhead Box P3 (FoxP3), CD39, protein tyrosine phosphatase receptor type C (CD45RA), Interleukin-2 (IL-2), or a Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4).

210. The composition of any one of claims 202-204, wherein said engineered EPO protein does not affect immune response.

211. The composition of any one of claims 189-210, wherein said engineered EPO has a half-life of at least 5 hours.

212. The composition of any one of claims 189-211, wherein said engineered EPO protein comprises an amino acid sequence with at least 80% sequence identity to any one of SEQ ID NOs: 1973-2019.

213. The composition of any one of claims 189-211, wherein said homo-EPOR is on an erythroid progenitor cell.

214. A composition comprising a nucleic acid sequence encoding said EPO protein of the composition of any one of claims 189-213.

215. A cell comprising the composition of any one of claims 189-214.

216. A method of treating a disease or a condition in a subject in need thereof, said method comprising administering to said subject the composition of any one of claims 189-214 or the cell of claim 215.

217. The method of claim 216, wherein the disease or the condition comprises a cancer.

218. A method of treating anemia in a subject in need thereof, said method comprising administering to said subject the composition of any one of claims 189-214 or the cell of claim 215, wherein said subject has a cancer.

219. The method of claim 217 or 218, wherein said cancer comprises a lung cancer, a breast cancer, a colon cancer, a brain cancer, a melanoma, hepatocarcinoma, or a liver cancer.

220. The method of claim 217 or 218, wherein said cancer is a melanoma.

221. The method of claim 217 or 218, wherein said cancer is a liver cancer.

222. The method of claim 217 or 218, wherein said cancer is a colon cancer.

223. The method of claim 217 or 218, wherein said cancer is a breast cancer.

224. A composition for administering to a subject having cancer or chronic infection condition, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound inhibits an erythropoietin (EPO) receptor activity in a myeloid cell in said subject.

225. The composition of claim 224, wherein the EPO receptor is a hetero-EPO receptor.

226. The composition of claim 224 or 225, wherein the hetero-EPO receptor comprises an EPO subunit and a CD131 subunit.

227. The composition of any one of claims 224 to 226, wherein the hetero-EPO receptor is on a macrophage, monocyte, dendritic cell, basophil, neutrophil, or eosinophil.

228. The composition of any one of claims 224 to 227, wherein the compound is an inhibitor of hypoxia-inducible factor (HIF), IL-1α, IL-1β, TNF-α, IL-6, estrogen receptors, phospholipase C-γ1, or promotion of the Cbl/p85/Episin-1 pathway.

229. The composition of any one of claims 224 to 228, wherein the compound is an inhibitor of hypoxia-inducible factor (HIF), IL-1α, IL-1β, TNF-α, IL-6, or estrogen receptors.

230. The composition of any one of claims 224 to 229, wherein the compound is an inhibitor of hypoxia-inducible factor (HIF).

231. The composition of any one of claims 224 to 230, wherein the compound is CAY10585 (LW6), Chetomin, Chrysin, Dimethyl-bisphenol A, Echinomycin, 2-Methoxyestradiol (2ME2), SYP-5, PX-478 2HCl, KC7F2, GN44028, Verucopeptin, FM19G11, PT2399,

PT2385, Belzutifan, HIF-2a-IN-1, HIF-2a-IN-2, HIF-2a-IN-3, HIF-2a-IN-4, TC-S 700, IDF-11774, Paeoniflorin, Emetine hydrochloride, Glucosamine, PX12, Vitexin, BAY 87-2243, Lificiguat (YC-1), Vorinostat, Tanespimycin, Silibinin, diallyl trisulfide (DATS), Herboxidiene (GEX1A), Celastrol, Phenethyl isothiocyanate (PEITC), Gliotoxin, Sulforaphane, Acriflavin, Emodin, Cardenolide, 3,3'-Diindolylmethane (DIM), Pseudolaric acid-B (PAB), Bavachinin, Andrographolide, Isoliquiritigenin, Wondonin, Thymoquinone, or Curcumin.

232. The composition of any one of claims 224 to 231, wherein the compound is CAY10585 (LW6), Chetomin, Chrysin, Dimethyl-bisphenol A, Echinomycin, 2-Methoxyestradiol (2ME2), SYP-5, PX-478 2HCl, KC7F2, GN44028, Verucopeptin, FM19G11, PT2399, PT2385, Belzutifan, HIF-2a-IN-1, HIF-2a-IN-2, HIF-2a-IN-3, HIF-2a-IN-4, TC-S 700, IDF-11774, Paeoniflorin, Emetine hydrochloride, Glucosamine, PX12, Vitexin, BAY 87-2243, Lificiguat (YC-1), Vorinostat, or Tanespimycin.

233. The composition of any one of claims 224 to 232, wherein the compound is Chetomin, Echinomycin, PT2399, Belzutifan, Vorinostat, or Tanespimycin.

234. The composition of any one of claims 224 to 231, wherein the compound is Silibinin, diallyl trisulfide (DATS), Herboxidiene (GEX1A), Celastrol, Phenethyl isothiocyanate (PEITC), Gliotoxin, Sulforaphane, Acriflavin, Emodin, Cardenolide, 3,3'-Diindolylmethane (DIM), Pseudolaric acid-B (PAB), Bavachinin, Andrographolide, Isoliquiritigenin, Wondonin, Thymoquinone, or Curcumin.

235. A composition for administering to a subject having cancer or chronic infection condition, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound inhibits an erythropoietin (EPO) receptor activity so that an immune-checkpoint blockade resistance is reversed in said subject.

236. The composition of claim 235, wherein the EPO receptor is a hetero-EPO receptor.

237. The composition of claim 235 or 236, wherein the hetero-EPO receptor comprises an EPO subunit and a CD131 subunit.

238. The composition of any one of claims 235 to 237, wherein the immune-checkpoint blockade is an inhibitor of CTLA-4, PD-1, or PD-L1.

239. The composition of claim 238, wherein the inhibitor of CTLA-4, PD-1, or PD-L1 is Nivolumab, Pembrolizumab, Cemiplimab, Atezolizumab, Avelumab, Durvalumab, Ipilimumab, Lirilumab, and BMS-986016.

240. The composition of any one of claims 235 to 239, wherein the hetero-EPO receptor is on a macrophage, monocyte, dendritic cell, basophil, neutrophil, or eosinophil.

241. The composition of any one of claims 235 to 240, wherein the compound is an inhibitor of hypoxia-inducible factor (HIF), IL-1α, IL-1β, TNF-α, IL-6, estrogen receptors, phospholipase C-γ1, or Cbl/p85/Episin-1 pathway.

242. The composition of any one of claims 235 to 241, wherein the compound is an inhibitor of hypoxia-inducible factor (HIF), IL-1α, IL-1β, TNF-α, or IL-6.

243. The composition of any one of claims 235 to 242, wherein the compound is an inhibitor of hypoxia-inducible factor (HIF).

244. The composition of any one of claims 235 to 243, wherein the compound is CAY10585 (LW6), Chetomin, Chrysin, Dimethyl-bisphenol A, Echinomycin, 2-Methoxyestradiol (2ME2), SYP-5, PX-478 2HCl, KC7F2, GN44028, Verucopeptin, FM19G11, PT2399, PT2385, Belzutifan, HIF-2a-IN-1, HIF-2a-IN-2, HIF-2a-IN-3, HIF-2a-IN-4, TC-S 700, IDF-11774, Paeoniflorin, Emetine hydrochloride, Glucosamine, PX12, Vitexin, BAY 87-2243, Lificiguat (YC-1), Vorinostat, Tanespimycin, Silibinin, diallyl trisulfide (DATS), Herboxidiene (GEX1A), Celastrol, Phenethyl isothiocyanate (PEITC), Gliotoxin, Sulforaphane, Acriflavin, Emodin, Cardenolide, 3,3'-Diindolylmethane (DIM), Pseudolaric acid-B (PAB), Bavachinin, Andrographolide, Isoliquiritigenin, Wondonin, Thymoquinone, or Curcumin.

245. The composition of any one of claims 235 to 244, wherein the compound is CAY10585 (LW6), Chetomin, Chrysin, Dimethyl-bisphenol A, Echinomycin, 2-Methoxyestradiol (2ME2), SYP-5, PX-478 2HCl, KC7F2, GN44028, Verucopeptin, FM19G11, PT2399, PT2385, Belzutifan, HIF-2a-IN-1, HIF-2a-IN-2, HIF-2a-IN-3, HIF-2a-IN-4, TC-S 700, IDF-11774, Paeoniflorin, Emetine hydrochloride, Glucosamine, PX12, Vitexin, BAY 87-2243, Lificiguat (YC-1), Vorinostat, or Tanespimycin.

246. The composition of any one of claims 235 to 245, wherein the compound is Chetomin, Echinomycin, PT2399, Belzutifan, Vorinostat, or Tanespimycin.

247. The composition of any one of claims 235 to 244, wherein the compound is Silibinin, diallyl trisulfide (DATS), Herboxidiene (GEX1A), Celastrol, Phenethyl isothiocyanate (PEITC), Gliotoxin, Sulforaphane, Acriflavin, Emodin, Cardenolide, 3,3'-Diindolylmethane (DIM), Pseudolaric acid-B (PAB), Bavachinin, Andrographolide, Isoliquiritigenin, Wondonin, Thymoquinone, or Curcumin.

248. A composition for administering to a subject, comprising a compound, a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein said compound promotes a hetero-erythropoietin (EPO) receptor activity, wherein said hetero-EPO receptor comprises a EpoR subunit and CD131 subunit, so that immune tolerance to an antigen is increased in said subject; and wherein said compound has no substantial effect on a homo-EPO receptor activity wherein said homo-EPO receptor comprises at least two EPO receptor subunits.

249. The composition of claim 248, wherein the hetero-EPO receptor is on a macrophage, monocyte, dendritic cell, basophil, neutrophil, or eosinophil.

250. The composition of claim 248 or 249, wherein the compound is an inhibitor of HIF-Prolyl Hydroxylase (PHD), NHF-4, GATA factor, IL-17, AKT/NFkB/HIF1 pathway, estrogen receptor, Epithelial membrane protein 1 (EMP-1).

251. The composition of any one of claims 248 to 250, wherein the compound is an inhibitor of HIF-Prolyl Hydroxylase (PHD), NHF-4, GATA factor, or IL-17.

252. The composition of any one of claims 248 to 251, wherein the compound is an inhibitor of HIF-Prolyl Hydroxylase (PHD).

253. The composition of any one of claims 248 to 252, wherein the compound is Roxadustat, Vadadustat, Enarodustat, Desidustat, Molidustat, Dimethyloxaloylglycine, Daprodustat, Prolyl Hydroxylase inhibitor 1, TM6089, TRC160334, PHD-1-IN-1, MK-8617, JNJ-42041935, TP0463518, IOX (JICL38), IOX4, IOX3 (FG-2216), Dencichin, HIF-PHD-IN-1, AKB-6899, VH298, M1001, ML228, Dimethyloxalylglycine (DMOG), Mitoxantrone, Angiotensin II (Ang II), or 17β-estradiol.

254. The composition of any one of claims 248 to 253, wherein the compound is Roxadustat, Vadadustat, Enarodustat, Desidustat, Molidustat, Dimethyloxaloylglycine, Daprodustat, Prolyl Hydroxylase inhibitor 1, TM6089, TRC160334, PHD-1-IN-1, MK-8617, JNJ-

42041935, TP0463518, IOX (JICL38), IOX4, IOX3 (FG-2216), Dencichin, HIF-PHD-IN-1, AKB-6899, VH298, M1001, ML228, or Dimethyloxalylglycine (DMOG).

255. The composition of any one of claims 248 to 253, wherein the compound is Mitoxantrone, Angiotensin II (Ang II), or 17β-estradiol.

256. The composition of claim 248 or 249, wherein the compound is an EPOR agonist.

257. The composition of claim 256, wherein the compound is LG5640.

258. The composition of any one of claims 248 to 257, wherein the immune tolerance is to a transplant organ or self-antigen.

259. The composition of any one of claims 248 to 258, wherein the immune tolerance is to a transplant organ.

260. The composition of any one of claims 248 to 259, wherein the immune tolerance is to an immunosuppressed state.

261. The composition of any one of claims 248 to 258, wherein the immune tolerance is to a self-antigen.

262. The composition of any one of claims 248 to 258, wherein the immune tolerance is to a self-antigen.

263. A composition for administering to a subject having cancer, comprising an RNA interference (RNAi) molecule, wherein said RNAi binds to an RNA molecule that is selected from the group consisting of an mRNA molecule that encodes a erythropoietin (EPO) protein, an mRNA molecule that encodes a EPO receptor subunit, an mRNA molecule that encodes a CD131 subunit, and any combination thereof; wherein upon administering said RNAi to said subject, said subject's tumor mass is reduced.

264. The composition of claim 263, wherein the tumor mass is reduced to less than 0.5 cm^3.

265. The composition of claim 263 or 264, wherein the tumor mass is reduced to less than 0.2 cm^3.

266. The composition of claim 263 or 264, wherein the tumor mass is reduced to about 0.2 cm^3.

267. A composition for administering to a subject having cancer, comprising a RNA interference (RNAi) molecule, wherein said RNAi binds to an RNA molecule that is selected from the group consisting of an mRNA molecule that encodes a erythropoietin (EPO) protein, an mRNA molecule that encodes a EPO receptor subunit, an mRNA molecule that encodes a CD131 subunit, and any combination thereof; wherein upon administering said RNAi to said subject, said subject's immune response is increased by inducing more effector T (T_{eff}) cells.

268. The composition of any one of claims 263 to 267, wherein the cancer is hepatocarcinoma.

269. The composition of any one of claims 263 to 268, wherein the RNAi reduces EPO half-life in a subject.

270. The composition of any one of claims 263 to 268, wherein the RNAi reduces EPO levels in a subject.

271. The composition of claim 269, wherein the reduced EPO half-life increases survival rate.

272. The composition of claim 271, wherein the survival rate is increased two-fold.

273. The composition of any one of claims 263 to 272, wherein the RNAi is in a nanoparticle.

274. The composition of claim 273, wherein the nanoparticle is a lipid nanoparticle.

275. The composition of any one of claims 263 to 274, wherein the RNAi molecule is a siRNA molecule, a miRNA molecule, an antisense RNA molecule, or a lncRNA molecule.

276. The composition of any one of claims 263 to 275, wherein the RNAi is an siRNA molecule.

277. The composition of claim 276, wherein the siRNA molecule has a sequence length of about 15 to about 30 nucleotides.

278. The composition of claim 276 or 277, wherein the siRNA molecule has a sequence length of about 21 to about 30 nucleotides.

279. The composition of any one of claims 276 to 278, wherein the siRNA molecule is double-stranded or single stranded.

280. The composition of claim 279, wherein the single stranded siRNA molecule comprises a nucleic acid sequence that is at least 80%, 85%, 90%, or 95% identical to at least one of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9,

SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62.

281. The composition of claim 280, wherein the single stranded siRNA molecule comprises a nucleic acid sequence that is 100% identical to at least one of SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34, SEQ ID NO: 35, SEQ ID NO: 36, SEQ ID NO: 37, SEQ ID NO: 38, SEQ ID NO: 39, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 43, SEQ ID NO: 44, SEQ ID NO: 45, SEQ ID NO: 46, SEQ ID NO: 47, SEQ ID NO: 48, SEQ ID NO: 49, SEQ ID NO: 50, SEQ ID NO: 51, SEQ ID NO: 52, SEQ ID NO: 53, SEQ ID NO: 54, SEQ ID NO: 55, SEQ ID NO: 56, SEQ ID NO: 57, SEQ ID NO: 58, SEQ ID NO: 59, SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62.

282. A method for treating cancer in a subject, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising single stranded siRNA from claim 280 or claim 281 to said subject in a dose and schedule sufficient to reduce an expression level of a erythropoietin (EPO) protein, a EPO receptor subunit, or a CD131 subunit.

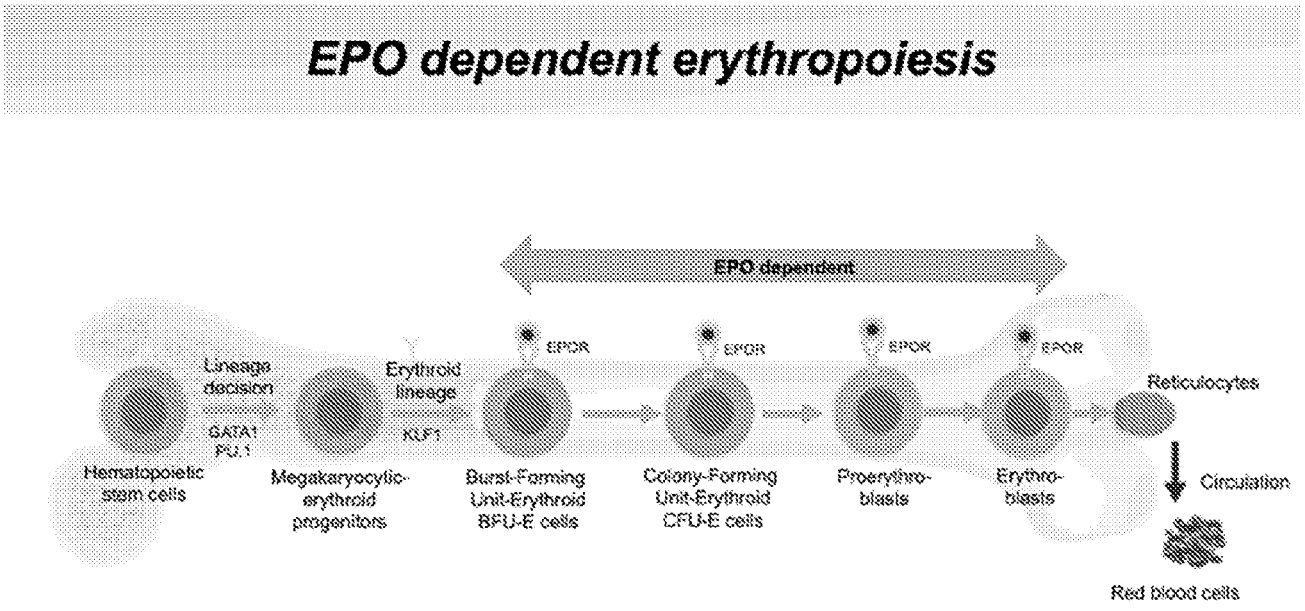

EPO dependent erythropoiesis
EPO dependent
EPOR
EPOR
EPOR
EPOR
Lineage decision
GATA1
PU.1
Erythroid lineage
KLF1
Reticulocytes
Circulation
Red blood cells
Hematopoietic stem cells
Megakaryocytic-erythroid progenitors
Burst-Forming Unit-Erythroid BFU-E cells
Colony-Forming Unit-Erythroid CFU-E cells
Proerythro-blasts
Erythro-blasts

FIG. 1

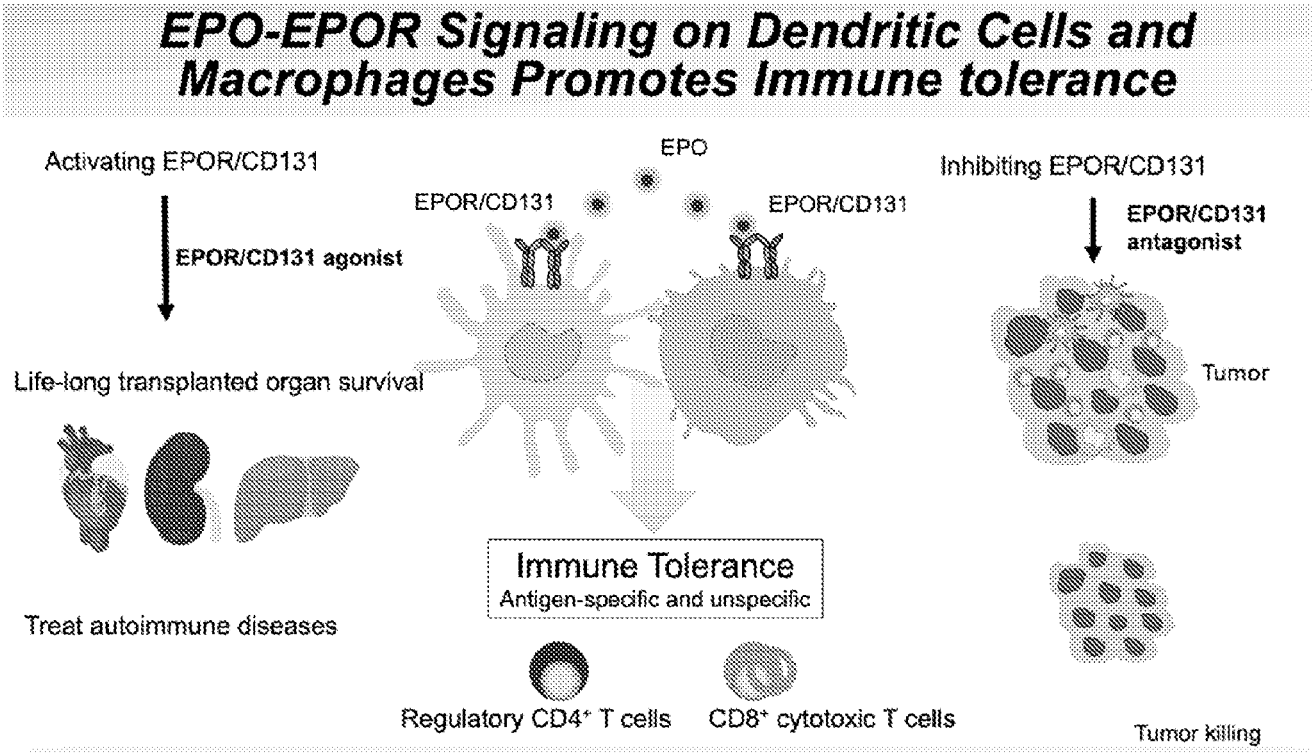

EPO-EPOR Signaling on Dendritic Cells and Macrophages Promotes Immune tolerance
Activating EPOR/CD131
EPOR/CD131 agonist
Life-long transplanted organ survival
Treat autoimmune diseases
EPO
EPOR/CD131
EPOR/CD131
Immune Tolerance
Antigen-specific and unspecific
Regulatory CD4+ T cells
CD8+ cytotoxic T cells
Inhibiting EPOR/CD131
EPOR/CD131 antagonist
Tumor
Tumor killing

FIG. 2

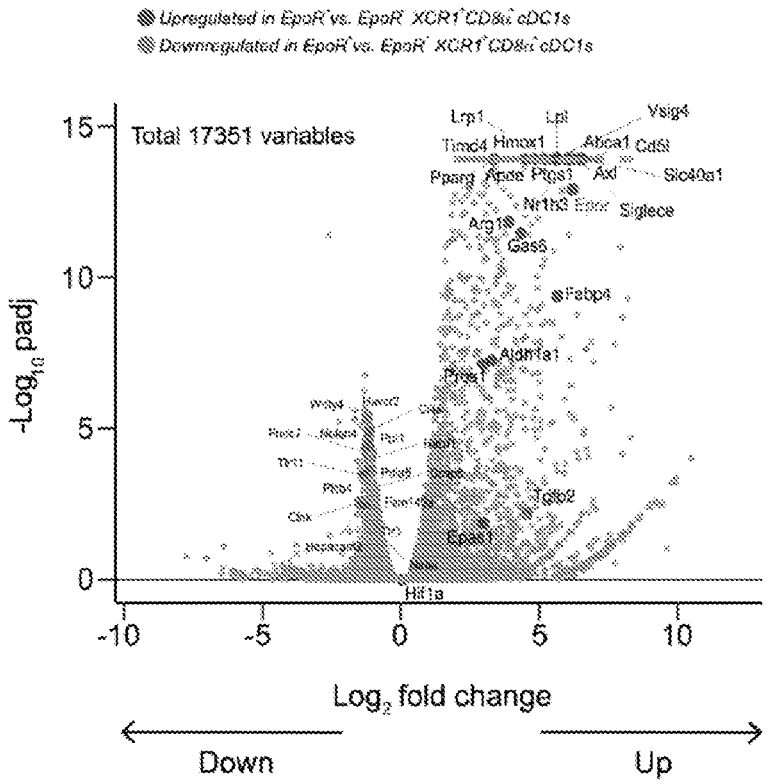

Upregulated in EpoR+ vs. EpoR- XCR1+CD8α+ cDC1s
Downregulated in EpoR+ vs. EpoR- XCR1+CD8α+ cDC1s
Total 17351 variables
-Log10 padj
Log2 fold change
Down
Up
Lrp1
Lpl
Vsig4
Timd4
Hmox1
Abca1
Cd5l
Pparg
Apoe
Ptgs1
Axl
Slc40a1
Nr1h3
Siglece
Arg1
Gas6
Fabp4
Aldh1a1
Pros1
Tgfb2
Epas1
Hif1a

FIG. 3A

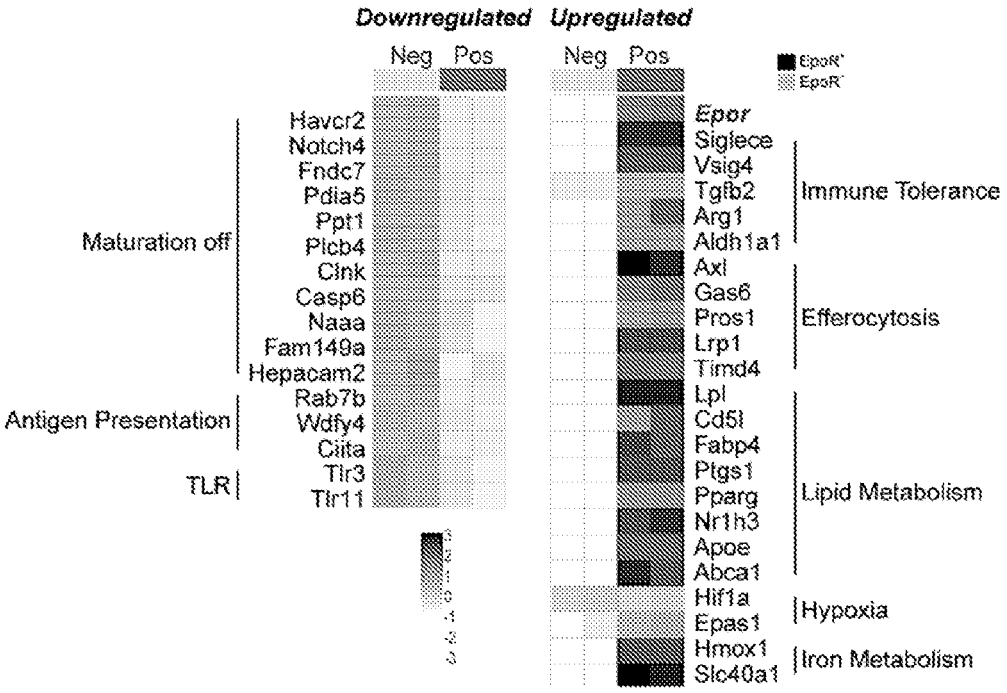

Downregulated
Upregulated
Neg
Pos
Neg
Pos
EpoR+
EpoR-
Havcr2
Notch4
Fndc7
Pdia5
Ppt1
Plcb4
Clnk
Casp6
Naaa
Fam149a
Hepacam2
Rab7b
Wdfy4
Ciita
Tlr3
Tlr11
Maturation off
Antigen Presentation
TLR
Epor
Siglece
Vsig4
Tgfb2
Arg1
Aldh1a1
Axl
Gas6
Pros1
Lrp1
Timd4
Lpl
Cd5l
Fabp4
Ptgs1
Pparg
Nr1h3
Apoe
Abca1
Hif1a
Epas1
Hmox1
Slc40a1
Immune Tolerance
Efferocytosis
Lipid Metabolism
Hypoxia
Iron Metabolism

FIG. 3B

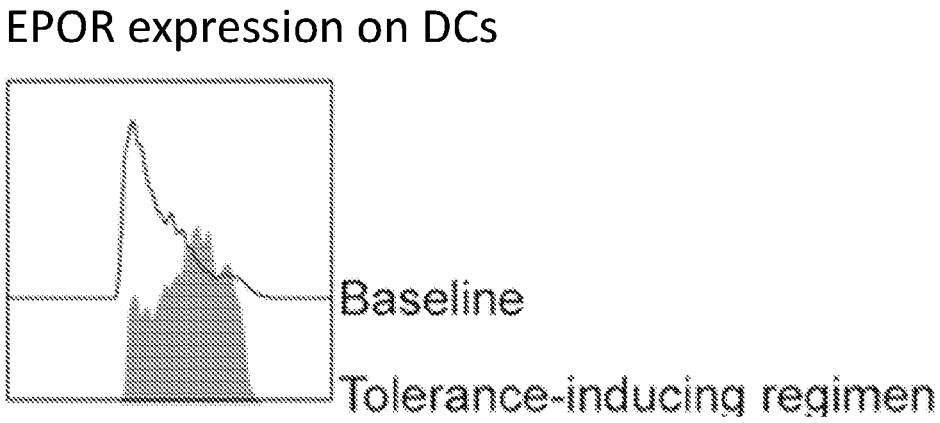


FIG. 4A

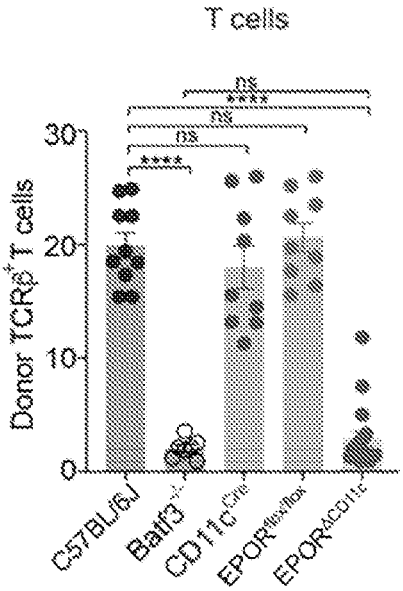


FIG. 4B

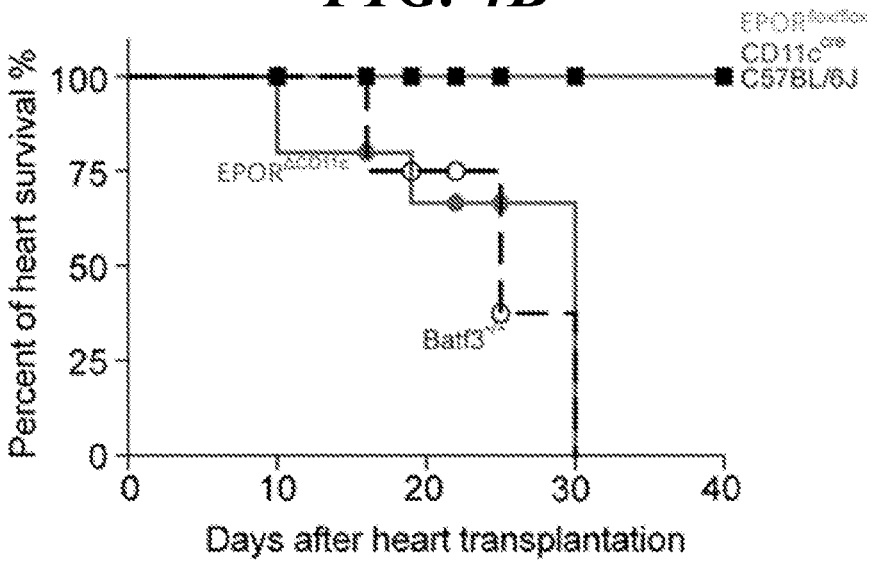


FIG. 4C

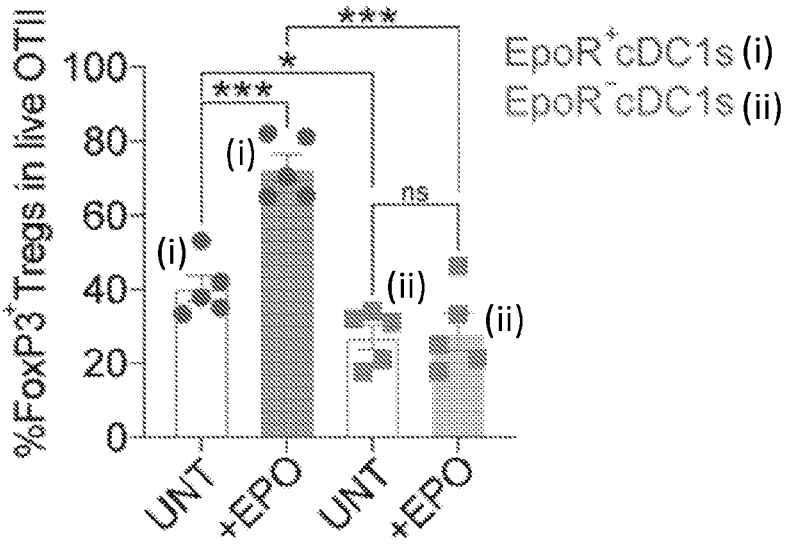

%FoxP3+Tregs in live OTII
100
80
60
40
20
0
***
*
***
ns
(i)
(ii)
(i)
(ii)
UNT
+EPO
UNT
+EPO
EpoR+cDC1s (i)
EpoR-cDC1s (ii)

FIG. 5A

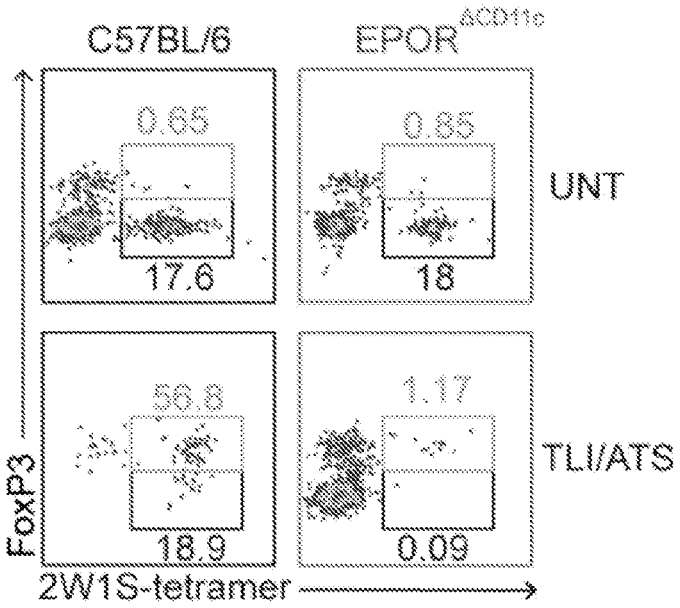

C57BL/6
EPOR ΔCD11c
0.65
17.6
0.65
18
UNT
56.8
18.9
1.17
0.09
TLI/ATS
FoxP3
2W1S-tetramer

FIG. 5B

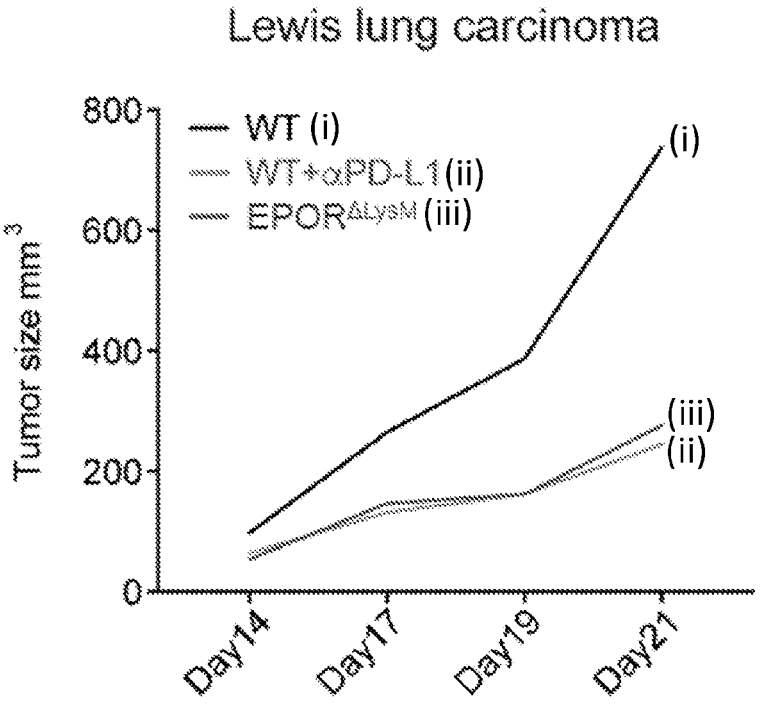

Lewis lung carcinoma
Tumor size mm3
800
600
400
200
0
WT (i)
WT+αPD-L1 (ii)
EPORΔLysM (iii)
(i)
(iii)
(ii)
Day14
Day17
Day19
Day21

FIG. 6A

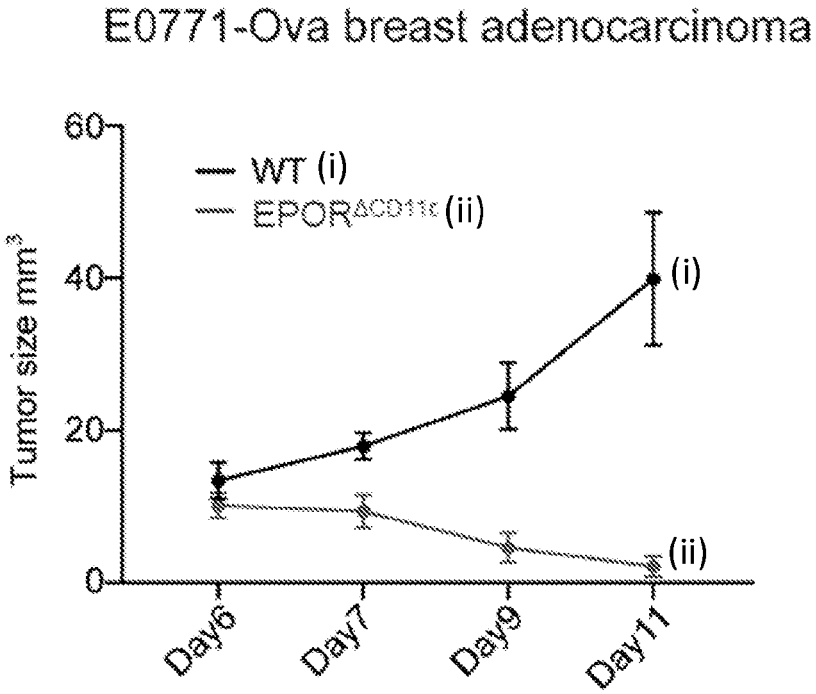

E0771-Ova breast adenocarcinoma
Tumor size mm3
60
40
20
0
WT (i)
EPORΔCD11c (ii)
(i)
(ii)
Day6
Day7
Day9
Day11

FIG. 6B

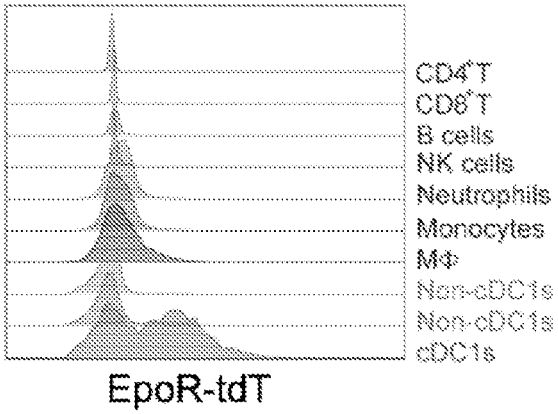


FIG. 7A

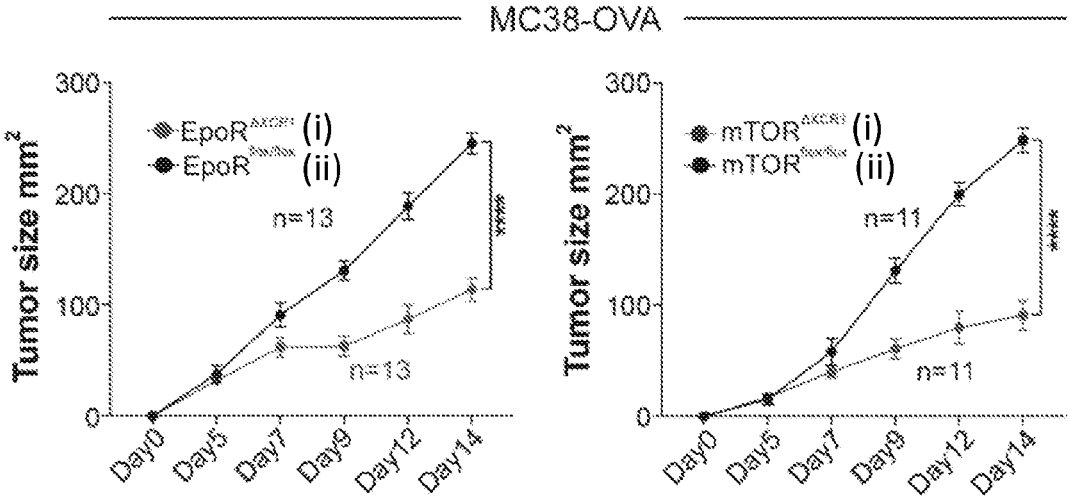


FIG. 7B

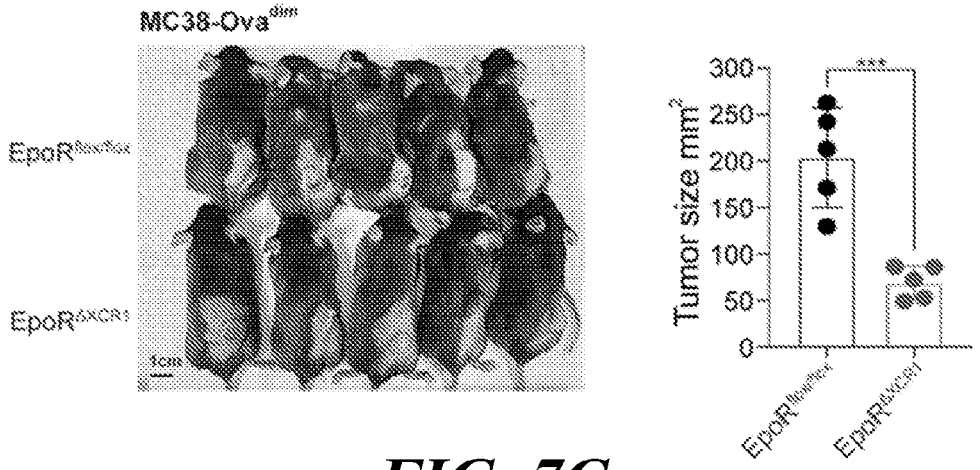


FIG. 7C

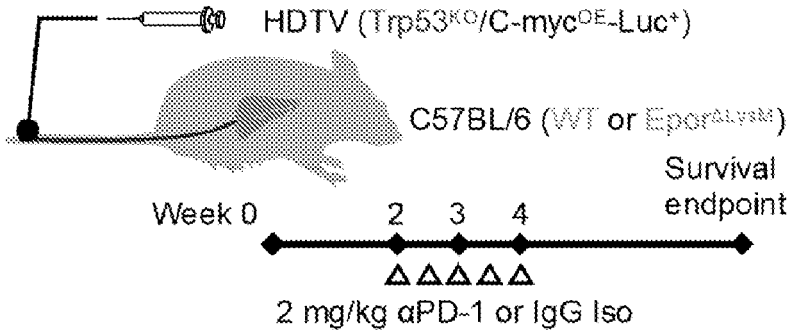


FIG. 8A

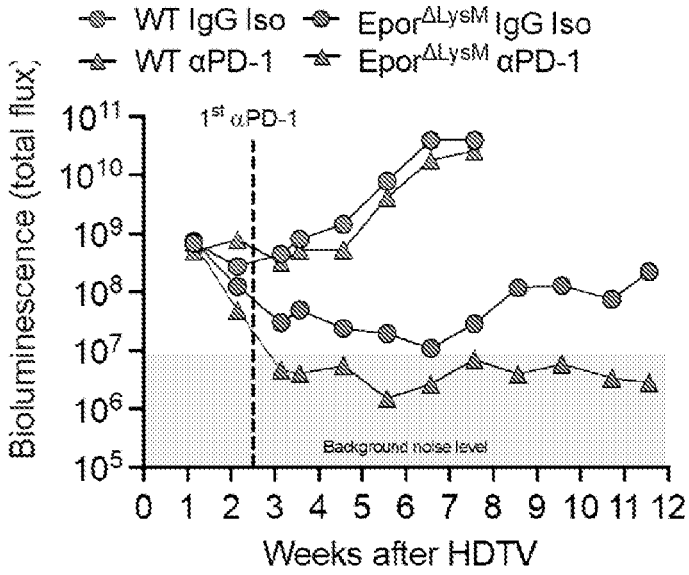


FIG. 8B

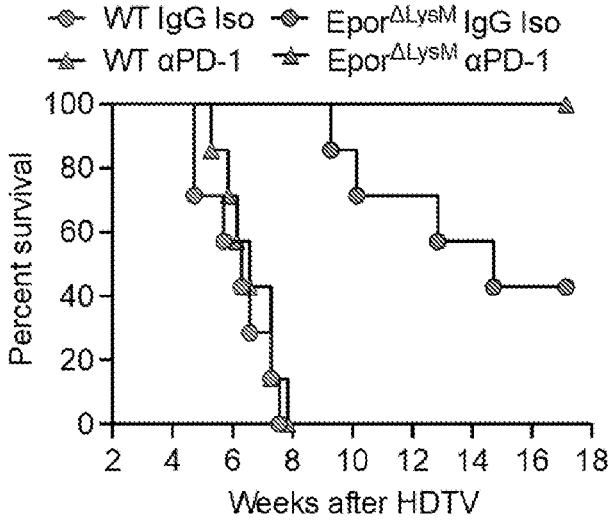


FIG. 8C

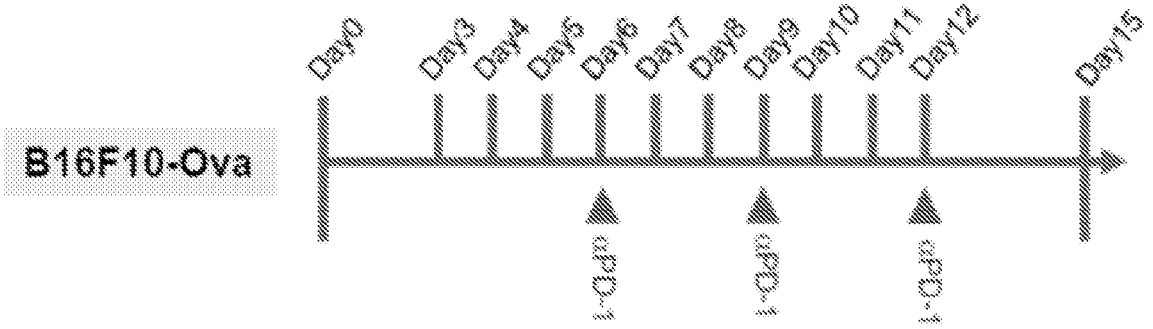


FIG. 9A

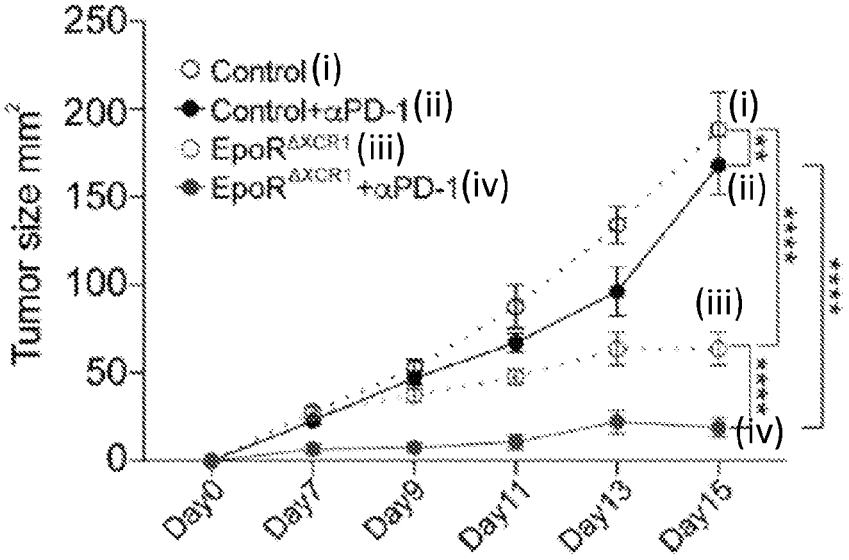


FIG. 9B

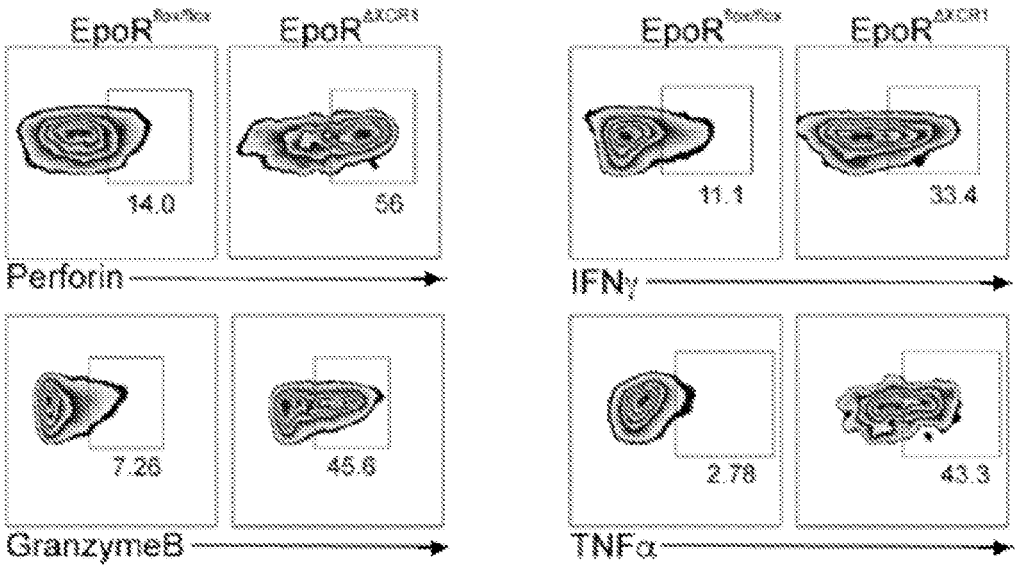


FIG. 9C

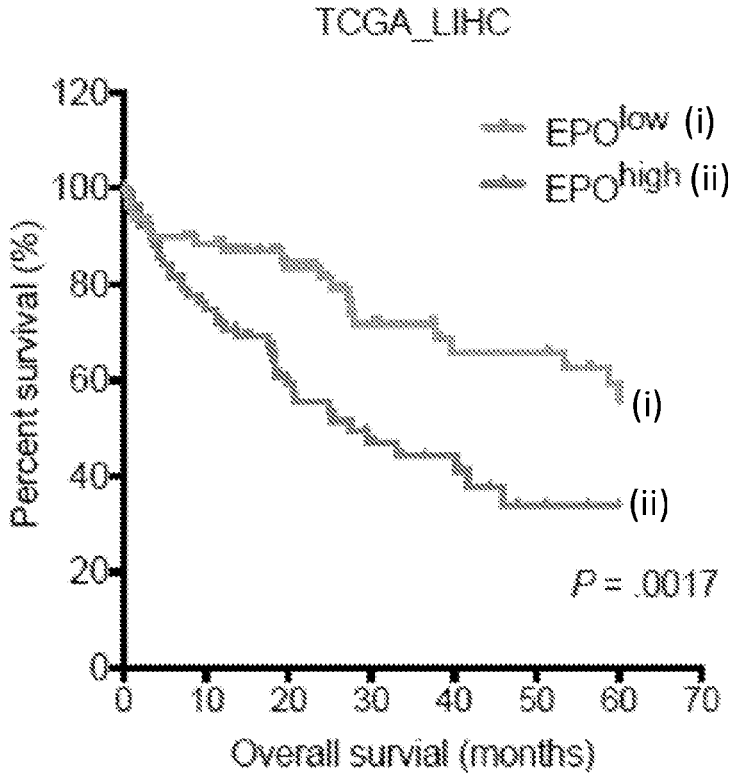

TCGA_LIHC
EPO^low (i)
EPO^high (ii)
Percent survival (%)
120
100
80
60
40
20
0
(i)
(ii)
P = .0017
0
10
20
30
40
50
60
70
Overall survial (months)

FIG. 10

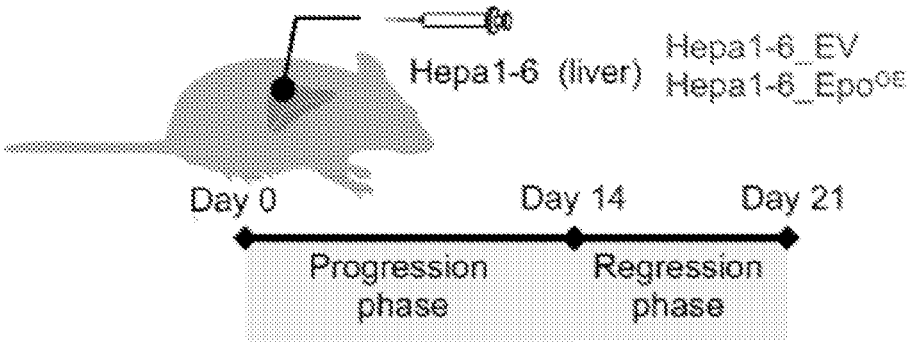


FIG. 11A

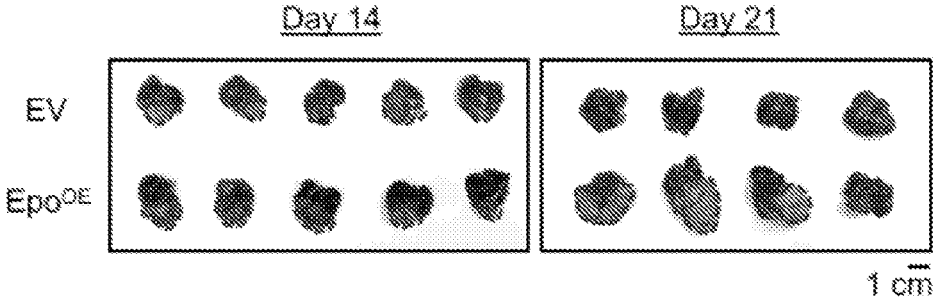
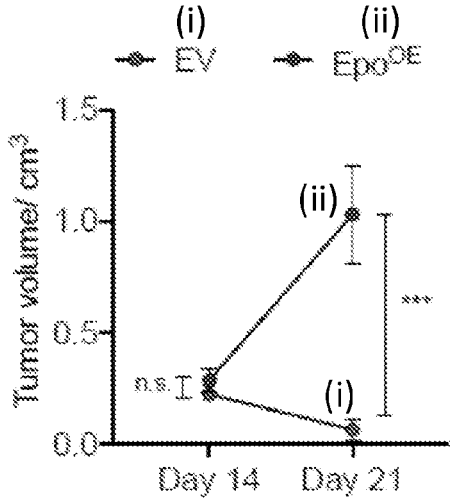


FIG. 11B



	CR rate (Day 21)	P value (Fisher's exact)
EV	6/12	0.0137
Epo^{OE}	0/12	

CR: Complete Regression

FIG. 11C

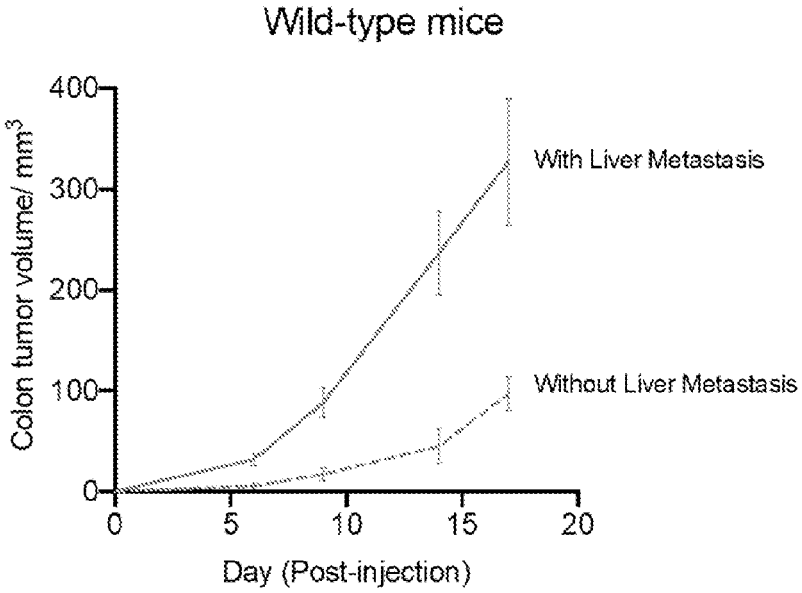


FIG. 12A

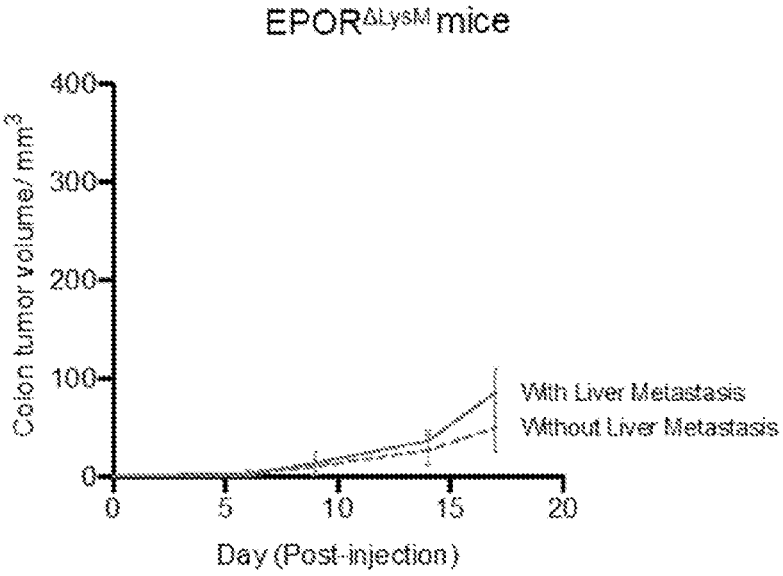


FIG. 12B

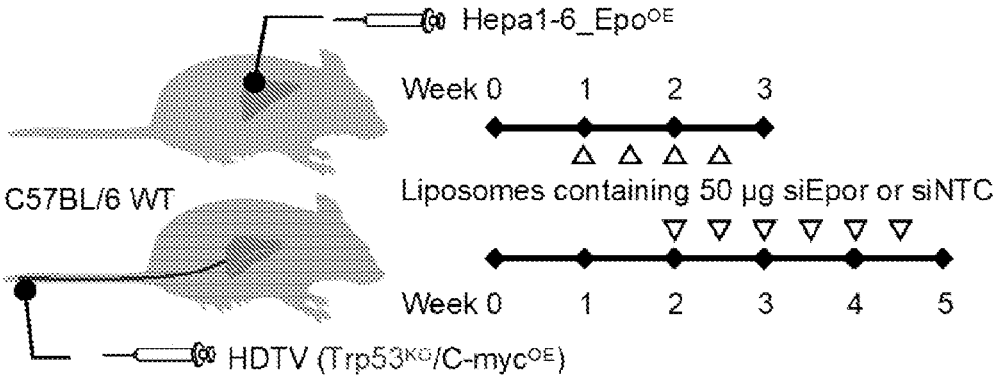


FIG. 13A

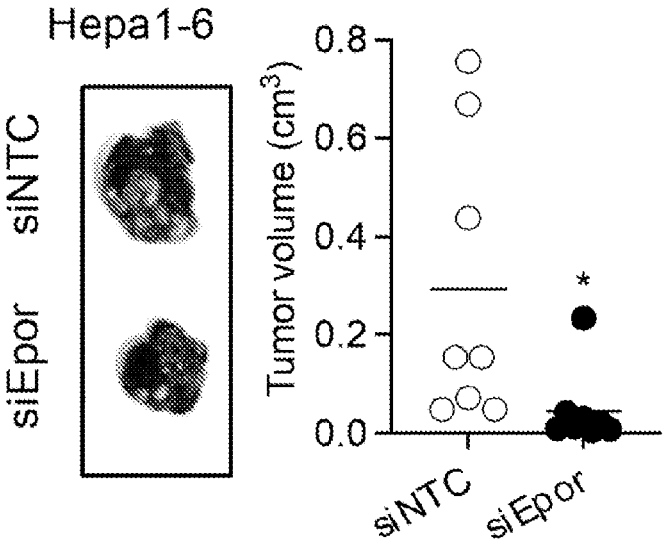


FIG. 13B

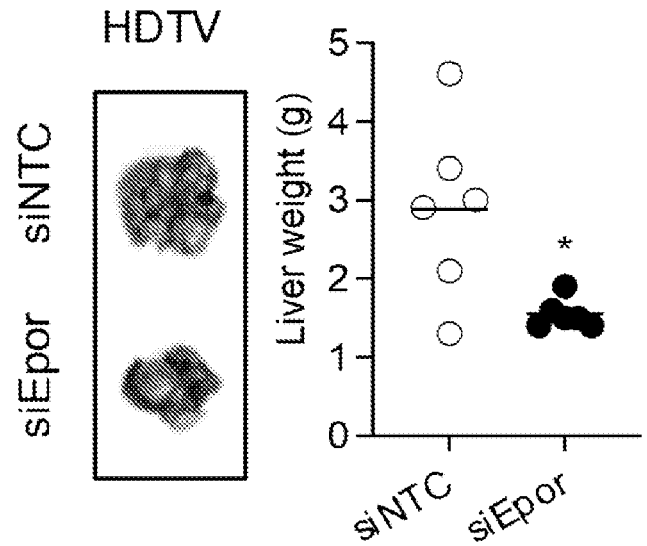


FIG. 13C

DSPC:DPPC:Cholesterol:DSPE-PEG-NH2 (1:1:0.5:0.4)

Z-average (nm)	245 ± 13
Polydispersity index	0.18 ± 0.05
Encapsulation efficiency (%) siRNA:NP 1:40 w/w	81.7 ± 3.54

FIG. 14A

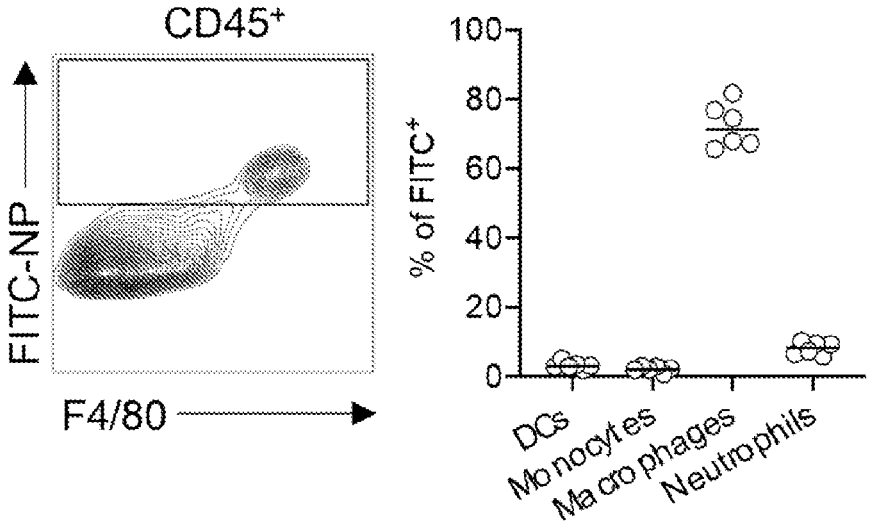


FIG. 14B

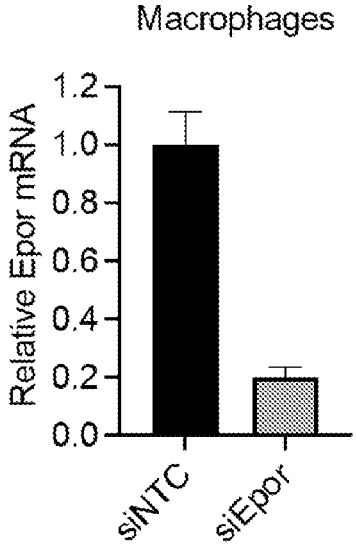


FIG. 14C

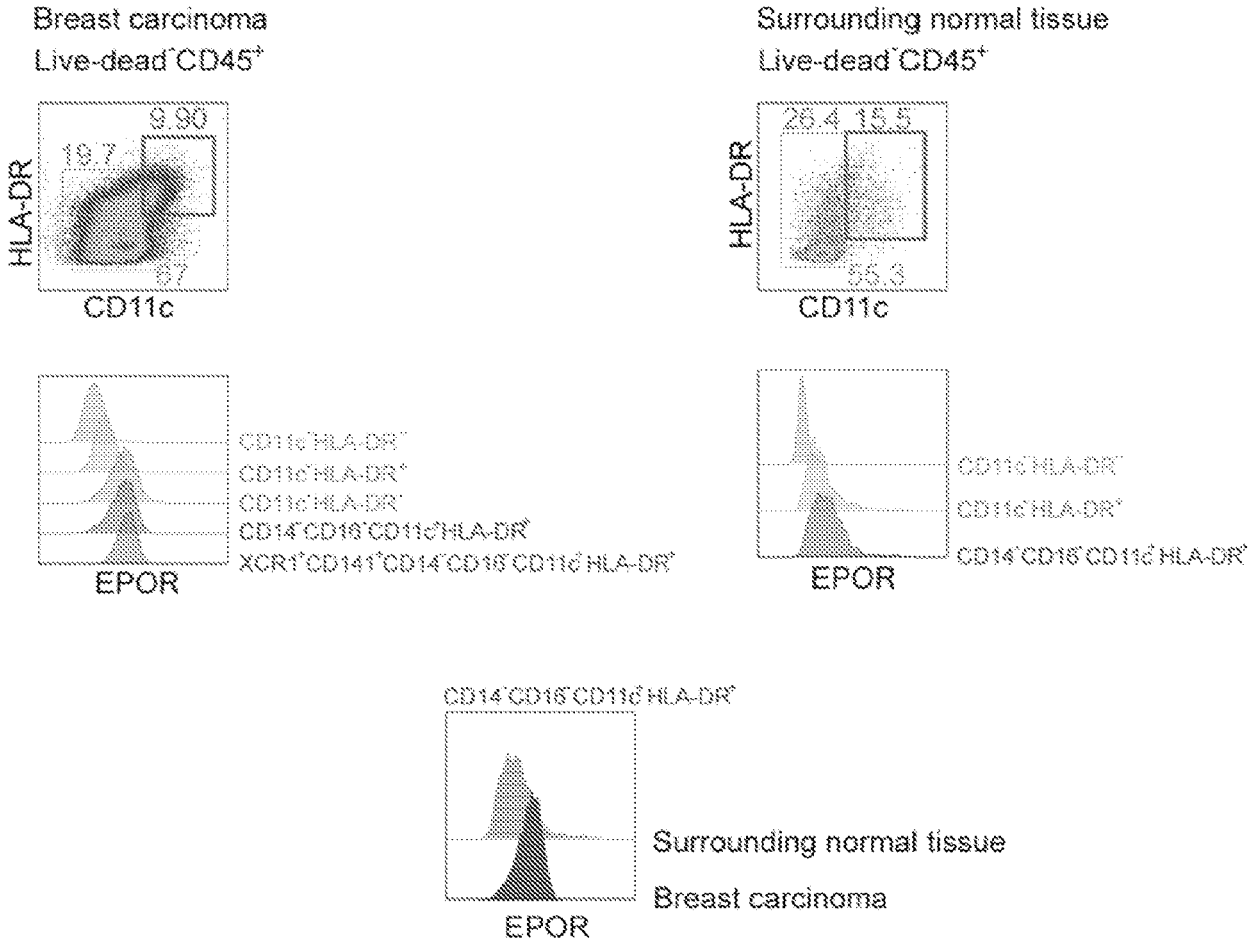

Breast carcinoma
Live-dead⁻CD45⁺
9.90
19.7
9.7
HLA-DR
CD11c
Surrounding normal tissue
Live-dead⁻CD45⁺
26.4
15.5
55.3
HLA-DR
CD11c
CD11c⁻HLA-DR⁻
CD11c⁺HLA-DR⁺
CD11c⁺HLA-DR⁻
CD14⁻CD16⁻CD11c⁺HLA-DR⁺
XCR1⁺CD141⁺CD14⁻CD16⁻CD11c⁺HLA-DR⁺
EPOR
CD11c⁻HLA-DR⁻
CD11c⁺HLA-DR⁺
CD14⁻CD16⁻CD11c⁺HLA-DR⁺
EPOR
CD14⁻CD16⁻CD11c⁺HLA-DR⁺
Surrounding normal tissue
Breast carcinoma
EPOR

FIG. 15A

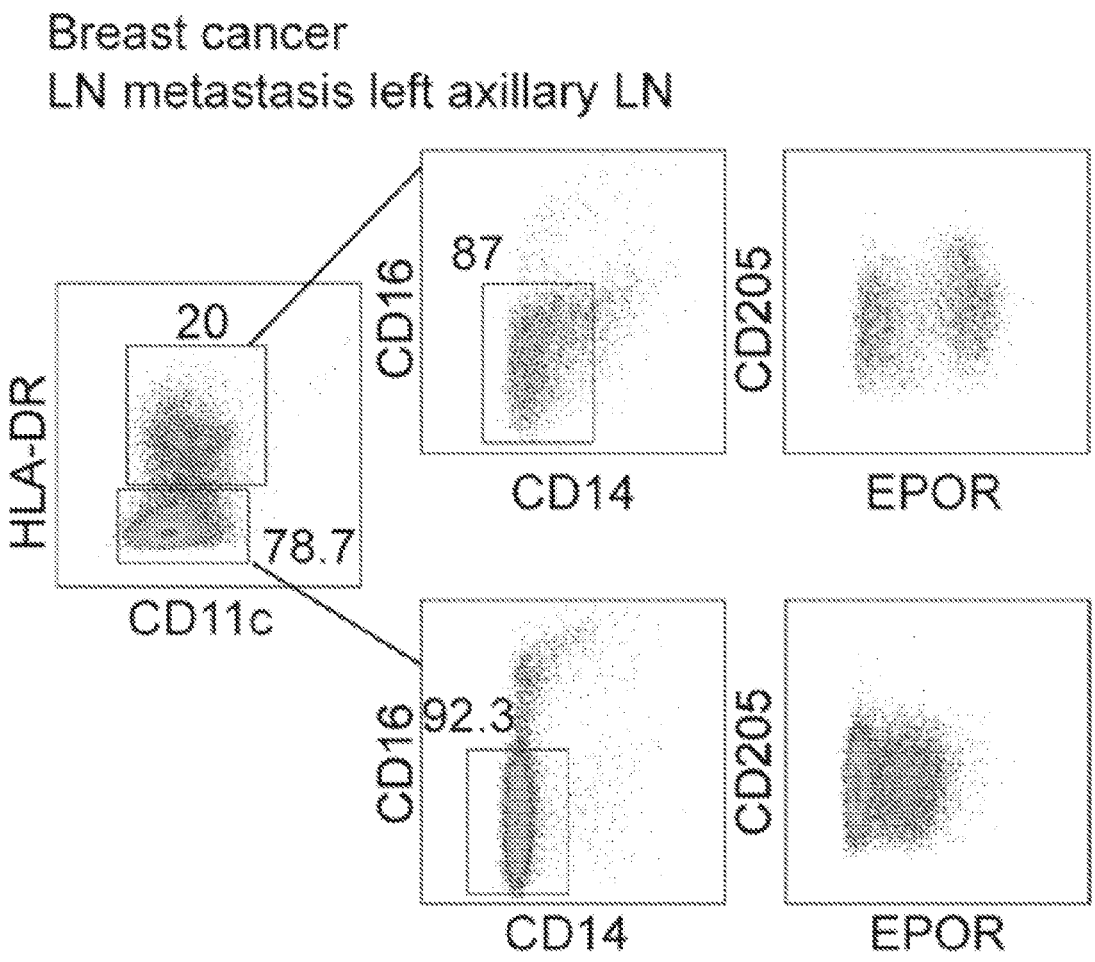

Breast cancer
LN metastasis left axillary LN
HLA-DR
CD11c
20
78.7
CD16
CD14
87
CD205
EPOR
CD16
CD14
92.3
CD205
EPOR

FIG. 15B

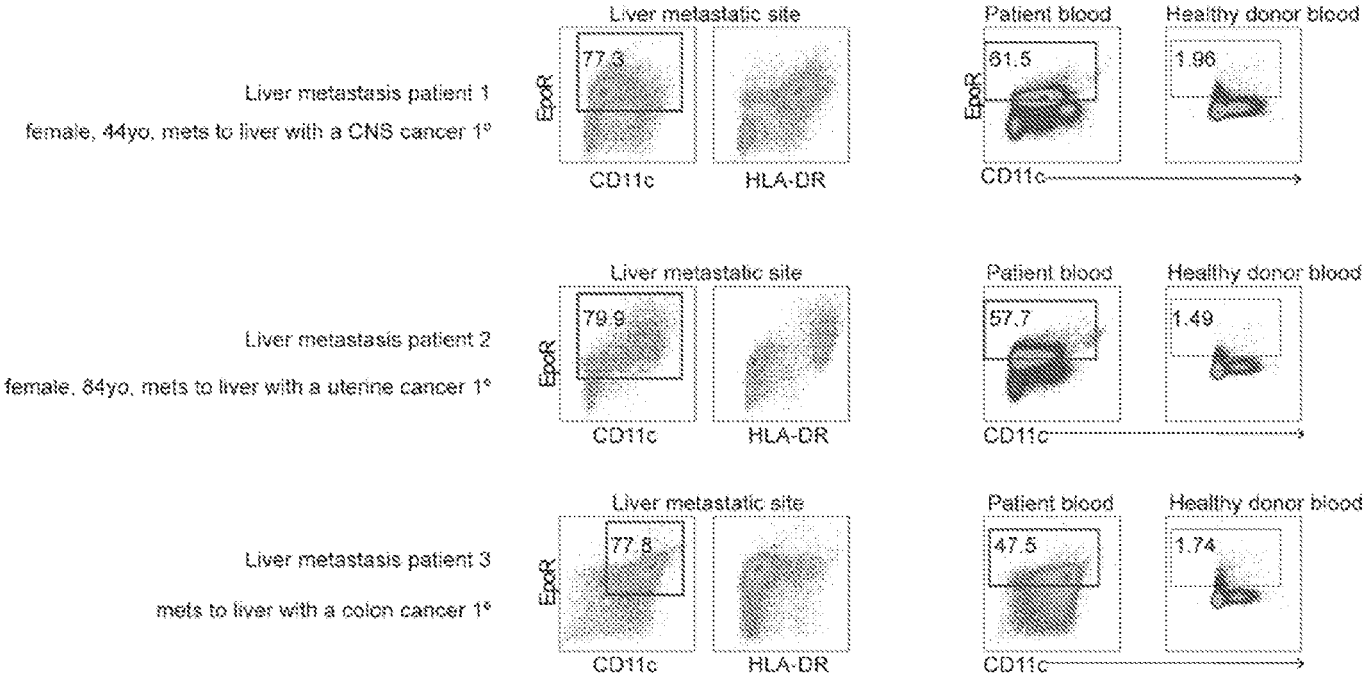


FIG. 16A

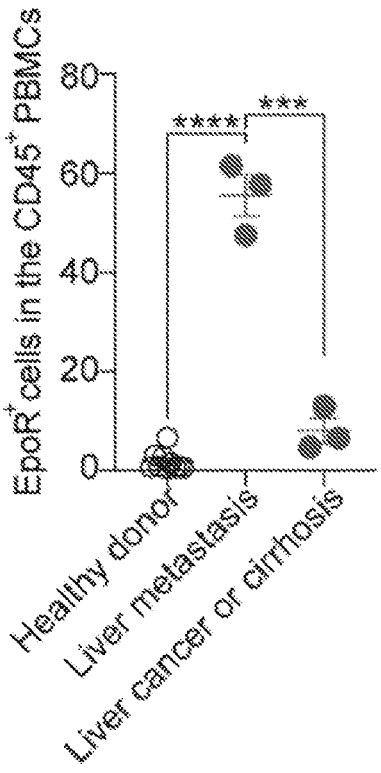
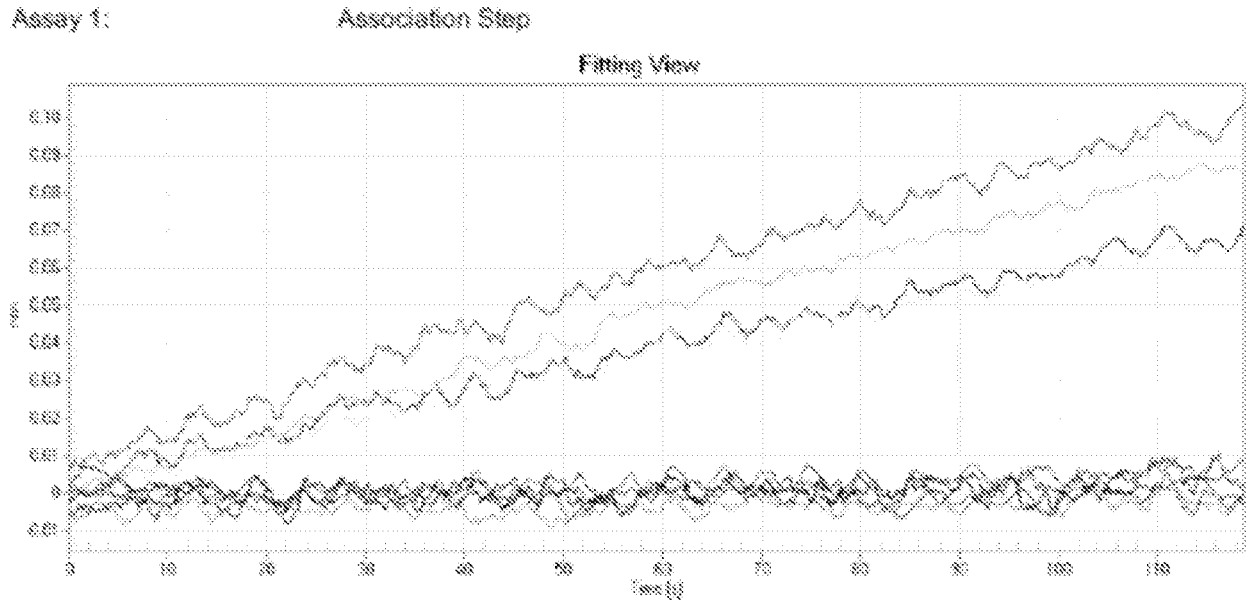


FIG. 16B



Test Group 1 Antibody ID	Analyte Conc. (nM)
EPORab - M1	10
EPORab - M2	10
EPORab - M3	10
EPORab - M4	10
EPORab - M5	10
EPORab - M6	10
EPORab - M7	10
Medium (EPO + No Ab)	10

FIG. 17

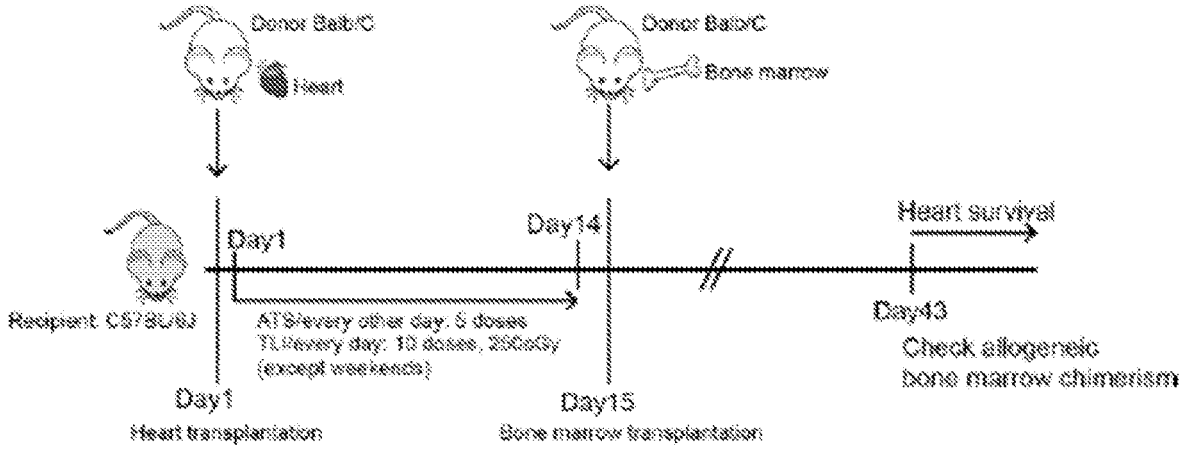


FIG. 18A

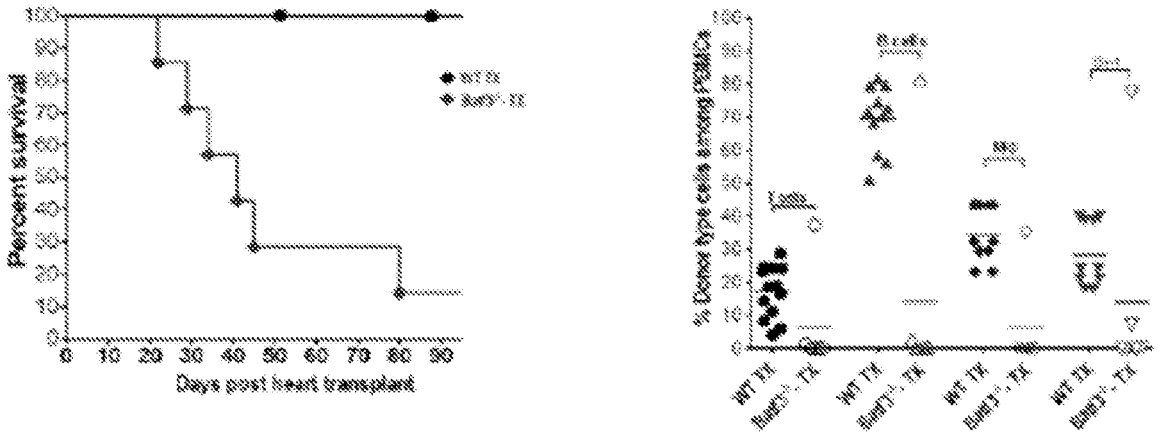


FIG. 18B

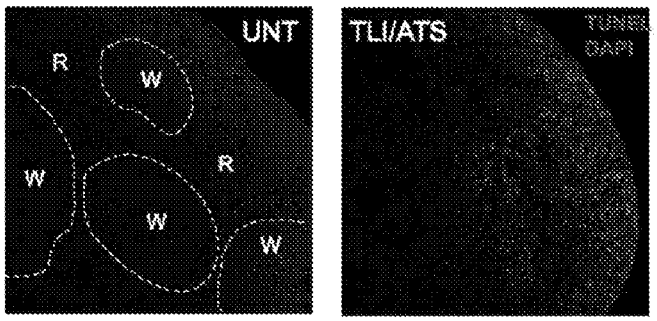


FIG. 19A

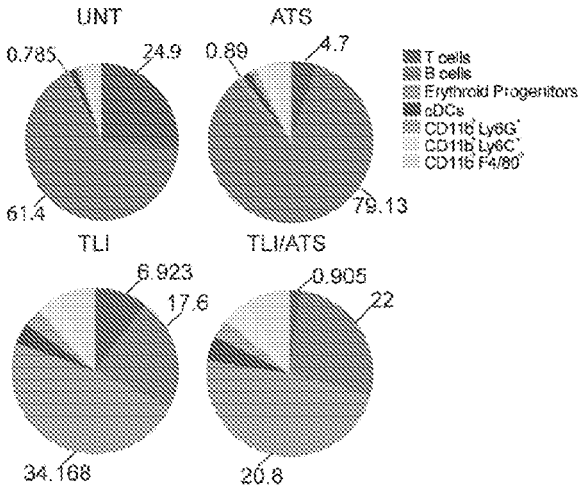


FIG. 19B

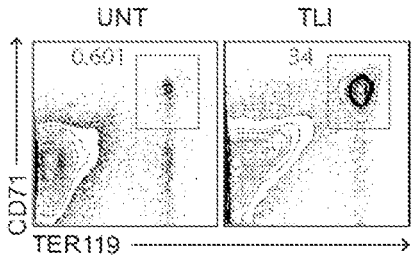


FIG. 19C

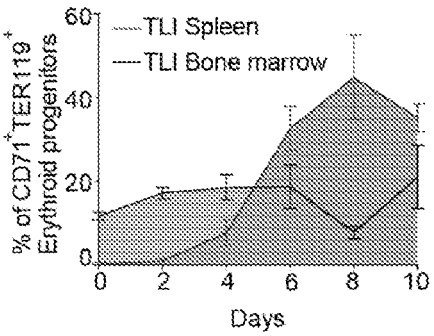


FIG. 19D

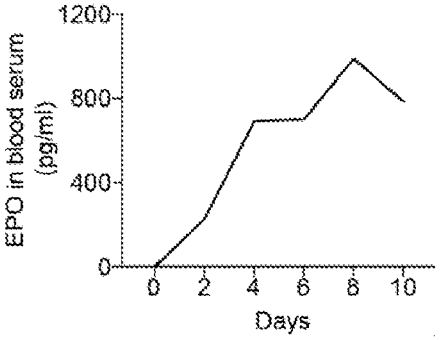
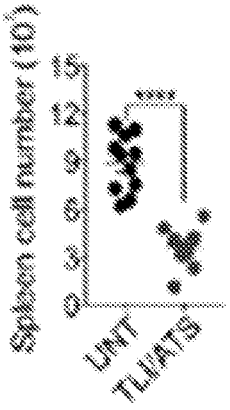
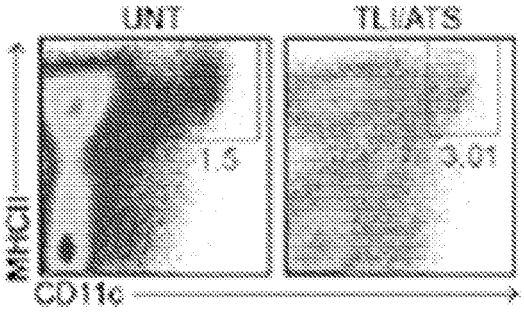


FIG. 19E





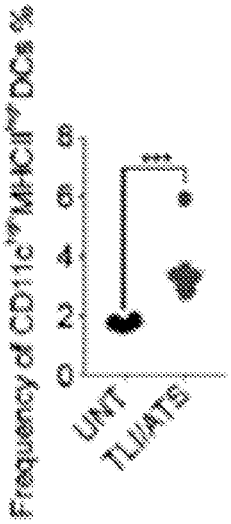
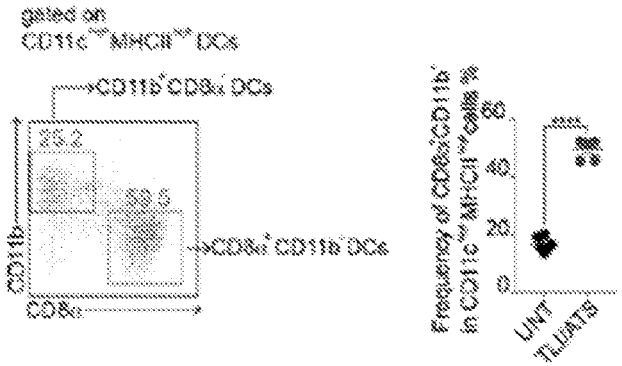


FIG. 20A

FIG. 20B



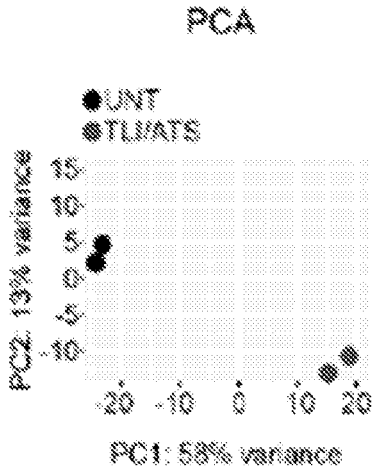


FIG. 20C

FIG. 20D

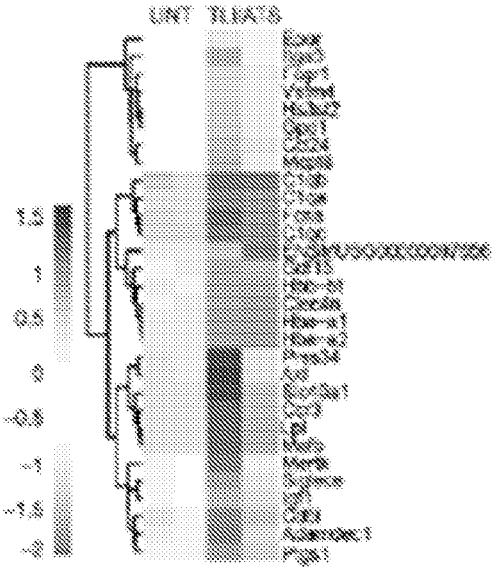


FIG. 20E

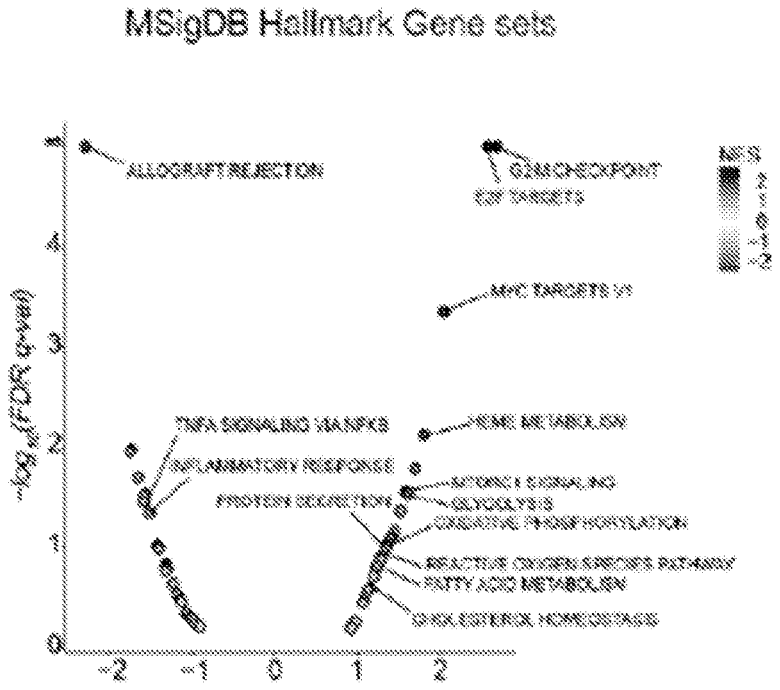


FIG. 20F

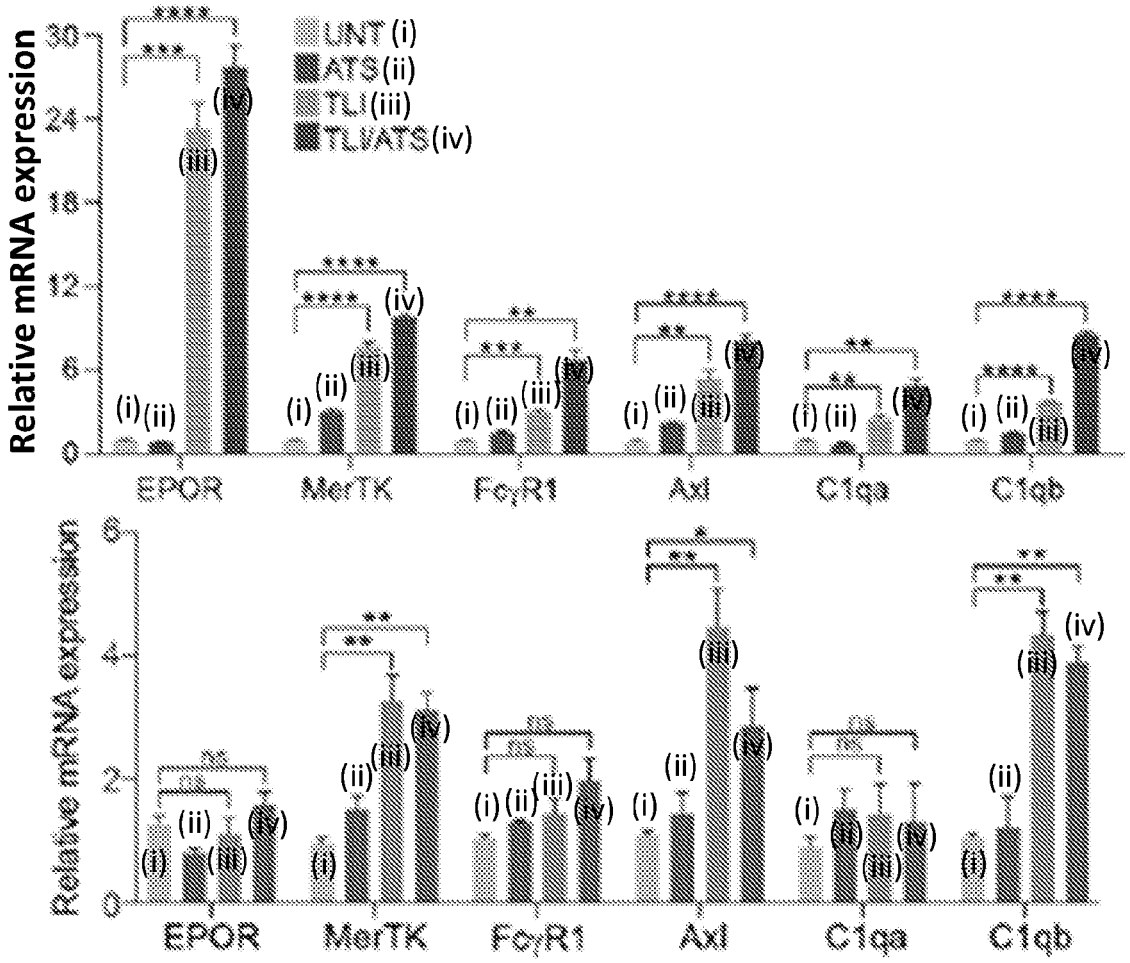


FIG. 20G

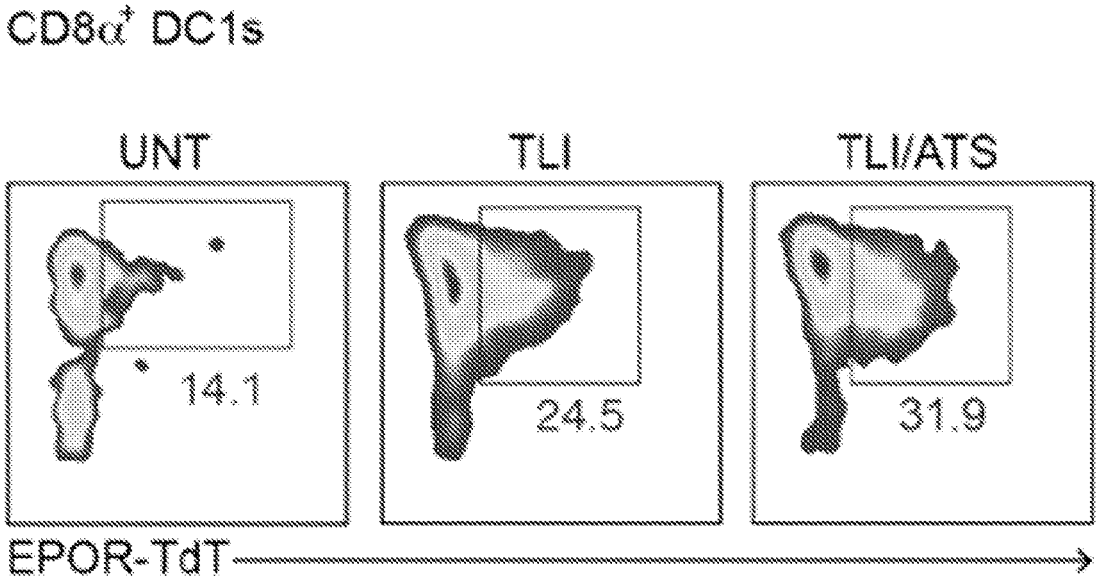


FIG. 20H

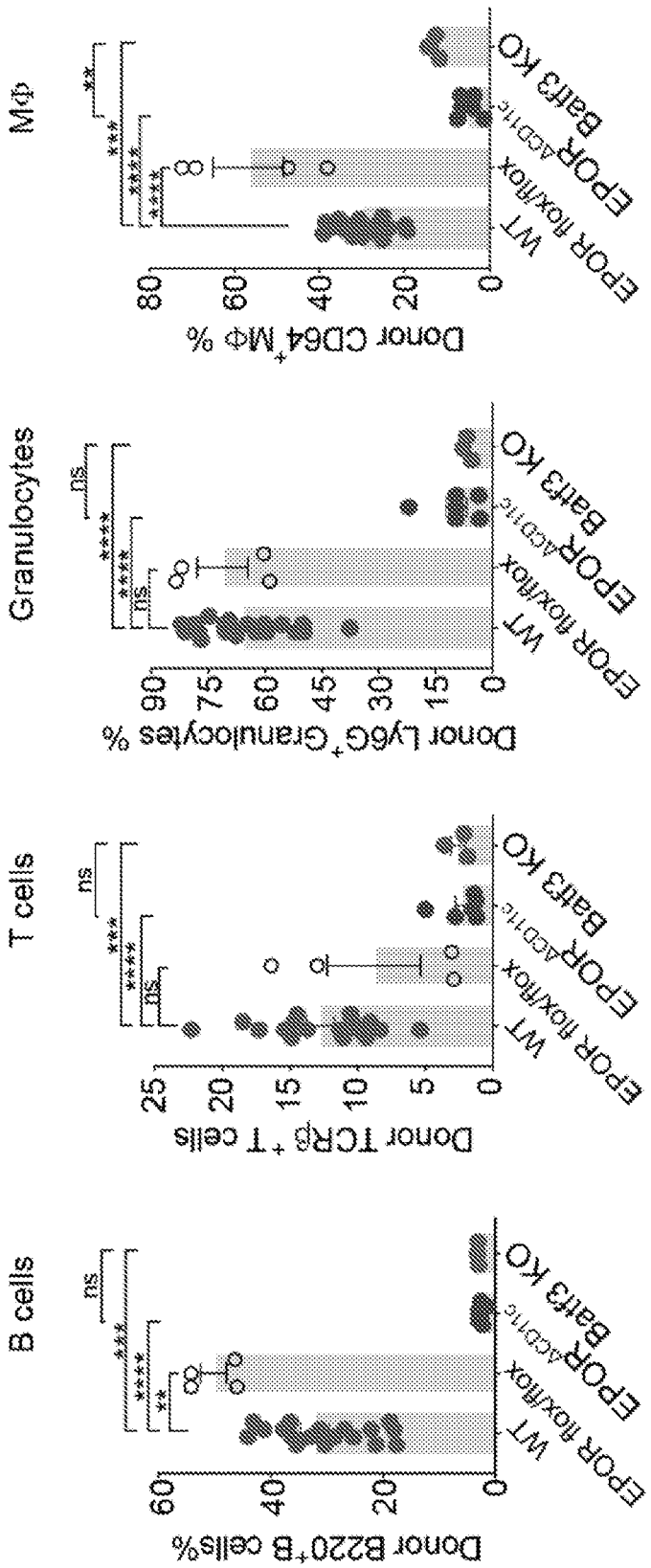

B cells
Donor B220+B cells%
T cells
Donor TCRβ+T cells
Granulocytes
Donor Ly6G+Granulocytes %
Mφ
Donor CD64+Mφ %
WT
EPOR flox/flox
EPOR ΔCD11c
Batf3 KO

FIG. 21

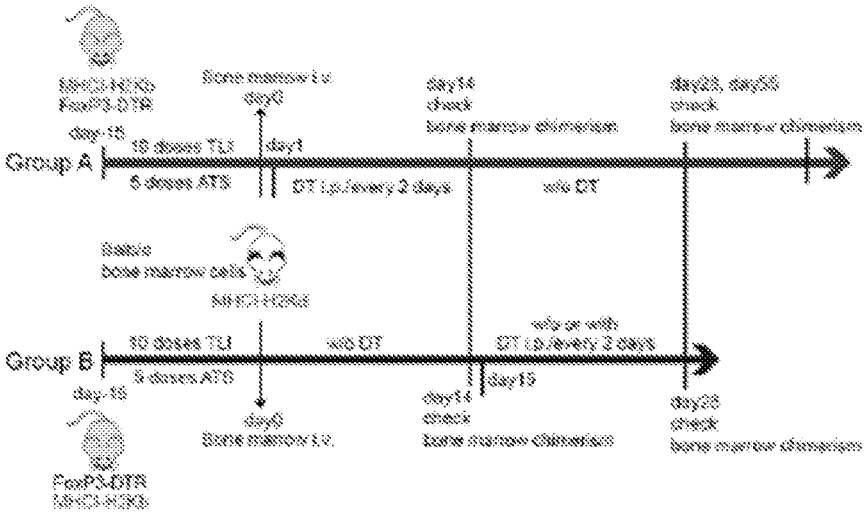


FIG. 22A

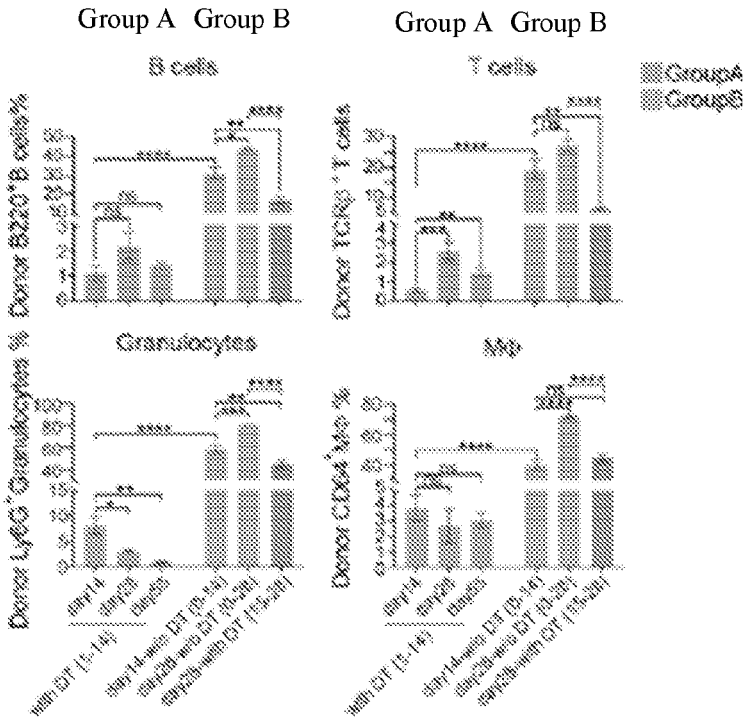


FIG. 22B

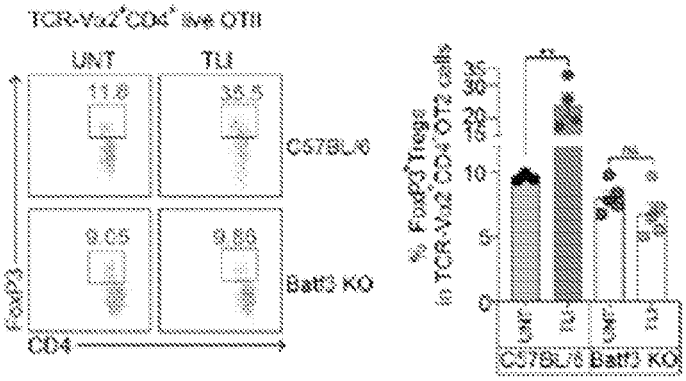


FIG. 23A

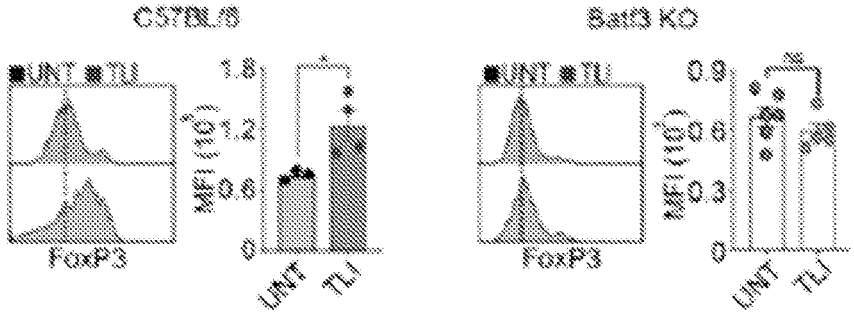


FIG. 23B

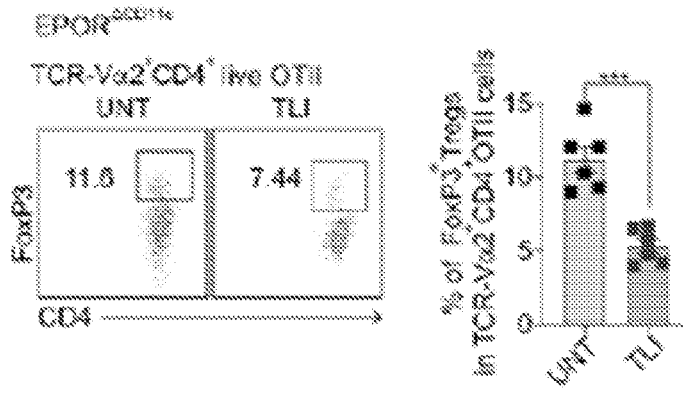


FIG. 23C

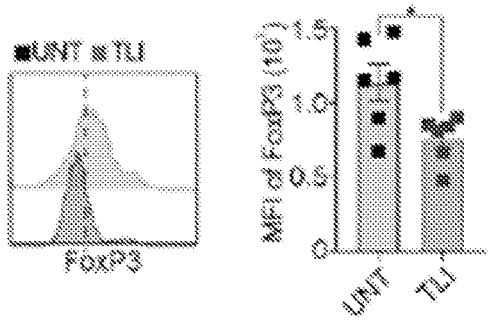


FIG. 23D

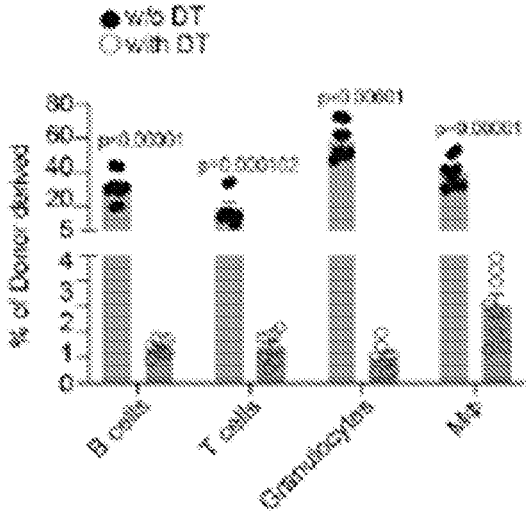


FIG. 24A

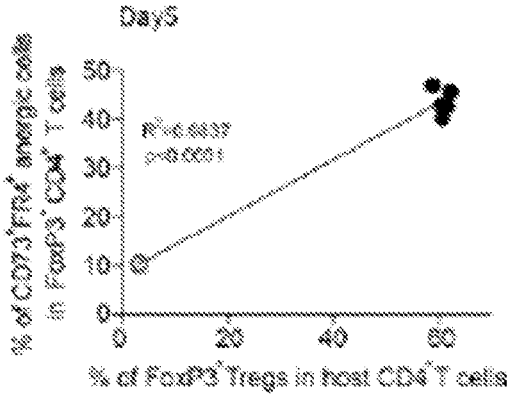


FIG. 24D

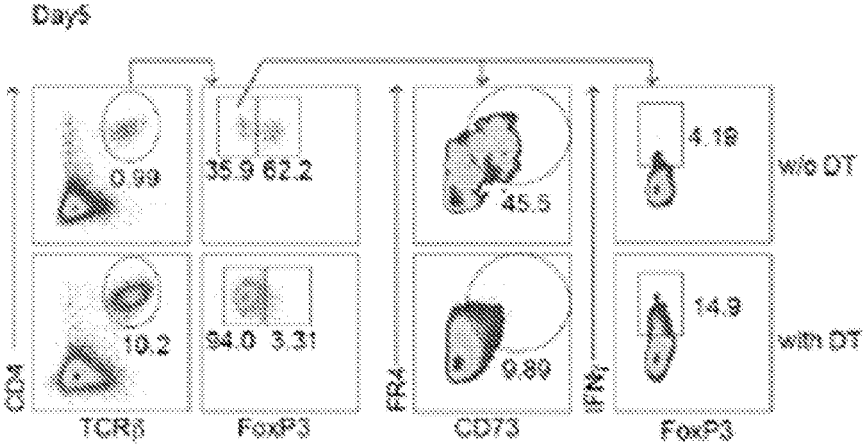


FIG. 24B

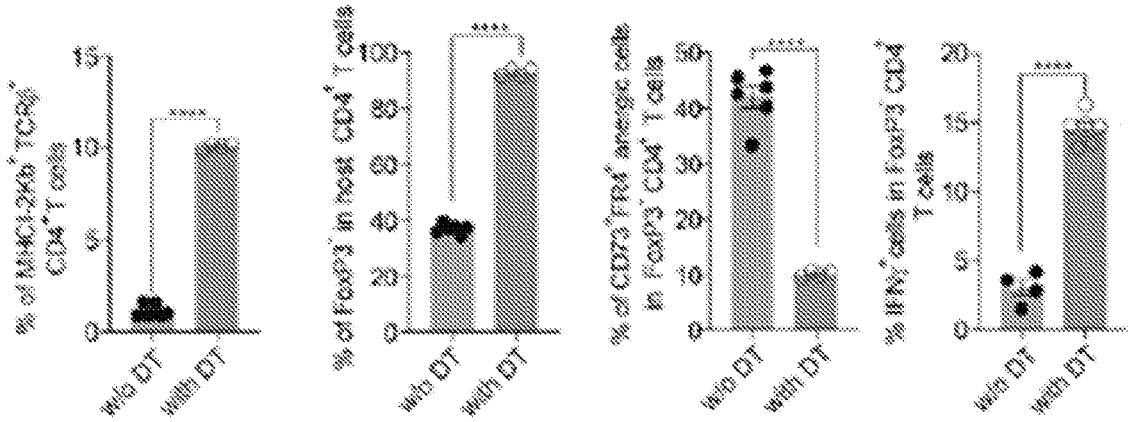


FIG. 24C

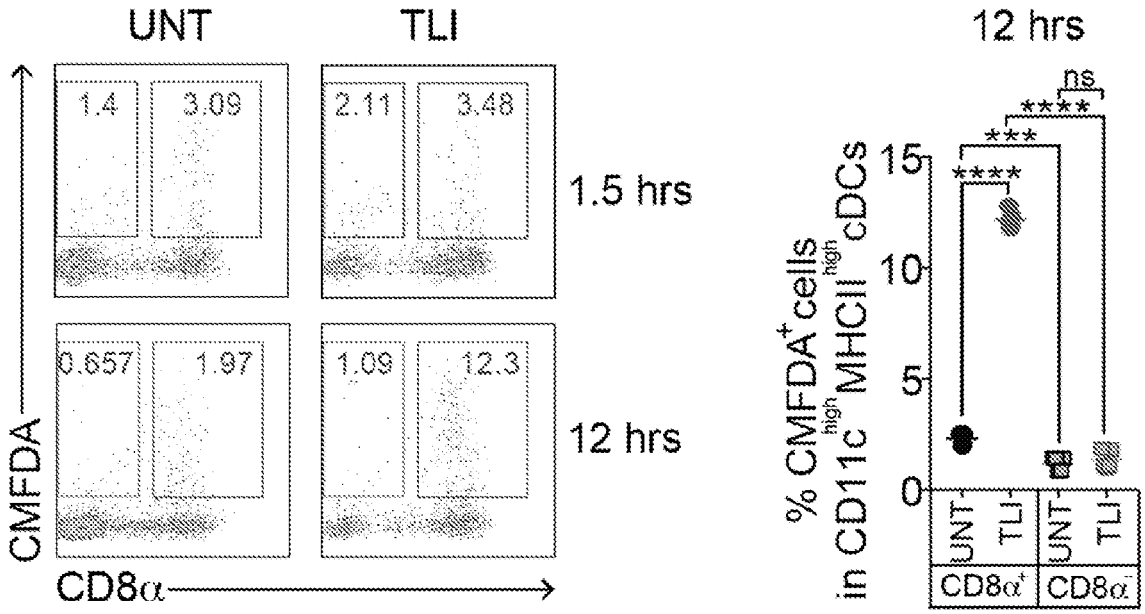


FIG. 25A

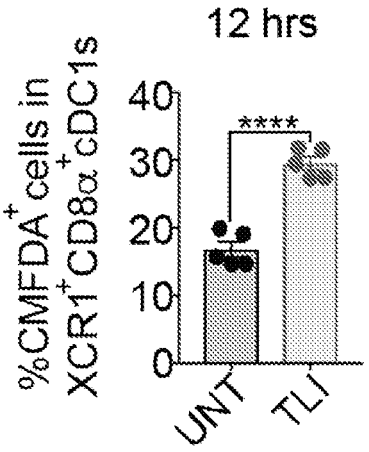


FIG. 25B

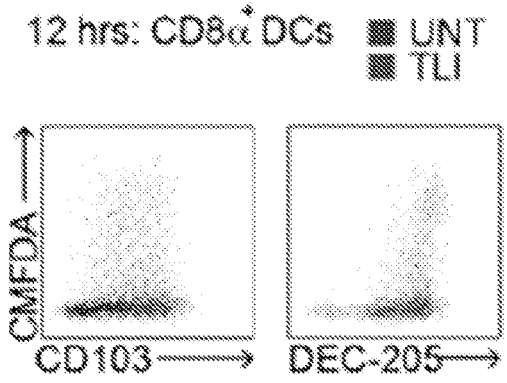


FIG. 25C

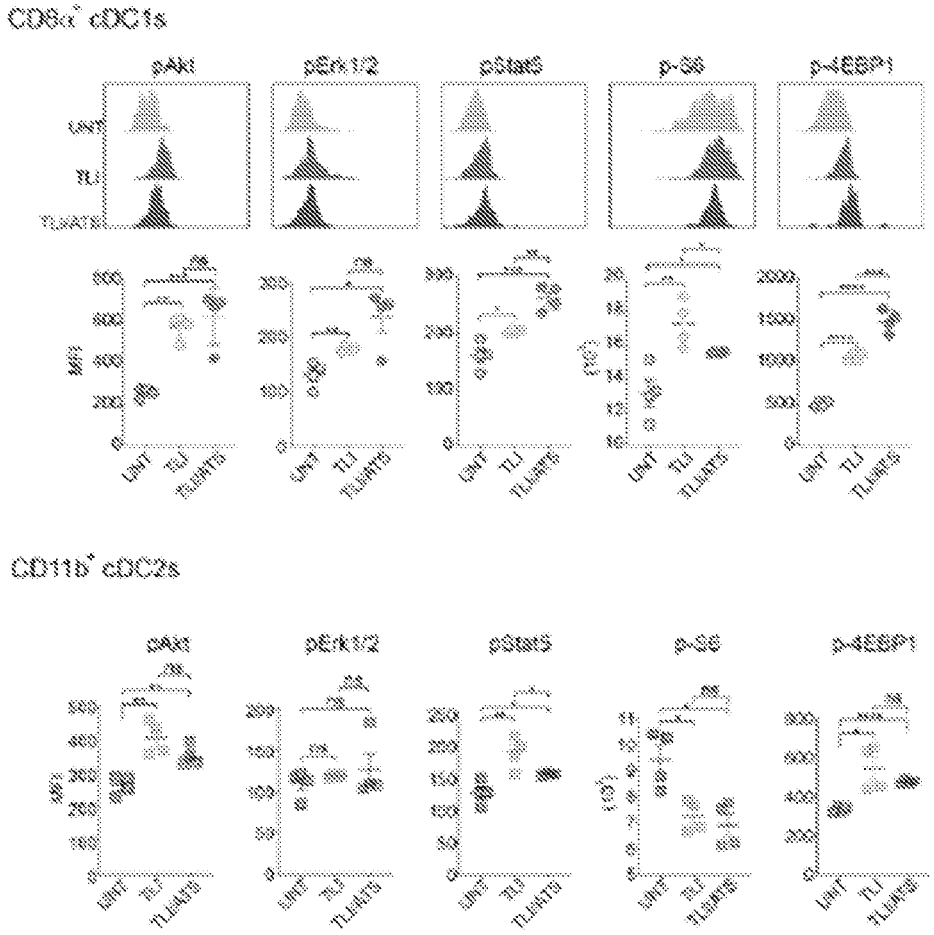


FIG. 26A

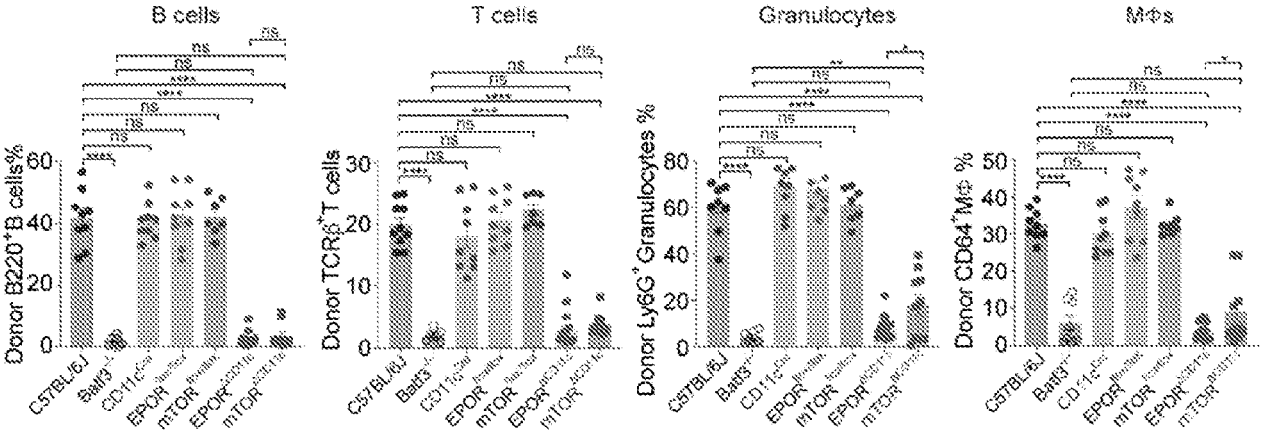


FIG. 26B

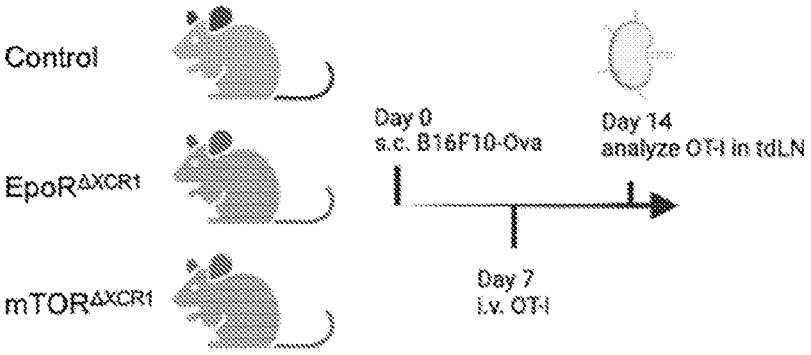


FIG. 27A

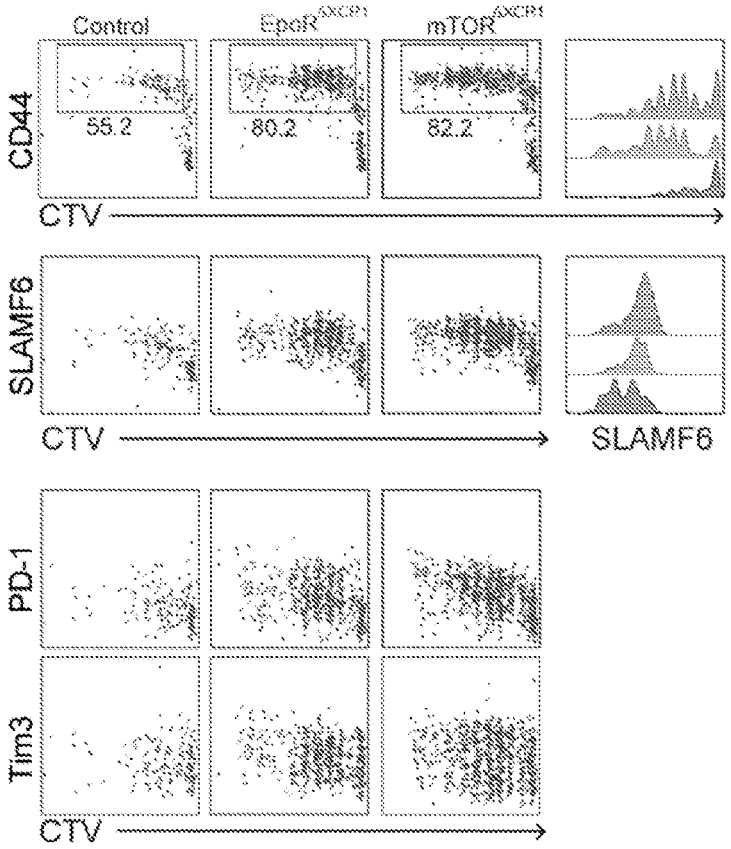


FIG. 27B

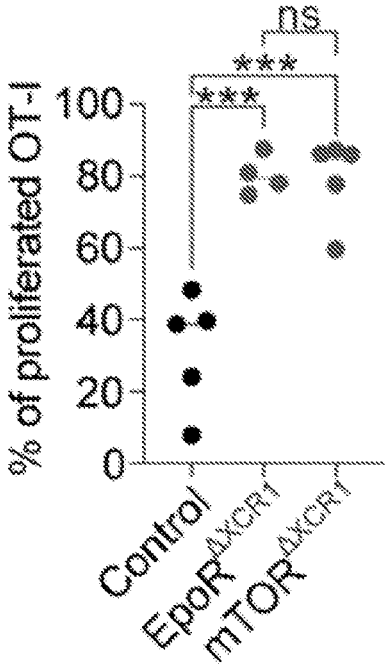


FIG. 27C

Clones	Cell staining (%)			Binding Kinetics of EPOR-CD131-Fc			Blocking EPO/EPOR interaction	Binding Kinetics of EPOR-Fc			Binding Kinetics of CD131-Fc		
	293T/EPOR/CD131	293T/EPOR	293T/CD131	K_D	k_{on}	k_{dis}		K_D	k_{on}	k_{dis}	K_D	k_{on}	k_{dis}
M1	53.2	55.1	20.9	8.093E-11	331600	2.684E-05	31.2%	1.124E-10	383100	4.31E-05	-	-	-
M2	63.9	69.6	21.8	1.735E-10	507200	8.801E-05	93.6%	1.307E-10	578000	7.56E-05	-	-	-
M3	9.5	9.9	11.6	-	-	-	13.4%	-	-	-	-	-	-
M9	30.5	36.9	36.9	-	-	-	18.1%	-	-	-	-	-	-
M19	13.2	9.2	15.8	-	-	-	10.4%	-	-	-	-	-	-
M24	12.9	13.0	15.1	-	-	-	9.5%	-	-	-	-	-	-
M26	18.0	15.3	22.1	<1.0E-12	336800	<1.0E-07	31.3%	<1.0E-12	326500	<1.0E-07	<1.0E-12	365000	<1.0E-07
M37	29.9	35.9	37.7	-	-	-	-7.1%	-	-	-	-	-	-
M38	26.1	26.4	30.8	-	-	-	0.5%	-	-	-	-	-	-
M41	14.2	12.8	14.1	-	-	-	18.7%	-	-	-	-	-	-
M43	28.6	27.7	28.7	-	-	-	-11.4%	-	-	-	-	-	-
M52	12.2	14.3	15.2	-	-	-	7.4%	-	-	-	-	-	-
M54	10.8	15.2	18.8	-	-	-	16.0%	-	-	-	-	-	-
M71	9.8	9.2	15.3	-	-	-	0.1%	-	-	-	-	-	-
M80	7.7	9.5	12.5	-	-	-	-1.8%	-	-	-	-	-	-
M82	17.5	23.4	14.8	<1.0E-12	79640	<1.0E-07	24.8%	-	-	-	<1.0E-12	1.77E+05	<1.0E-07
M87	11.3	10.2	12.1	-	-	-	11.5%	-	-	-	-	-	-

FIG. 28A

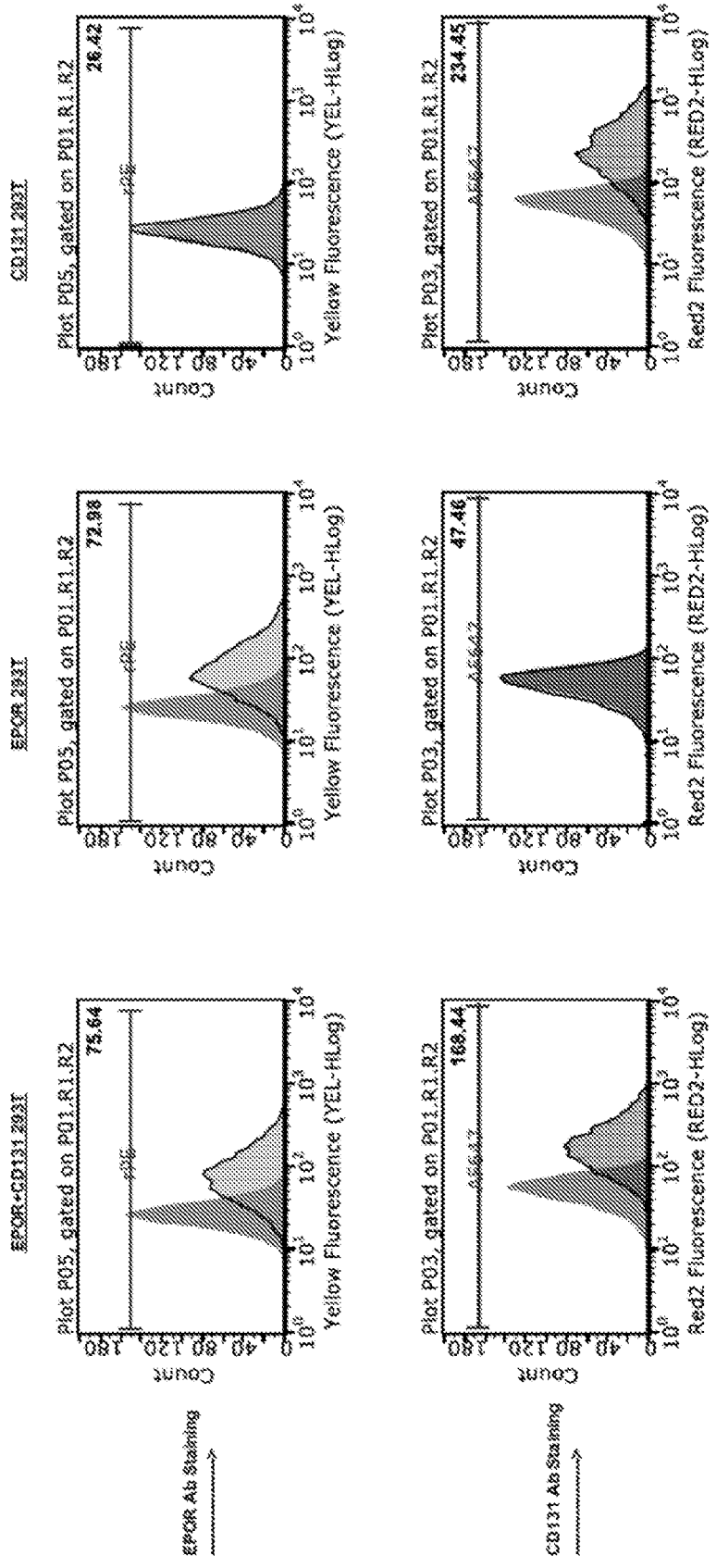

EPOR+CD131 293T
EPOR 293T
CD131 293T
EPOR Ab Staining
CD131 Ab Staining
Plot P05, gated on P01.R1.R2
75.64
72.98
26.42
Plot P03, gated on P01.R1.R2
168.44
47.46
234.45
Count
Yellow Fluorescence (YEL-HLog)
Red2 Fluorescence (RED2-HLog)

FIG. 28B

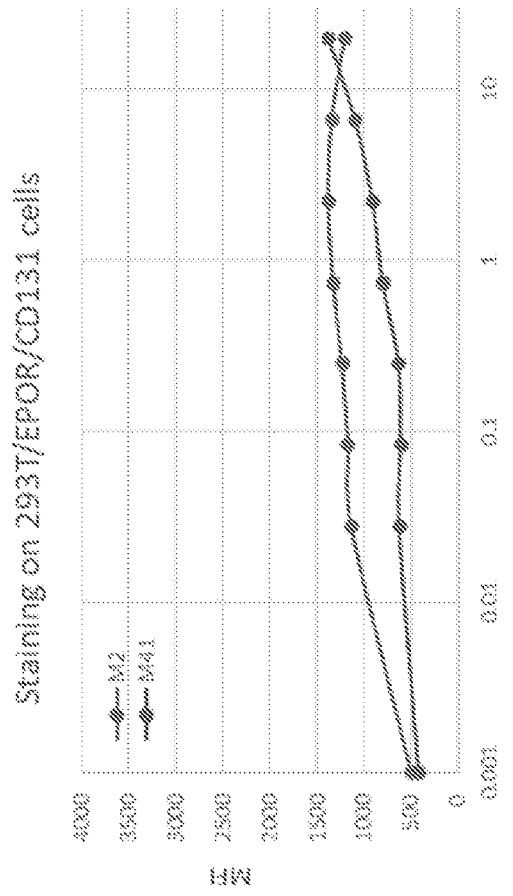


FIG. 29A

FIG. 29B

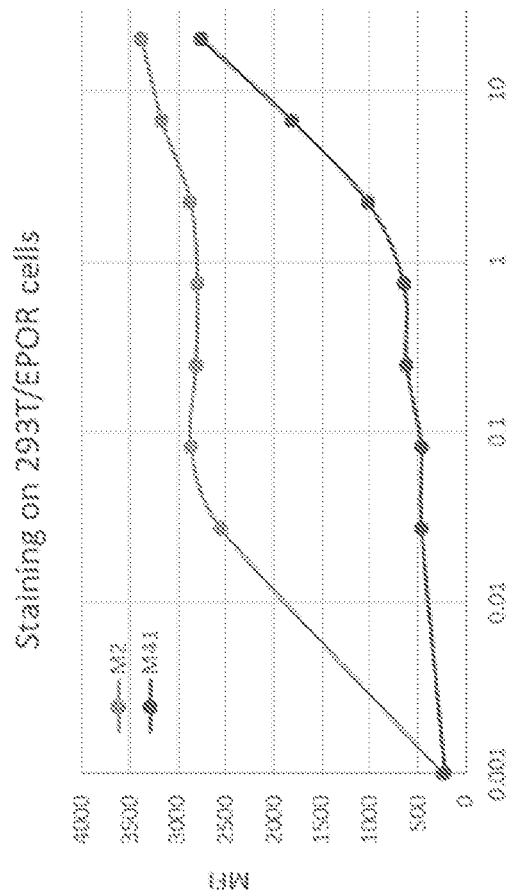


FIG. 29C

FIG. 29D

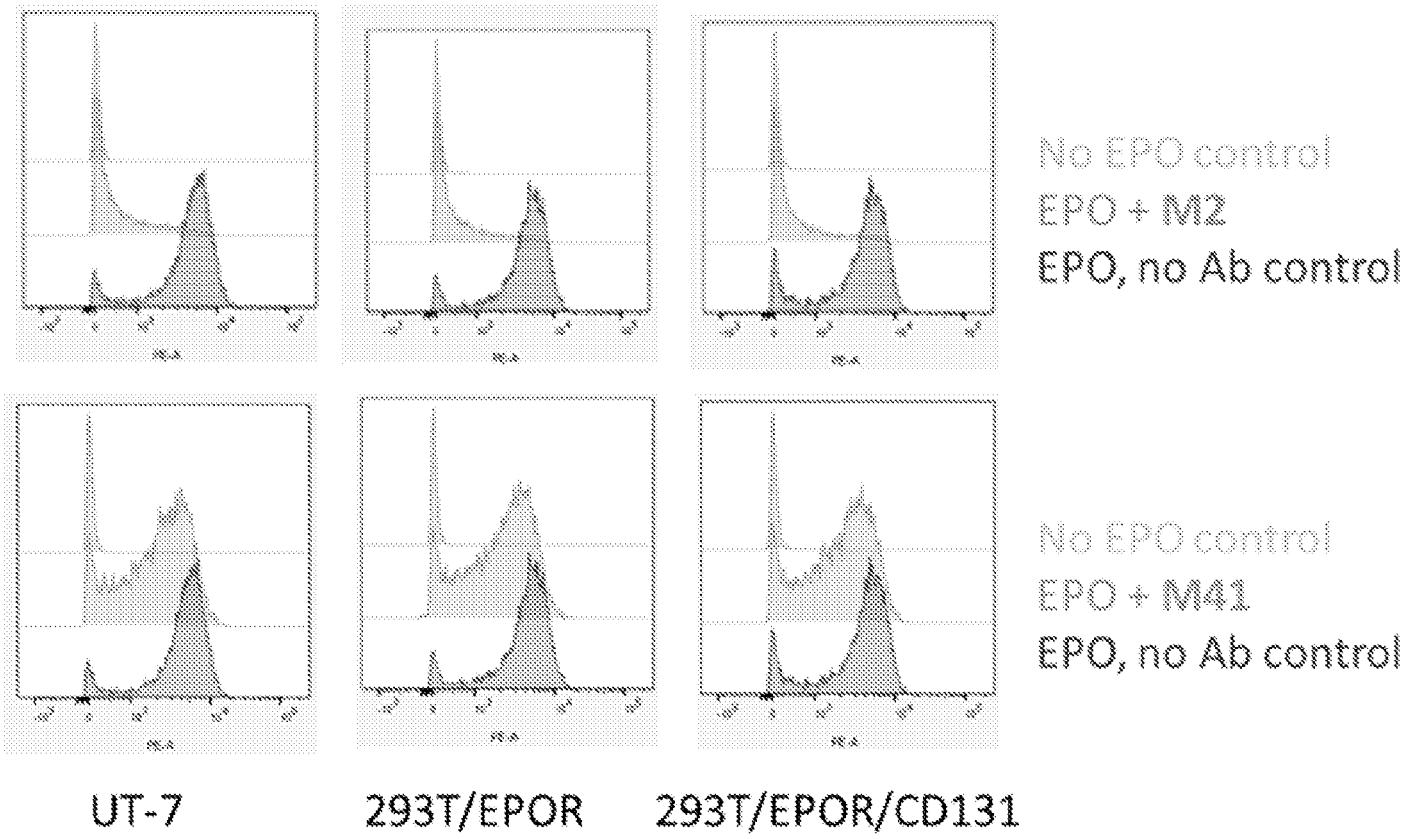

No EPO control
EPO + M2
EPO, no Ab control
No EPO control
EPO + M41
EPO, no Ab control
UT-7
293T/EPOR
293T/EPOR/CD131

FIG. 30

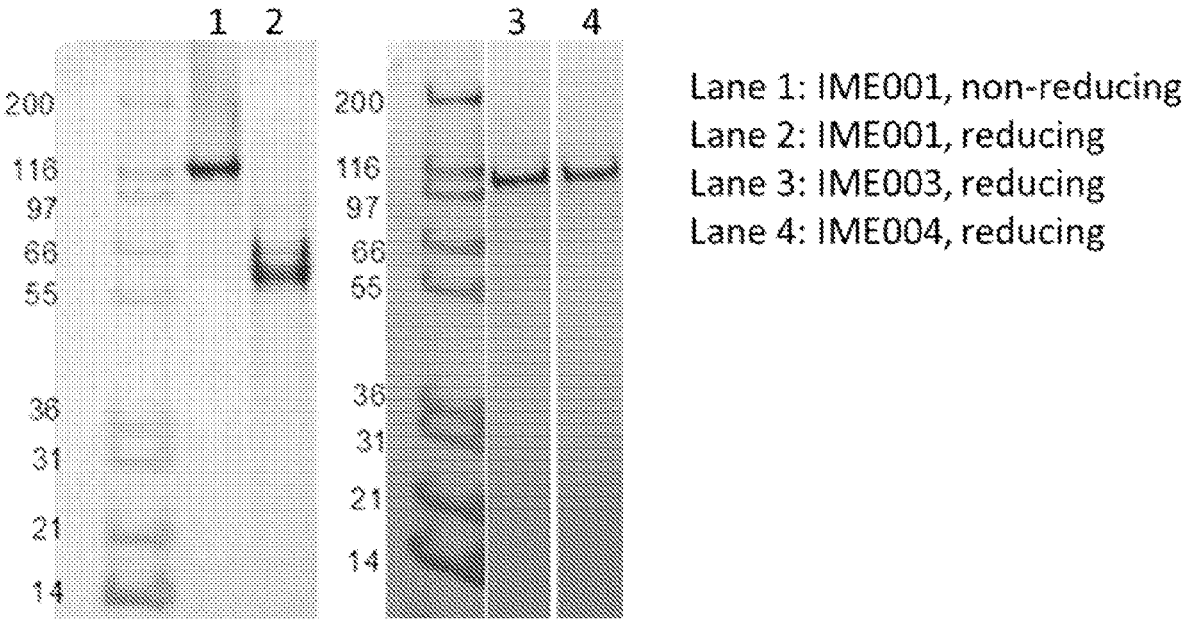


FIG. 31A

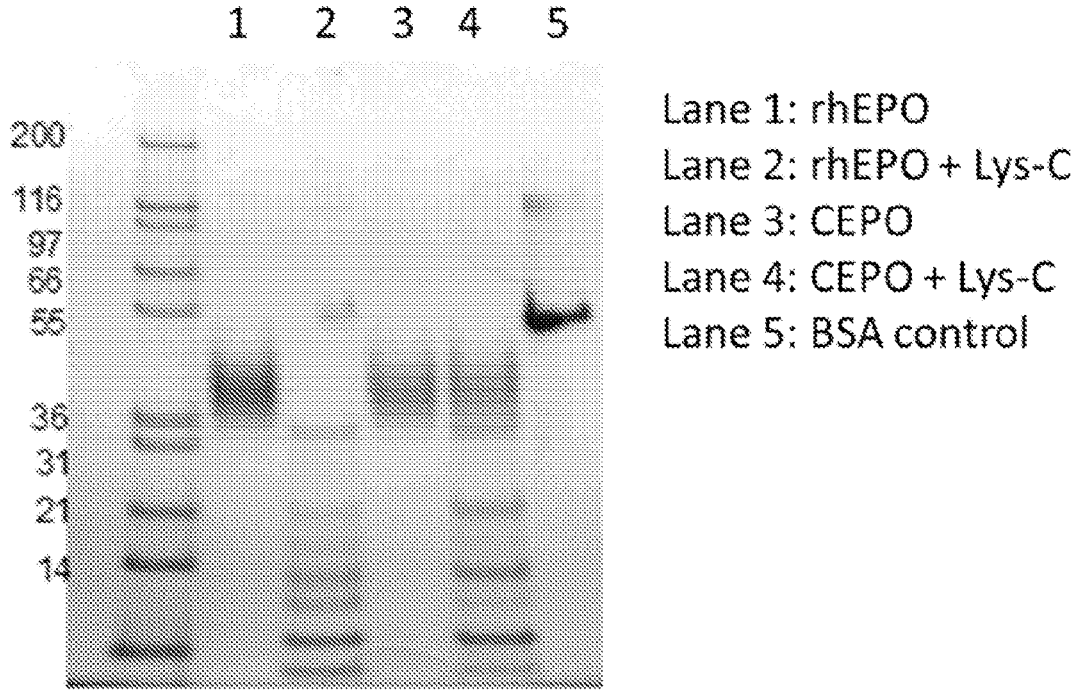


FIG. 31B

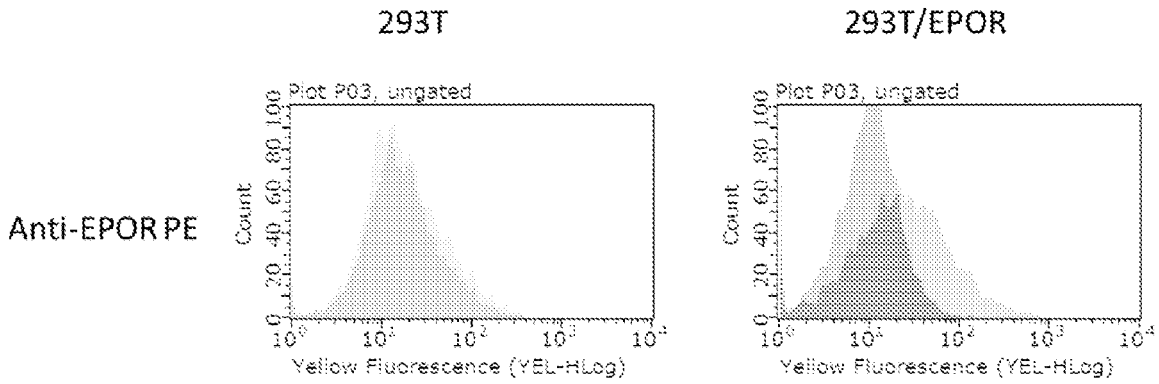


FIG. 32A

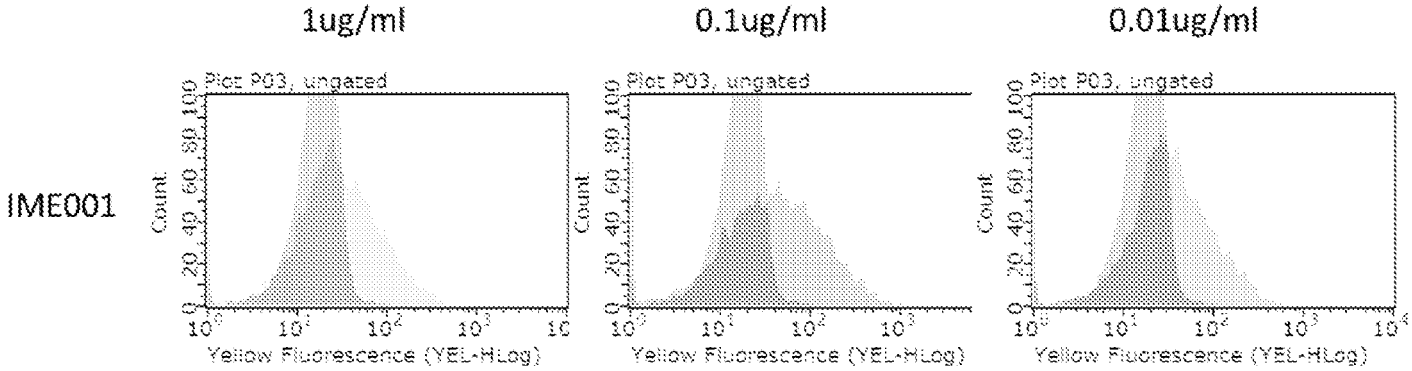


FIG. 32B

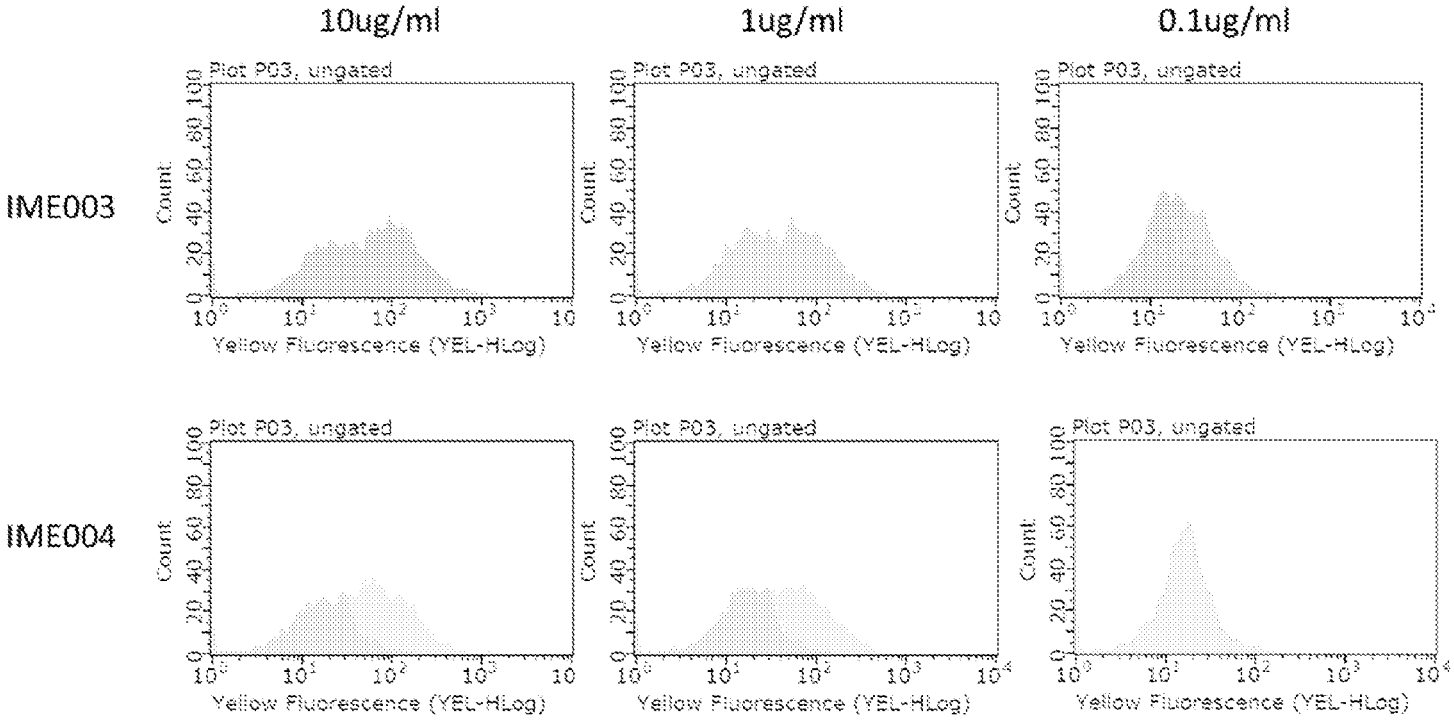


FIG. 32C

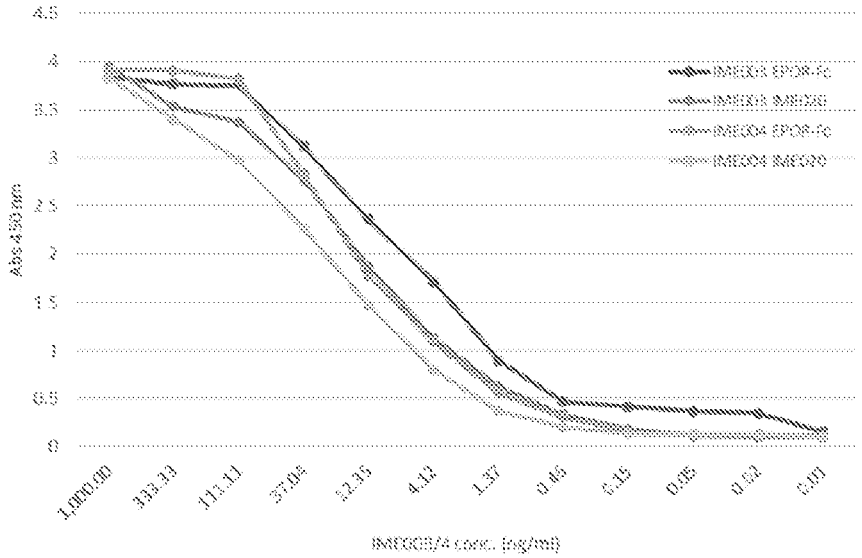


FIG. 32D

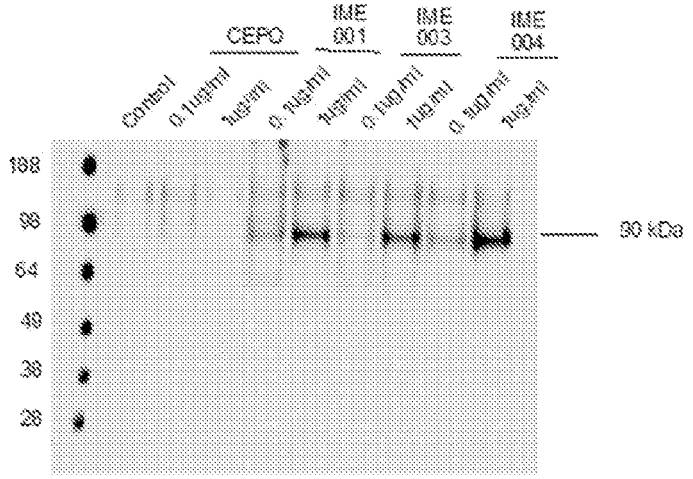


FIG. 33A

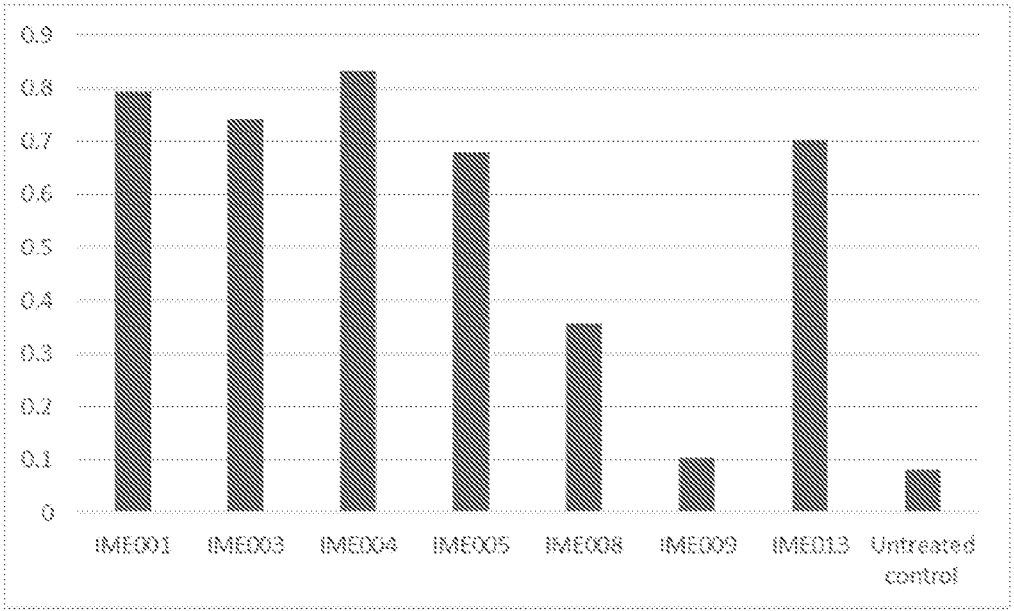


FIG. 33B

```
1   atgggggtgc acgaatgtcc tgcctggctg tggcttctcc tgtccctgct gtcgctccct ctgggcctcc
      M  G  V   H  E  C   P  A  W  L   W  L  L   L  S  L   L  S  L  P   L  G  L

71  cagtcctggg cgccccacca cgcctcatct gtgacagccg agtcctggag aggtacctct tggaggccaa
      P  V  L   G  A  P   P   R  L  I   C  D  S   R  V  L  E   R  V  L   L  E  A

141 ggaggccgag aatatcacga cgggctgtgc tgaacactgc agcttgaatg agaatatcac tgtcccagac
      K  E  A  E   N  I  T   T  G  C   A  E  H  C   S  L  N   E  N  I   T  V  P  D

211 accaaagtta atttctatgc ctggaagagg atggaggtcg ggcagcaggc cgtagaagtc tggcagggcc
      T  K  V   N  F  Y   A  W  K  R   M  E  V   G  Q  Q   A  V  E  V   W  Q  G

281 tggccctgct gtcggaagct gtcctgcggg gccaggccct gttggtcaac tcttcccagc cgtgggagcc
      L  A  L   L  S  E  A   V  L  R   G  Q  A   L  L  V  N   S  S  Q   P  W  E

351 cctgcagctg catgtggata aagccgtcag tggccttcgc agcctcacca ctctgcttcg ggctctggga
      P  L  Q  L   H  V  D   K  A  V   S  G  L  R   S  L  T   T  L  L   R  A  L  G

421 gcccagaagg aagccatctc ccctccagat gcggcctcag ctgctccact ccgaacaatc actgctgaca
      A  Q  K   E  A  I   S  P  P  D   A  A  S   A  A  P   L  R  T  I   T  A  D

491 ctttccgcaa actcttccga gtctactcca atttcctccg gggaaagctg aagctgtaca caggggaggc
      T  F  R   K  L  F  R   V  Y  S   N  F  L   R  G  K  L   K  L  Y   T  G  E

561 ctgcaggaca ggggacaga
      A  C  R  T   G  D  R
```

FIG. 34

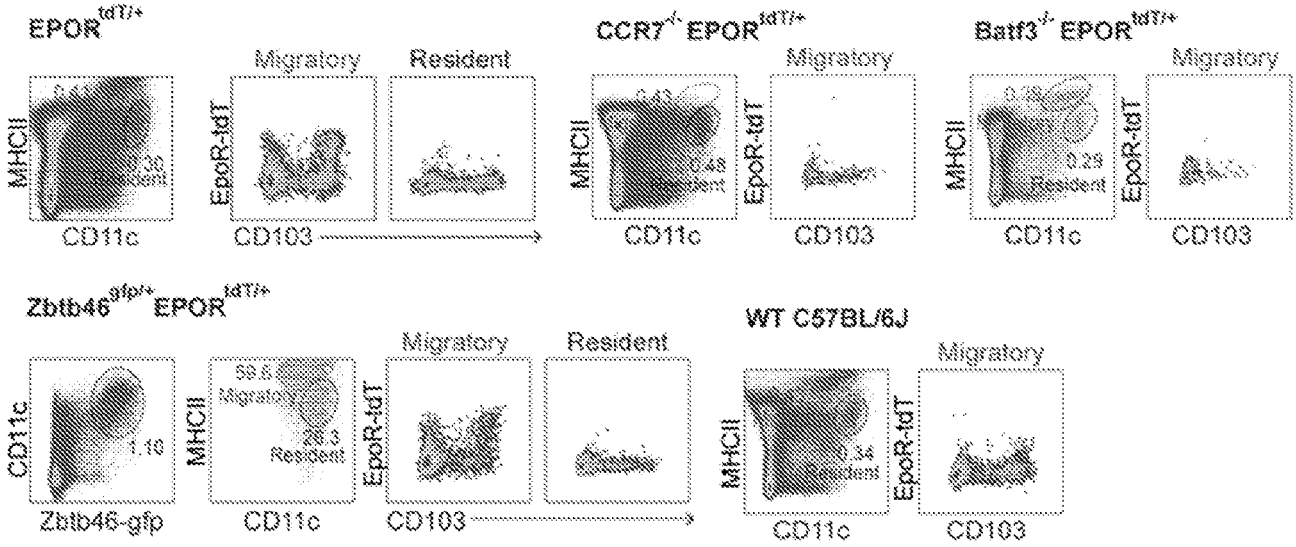


FIG. 35A

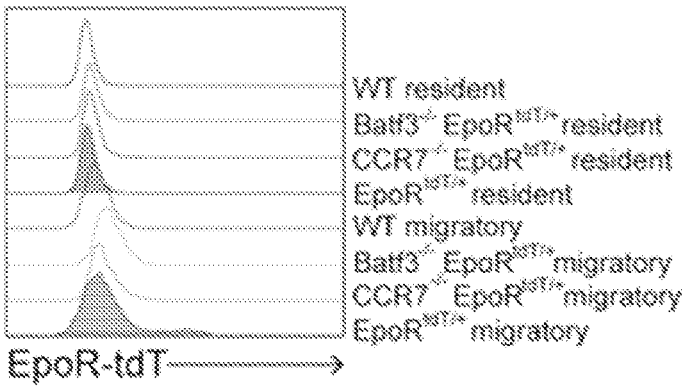


FIG. 35B

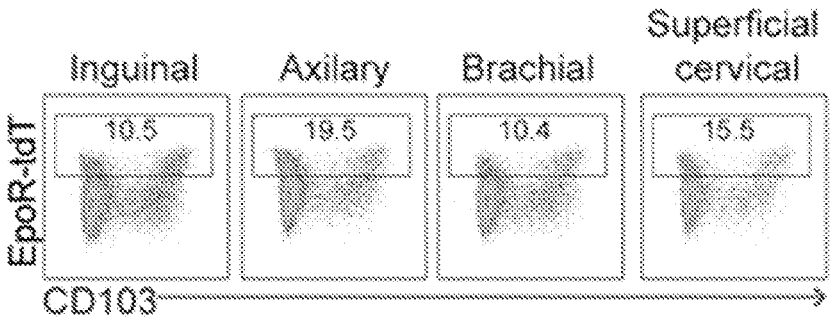


FIG. 35C

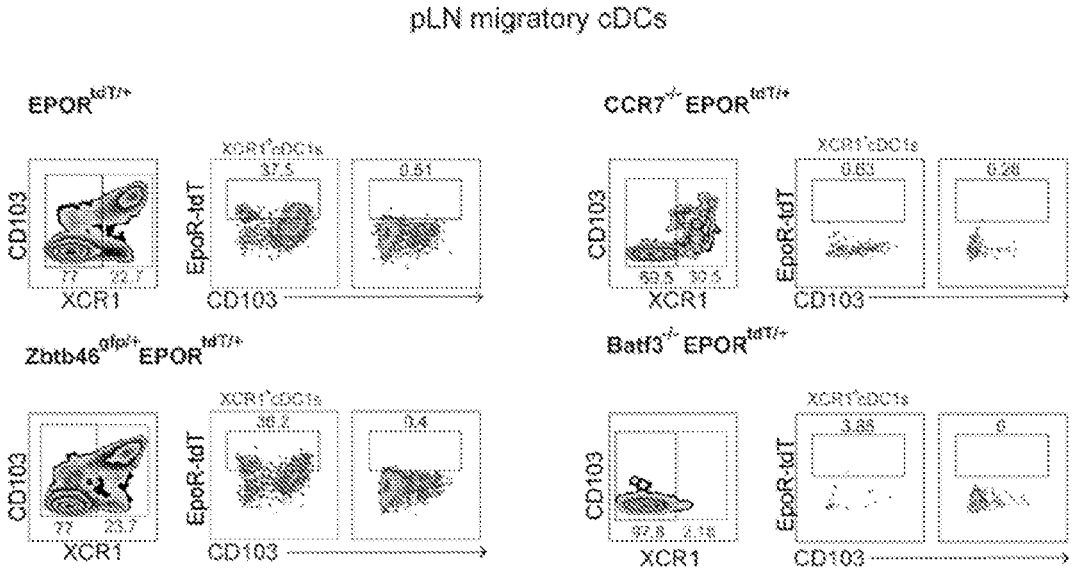


FIG. 35D

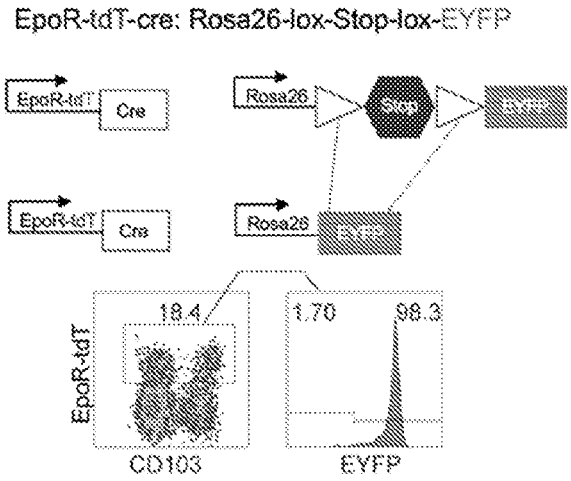


FIG. 35E

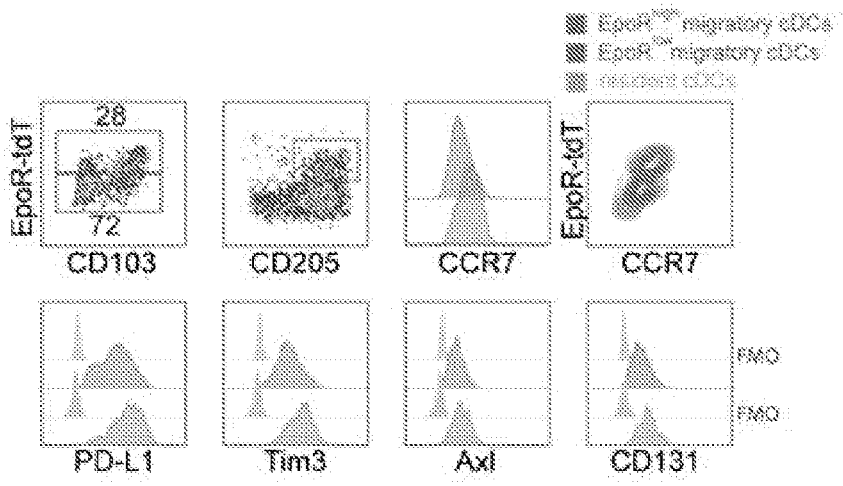

EpoR^hi migratory cDCs
EpoR^lo migratory cDCs
resident cDCs
EpoR-tdT
28
72
CD103
CD205
CCR7
EpoR-tdT
CCR7
FMO
FMO
PD-L1
Tim3
Axl
CD131

FIG. 36

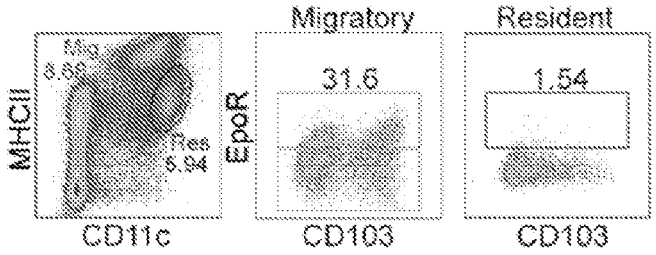


FIG. 37A

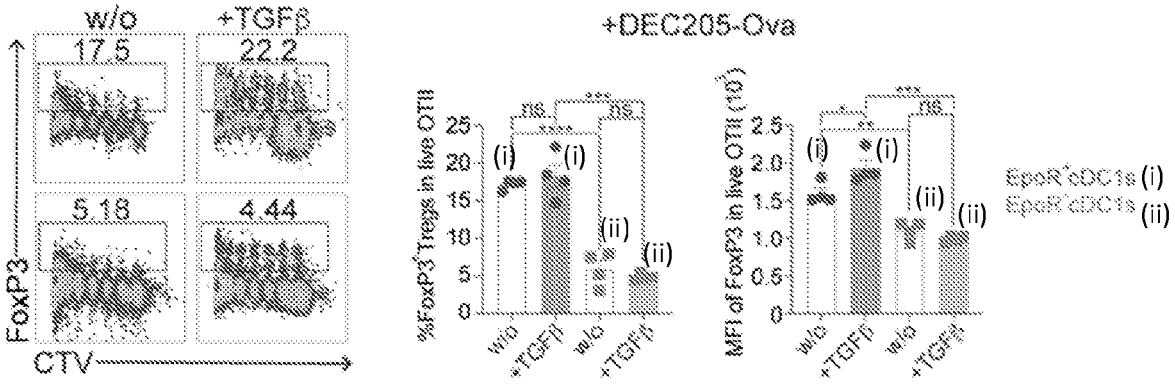


FIG. 37B

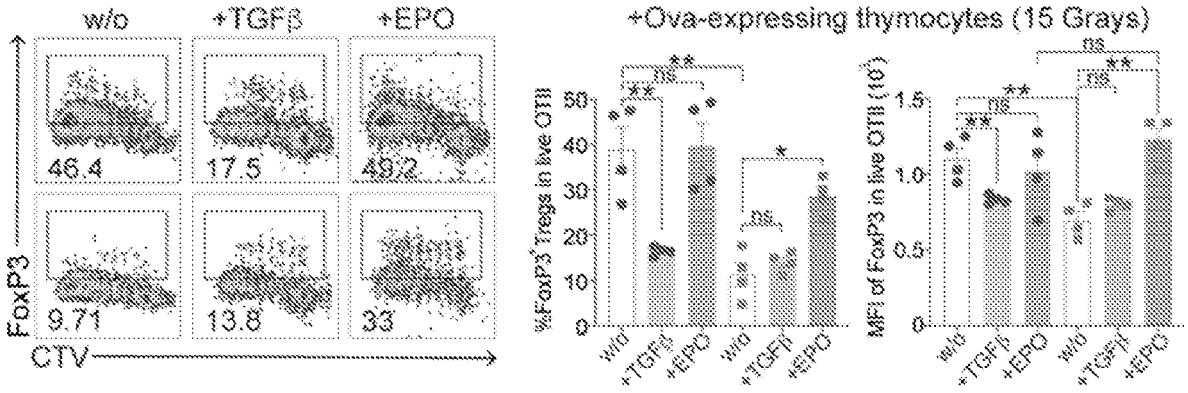


FIG. 37C

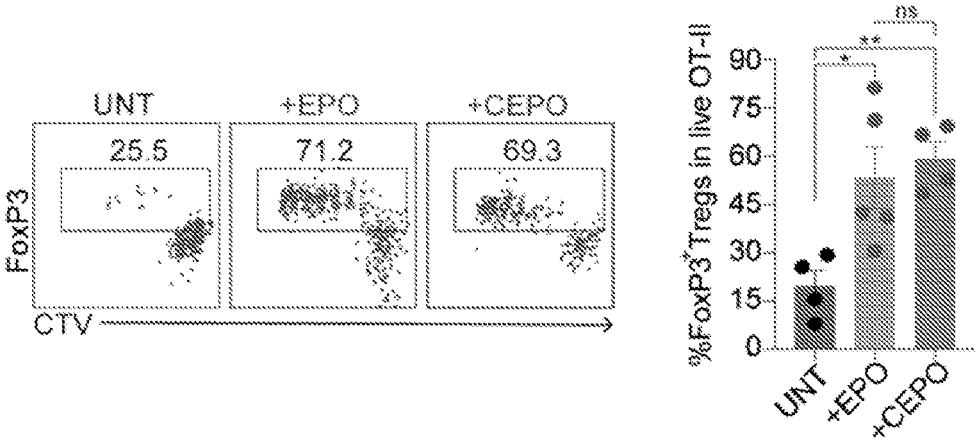


FIG. 38A

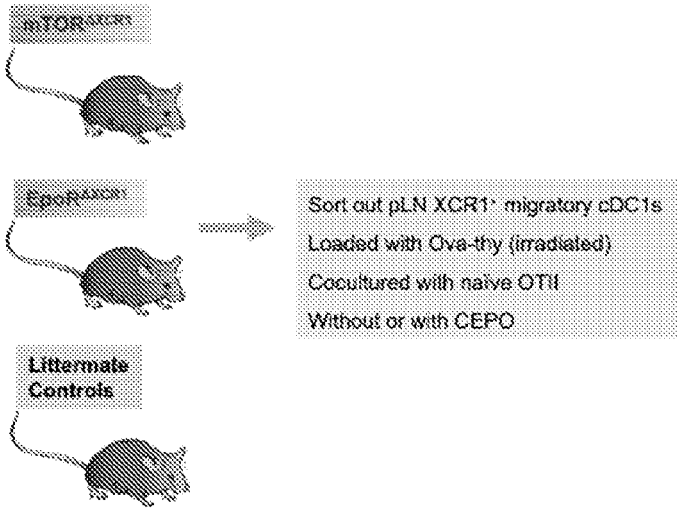


FIG. 38B

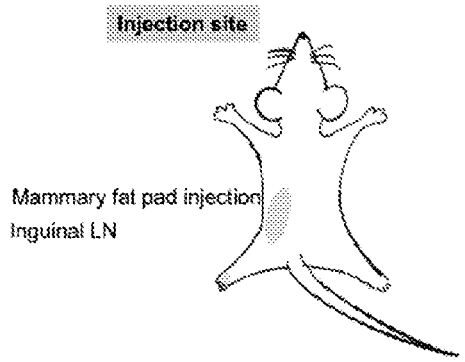


FIG. 39A

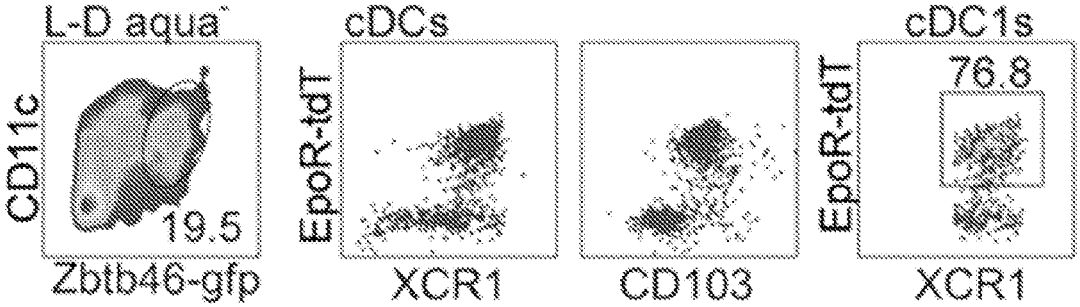


FIG. 39B

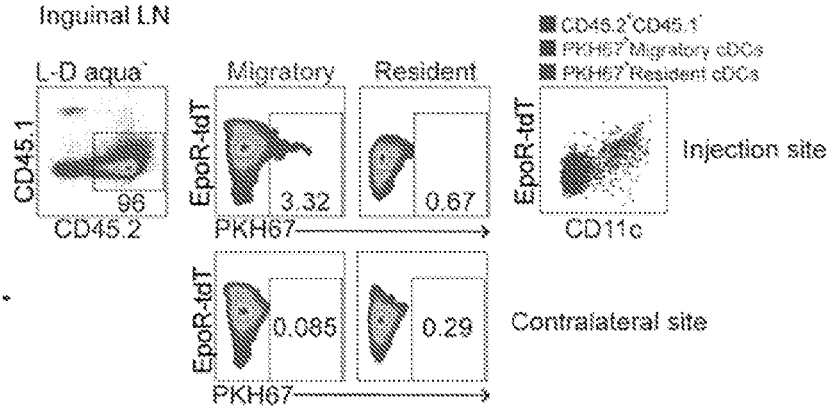


FIG. 39C

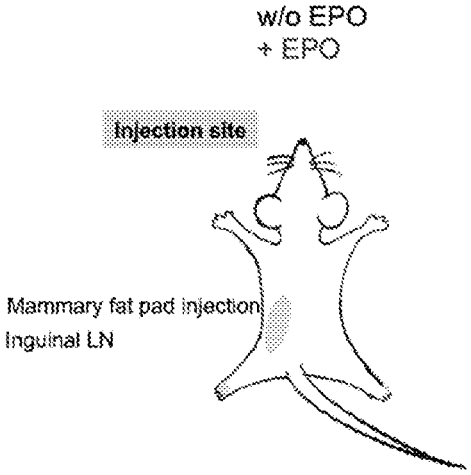


FIG. 40A

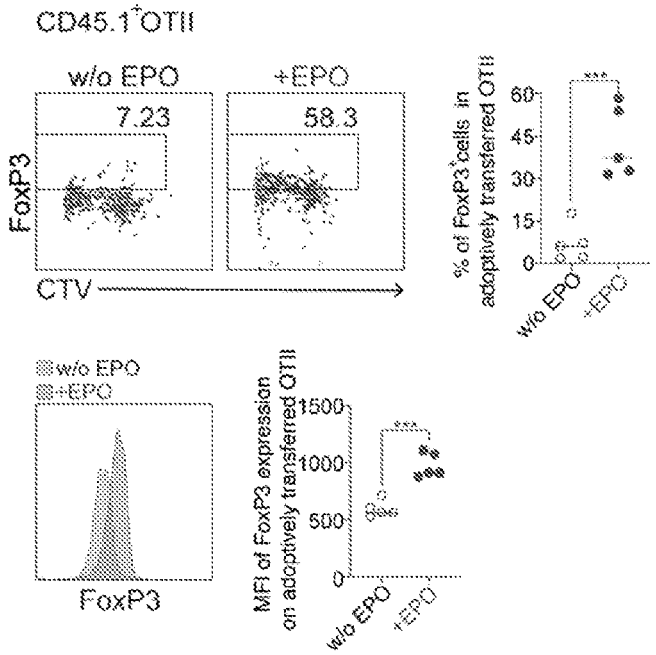


FIG. 40B

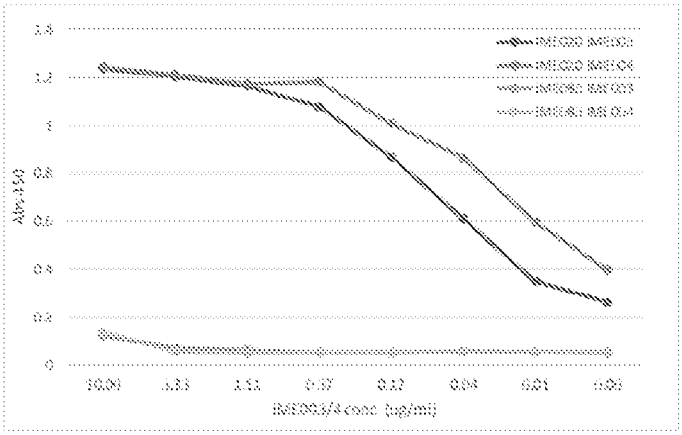


FIG. 41A

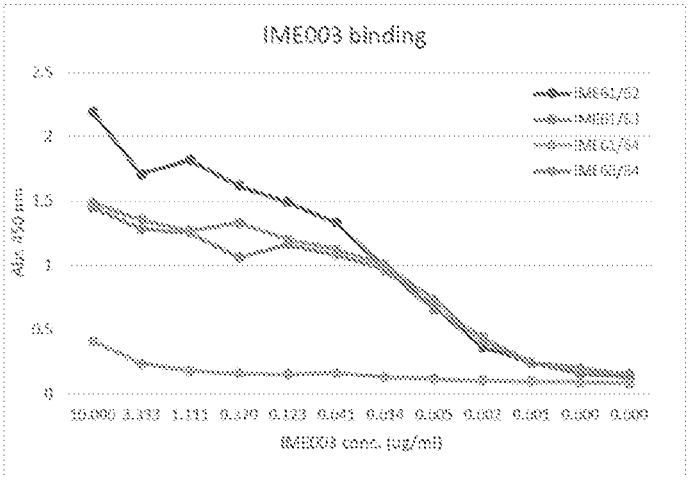


FIG. 41B

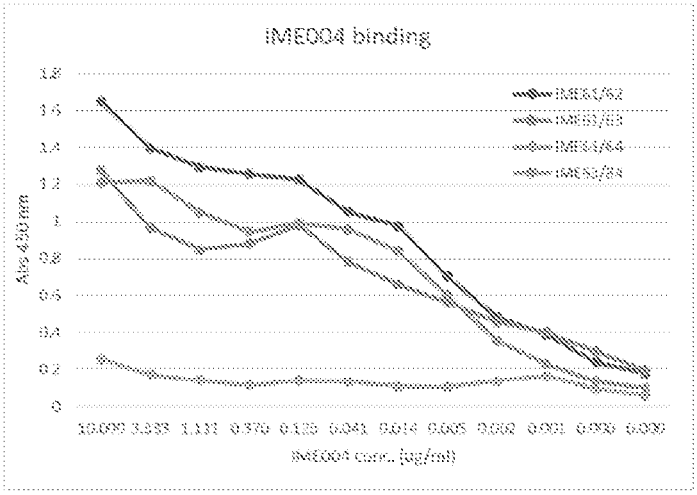


FIG. 41C

Signal peptide is in red.

```
   1  atggaccacc tcggggcgtc cctctggccc caggtcggct ccctttgtct cctgctcgct ggggccgcct
        M  D  H  L  G  A  S  L  W  P  Q  V  G  S  L  C  L  L  L  A  G  A  A

  71  gggctccgcc ccctaatctt ccagatccaa aatttgaatc caaggctgcg ctgttggctg caagaggccc
        W  A  P  P  P  P  N  L  P  D  P  K  P  E  S  R  A  A  L  L  A  A  R  G

 141  tgaggaactc ctctgttttа ctgaacgctt agaagatctc gtttgctttt gggaagaggc tgcttctgcc
        P  E  E  L  L  C  F  T  E  R  L  E  D  L  V  C  F  W  E  E  A  A  S  A

 211  ggcgttggac ccggtaatta ttcatttтct tatcaattag aagacgaacc ctggaaattg tgcagacttc
        G  V  G  P  G  N  Y  S  F  S  Y  Q  L  E  D  E  P  W  K  L  C  R  L

 281  atcaagcgcc tactgcccga ggcgccgtcc ggttttggtg ctcactcccc actgcggata catcctcttt
        H  Q  A  P  T  A  R  G  A  V  R  F  W  C  S  L  P  T  A  D  T  S  S

 351  tgtaccattg gaactgaggg taaccgccgc atcaggggca ccccgctacc atagagtaat tcatataaac
        F  V  P  L  E  L  R  V  T  A  A  G  A  P  R  Y  H  R  V  I  H  I  N

 421  gaggttgtcc tgttagatgc tcctgtagga cttgtcgccc gcctggcgga tgaatccggg catgtggttc
        E  V  V  L  L  D  A  P  V  G  L  V  A  R  L  A  D  E  S  G  H  V  V

 491  ttaggtggct gccccacca gaaaccccaa tgaccagtca tattcgatat gaagttgatg taagcgcggg
        L  R  W  L  P  P  P  E  T  P  M  T  S  H  I  R  Y  E  V  D  V  S  A

 561  gaatggggcc ggttctgtgc aaagagtaga aatacttgaa gggcgaactg aatgcgtcct ttccaatctc
        G  N  G  A  G  S  V  Q  R  V  F  I  L  E  G  R  T  E  C  V  L  S  N  L

 631  aggggtagga ctagatatac ttttgctgtg agggccagga tggcagaacc atcatttggt ggattttggt
        R  G  R  T  R  Y  T  F  A  V  R  A  R  M  A  E  P  S  F  G  G  F  N

 701  ccgcatggtc agaaccagtt tctctcctga caccatccga tttagatcct
        S  A  W  S  E  P  V  S  L  L  T  P  S  D  L  D  P
```

FIG. 42A

Signal peptide is in red.

```
   1  atggtgctgg ccccaggggct gctctccatg gccctgctgg ccctgtgctg ggagcgcagc ctggcagggg
        M  V  L   A  Q  G   L  L  S  M   A  L  L   A  L  C   W  E  R  S   L  A  G

  71  cagaagaaac catcccgctg cagaccctgc gctgctacaa cgactacacc agccacatca cctgcaggtg
        A  E  E   T  I  P  L   Q  T  L   R  C  Y   N  D  V  T   S  H  I   T  C  R

 141  ggcagacacc caggatgccc agcggctcgt caacgtgacc ctcattcgcc gggtgaatga ggacctcctg
        W  A  D  T   Q  D  A   Q  R  L   V  N  V  T   L  I  R   R  V  N   E  D  L  L

 211  gagcccagtgt cctgtgacct cagtgatgac atgccctggt cagcctgccc ccatccccgc tgcgtgccca
        E  P  V   S  C  D   L  S  D  D   M  P  W   S  A  C   P  H  P  R   C  V  P

 281  ggagatgtgt cattccctgc cagagttttg tcgtcactga cgttgactac ttctcattcc aaccagacag
        R  R  C   V  I  P  C   Q  S  F   V  V  T   D  V  D  V   F  S  F   Q  P  D

 351  gcctctgggc acccggctca ccgtcactct gacccagcat gtccagcctc ctgagcccag ggacctgcag
        R  P  L  G   T  R  L   T  V  T   L  T  Q  H   V  Q  P   P  E  P   R  D  L  Q

 421  atcagcaccg accaggacca cttcctgctg acctggagtg tggcccttgg gagtccccag agccactggt
        I  S  T   D  Q  D   H  F  L  L   T  W  S   V  A  L   G  S  P  Q   S  H  W

 491  tgtccccagg ggatctggag tttgaggtgg tctacaagcg gcttcaggac tcttgggagg acgcagccat
        L  S  P   G  D  L  E   F  E  V   V  Y  K   R  L  Q  D   S  W  E   D  A  A

 561  cctcctctcc aacacctccc aggccaccct ggggccagag cacctcatgc ccagcagcac ctacgtggcc
        I  L  L  S   N  T  S   Q  A  T   L  G  P  E   H  L  M   P  G  S   T  Y  V  A

 631  cgagtacgga cccgcctggc cccaggttct cggctctcag gacgtcccag caagtggagc ccagaggttt
        R  V  R   T  R  L   A  P  G  S   R  L  S   G  R  P   S  K  W  S   P  E  V

 701  gctggggctc ccagccaggg gatgaggccc agccccagaa cctggagtgc ttctttgacg gggccgccgt
        C  W  D   S  Q  P  G   D  E  A   Q  P  Q   N  L  E  C   F  F  D   G  A  A

 771  gctcagctgc tcctgggagg tgaggaagga ggtggccagc tcggtctcct ttggcctatt ctacaagccc
        V  L  S  C   S  W  E   V  R  K   E  V  A  S   S  V  S   F  G  L   F  Y  K  P

 841  agcccagatg caggggagga agagtgctcc ccagtgctga gggaggggct cggcagcctc cacaccaggc
        S  P  D   A  G  E   E  E  C  S   P  V  L   R  C  G   L  G  S  L   H  T  R

 911  accactgcca gattcccgtg cccgacccca cgacccacgg ccaatacatc gtctctgttc agccaaggag
        N  H  C   Q  I  P  V   P  D  P   A  T  R   G  Q  Y  I   V  S  V   Q  P  R

 981  ggcagagaaa cacataaaga gctcagtgaa catccagatg gcccctccat ccctcaacgt gaccaaggat
        R  A  E  K   H  I  K   S  S  V   N  I  Q  M   A  P  P   S  L  N   V  T  K  D

1051  ggagacagct acagcctgcg ctgggaaaca atgaaaatgc gatacgaaca catagaccac acatttgaga
        G  D  S   Y  S  L   R  W  E  T   M  K  M   R  Y  E   H  I  D  H   T  F  E

1121  tccagtacag gaaagacacg gccacgtgga aggacagcaa gaccgagacc ctccagaacg cccacagcat
        I  Q  Y   R  K  D  T   A  T  W   K  D  S   K  T  E  T   L  Q  N   A  H  S

1191  ggcccctgcca gcccctggagc cctccaccag gtactgggcc agggtgaggg tcaggacctc ccgcaccggc
        M  A  L  P   A  L  E   P  S  T   R  Y  W  A   R  V  R   V  R  T   S  R  T  G

1261  tacaacggga tctggagcga gtggagtgag gcgcgctcct gggacaccga gtcggtgctg cctatgtgg
        Y  N  G   I  W  S   E  W  S  E   A  R  S   W  D  T   E  S  V  L   P  M  W
```

FIG. 42B

Signal peptide is in red.

```
  1  atggcctgga tgatgcttct cctcggactc cttgcttatg gatcaggagt cgactctgag gcccagcccc
       M  A  W  M  M  L  L  L  G  L  L  A  Y  G  S  G  V  D  S  E  A  Q  P

 71  agaacctgga gtgcttcttt gacggggccg ccgtgctcag ctgctcctgg gaggtgagga aggaggtggc
       Q  N  L  E  C  F  F  D  G  A  A  V  L  S  C  S  W  E  V  R  K  E  V

141  cagctcggtc tcctttggcc tattctacaa gcccagccca gatgcagggg aggaagagtg ctccccagtg
       A  S  S  V  S  F  G  L  F  Y  K  P  S  P  D  A  G  E  E  E  C  S  P  V

211  ctgagggagg ggctcggcag cctccacacc aggcaccact gccagattcc cgtgccccgac ccccgcgaccc
       L  R  E  G  L  G  S  L  H  T  R  H  H  C  Q  I  P  V  P  D  P  A  T

281  acggccaata catcgtctct gttcagccaa ggagggcaga gaaacacata aagagctcag tgaacatcca
       H  G  Q  Y  I  V  S  V  Q  P  R  R  A  E  K  H  I  K  S  S  V  N  I

351  gatggccctt ccatccctca acgtgaccaa ggatggagac agctacagcc tgcgctggga aacaatgaaa
       Q  M  A  P  P  S  L  N  V  T  K  D  G  D  S  Y  S  L  R  W  E  T  M  K

421  atgcgatacg aacacataga ccacacattt gagatccagt acaggaaaga cacggccacg tggaaggaca
       M  R  Y  E  H  I  D  H  T  F  E  I  Q  Y  R  K  D  T  A  T  W  K  D

491  gcaagaccga gaccctccag aacgcccaca gcatggccct gccagccctg gagccctcca ccaggtactg
       S  K  T  E  T  L  Q  N  A  H  S  M  A  L  P  A  L  E  P  S  T  R  Y

561  ggccagggtg agggtcagga cctcccgcac cggctacaac gggatctgga gcgagtggag tgaggcgcgc
       W  A  R  V  R  V  R  T  S  R  T  G  Y  N  G  I  W  S  E  W  S  E  A  R

631  tcctgggaca ccgagtcggt gctgcctatg tgg
       S  W  D  T  E  S  V  L  P  N  W
```

FIG. 42C

Signal peptide is in red.

```
   1  atggaccacc tcggggcgtc cctctggccc caggtcggct cccttttgtct cctgctcgct ggggccgcct
        M  D  H  L  G  A  S  L  W  P  Q  V  G  S  L  C  L  L  L  A  G  A  A

  71  gggctccgcc ccctaatctt ccagatccaa aatttgaatc caaggctgcg ctgttggctg caagaggccc
        W  A  P  P  P  N  L  P  D  P  K  F  E  S  K  A  A  L  L  A  A  R  G

 141  tgaggaactc ctctgtttta ctgaacgctt agaagatctc gtttgctttt gggaagaggc tgcttctgcc
        P  E  E  L  L  C  F  T  E  R  L  E  D  L  V  C  F  W  E  E  A  A  S  A

 211  ggcgttggac ccggtaatta ttcatttttct tatcaattag aagacgaacc ctggaaattg tgcagacttc
        G  V  G  P  G  N  Y  S  F  S  Y  Q  L  E  D  E  P  W  K  L  C  R  L

 281  atcaagcgcc tactgcccga ggcgccgtcc ggttttggtg ctcactcccc actgcggata catcctctgc
        H  Q  A  P  T  A  R  G  A  V  R  F  W  C  S  L  P  Y  A  D  T  S  S

 351  agtaccattg gaactgaggg taaccgccgc atcaggggca ccccgctacc atagagtaat tcatataaac
        A  V  P  L  E  L  R  V  T  A  A  S  G  A  P  R  Y  H  R  V  I  N  I  N

 421  gaggttgtcc tgttagatgc tcctgtagga cttgtcgccc gcctggcgga tgaatccggg catgtggttc
        E  V  V  L  L  D  A  P  V  G  L  V  A  R  L  A  D  E  S  G  H  V  V

 491  ttaggtggct gccccccacca gaaaccccaa tgaccagtca tattcgatat gaagttgatg taagcgcggg
        L  R  W  L  P  P  P  E  T  P  M  T  S  H  I  R  Y  E  V  D  V  S  A

 561  gaatggggcc ggttctgtgc aaagagtaga aatacttgaa gggcgaactg aatgcgtcct ttccaatctc
        G  N  G  A  G  S  V  Q  R  V  E  I  L  E  G  R  T  E  C  V  L  S  N  L

 631  aggggtagga ctagatatac ttttgctgtg agggccagga tggcagaacc atcatttggt ggattttggt
        R  G  R  T  R  Y  T  F  A  V  R  A  R  M  A  E  P  S  F  G  G  F  W

 701  ccgcatggtc agaaccagtt tctctcctga caccatccga tttagatcct
        S  A  W  S  E  P  V  S  L  L  T  P  S  D  L  D  P
```

FIG. 42D