COMPOSITIONS FOR MODIFYING CELLS

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S. C. § 119(e) of U.S. Provisional Application No. 63/532,093, filed August 11, 2023, and U.S. Provisional Application No. 63/540,344, filed September 25, 2023, and each of which is incorporated by reference herein in its entirety.

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with this application is provided in XML format in lieu of a paper copy and is hereby incorporated by reference into the specification. The name of the XML file containing the Sequence Listing is KELO-010-WO1_ST26.xml. The XML file is 744 KB, was created on July 25, 2024, and is being submitted electronically via Patent Center, concurrent with the filing of the specification.

Technical Field

The present disclosure relates to recombinant particles engineered to deliver one or more engineered receptors to a cell. More particularly, the disclosure relates to recombinant particles engineered to deliver one or more engineered receptors to cells *in vivo*.

Description of the Related Art

Ex vivo gene therapies are potentially one-time therapeutic modalities that generally involve harvesting cells from a subject, modifying the cells by culturing them with a gene therapy vector, and delivering the modified cells back to the subject. Because *ex vivo* gene therapies are manufactured in a controlled environment, they do not generally require specialized targeting moieties and instead, targeting moieties with a broad tropism and that are highly efficient in delivering a gene therapy to most cell types are used.

In contrast, *in vivo* gene therapies are manufactured in the patient, in an uncontrolled environment. Accordingly, *in vivo* delivery of gene therapy vectors to specific cell types is

orders of magnitude more complex than *ex vivo* delivery. *In vivo* gene therapy vectors encounter many non-target or off-target cells and may require a narrower or more specific tropism to deliver therapeutic payloads to a particular cell type. The potential of *in vivo* gene therapies has yet to be realized primarily due to inefficient delivery to desired cell types in combination with substantial off-target delivery. Use of specialized targeting moieties to deliver gene therapies *in vivo* has proven difficult in abrogating the off-target delivery to undesired cell types. In addition, on-target delivery of *in vivo* gene therapies using such specialized targeting moieties is often inefficient.

BRIEF SUMMARY

The present disclosure generally relates, in part, to a recombinant particle comprising a fusogen and one or more tropism polypeptides that are suitable for delivering a payload to one or more desired cell types *in vivo*. The present disclosure more particularly relates to recombinant viral, *e.g.,* retroviral or lentiviral particles comprising a detargeted viral-based fusogen, one or more non-viral membrane bound tropism polypeptides and a vector, *e.g.,* a viral, retroviral, or lentiviral vector encoding an expressible polynucleotide encoding an engineered receptor.

Disclosed herein is a recombinant lentiviral particle comprising: (a) a viral envelope comprising: (i) a mutated vesiculovirus G protein that retains fusogenic activity and that lacks cognate receptor binding activity; and (ii) a non-viral membrane-bound tropism polypeptide comprising: (x) an antibody or antigen binding fragment comprising a heavy chain variable region (VH); a polypeptide linker; and a light chain variable region (VL), wherein the VH comprises: a CDRH1 comprising the amino acid sequence set forth in SEQ ID NO: 92; a CDRH2 comprising the amino acid sequence set forth in SEQ ID NO: 93; and a CDRH3 comprising the amino acid sequence set forth in any one of SEQ ID NOs: 94, 104, 114, 124, 134, 144, 154, and 164; and wherein the VL comprises: a CDRL1 comprising the amino acid sequence set forth in SEQ ID NO: 96; a CDRL2 comprising the amino acid sequence set forth in SEQ ID NO: 97; and a CDRL3 comprising the amino acid sequence set forth in SEQ ID NO: 98; (y) a spacer polypeptide; and (z) a transmembrane domain; and (b) a recombinant lentiviral vector comprising a polynucleotide encoding a promoter operably linked to a polynucleotide encoding one or more engineered receptors.

In various embodiments, a recombinant particle is contemplated, comprising: (a) a surface comprising (i) one or more mutated viral envelope glycoproteins that retain fusogenic activity and that lack cognate receptor binding activity and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof that binds an antigen expressed on an immune effector cell, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a therapeutic payload.

In particular embodiments, the particle is a fusosome; an extracellular vesicle, including a microvesicle, an apoptotic body, and an exosome; a lipid nanoparticle; a virus-like particle (VLPs); or a recombinant viral particle.

In certain embodiments, the surface comprises a single layer of phospholipid, a phospholipid bilayer, a cell membrane, a capsid, or a viral envelope.

In some embodiments, the payload comprises one or more polynucleotides and/or polypeptides.

In particular embodiments, the payload comprises a vector that encodes a therapeutic polynucleotide or polypeptide.

In particular embodiments, the payload comprises a vector that encodes one or more engineered receptors.

In further embodiments, the payload comprises a vector that encodes a promoter operably linked to a polynucleotide encoding one or more engineered receptors.

In various embodiments, a recombinant lentiviral particle is contemplated, comprising: (a) a viral envelope comprising (i) one or more mutated viral envelope glycoproteins that retain fusogenic activity and that lack cognate receptor binding activity and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof that binds an antigen expressed on an immune effector cell, a spacer polypeptide, a GPI domain or transmembrane domain and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a recombinant lentiviral vector comprising a polynucleotide encoding a promoter operably linked to a polynucleotide encoding one or more engineered receptors.

Disclosed herein is a recombinant lentiviral particle comprising: (a) a surface comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 99% identical to or identical to any one of SEQ ID NOs: 630, 634, 638, and 642, wherein the mutated VSIV-G envelope glycoprotein comprises the amino acid

substitutions K47A or K47Q and R354A or R354Q, and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof comprising an amino acid sequence set forth in any one of SEQ ID NOs: 99, 109, 119, 129, 139, 149, 159 and 169, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a therapeutic payload encoding a chimeric antigen receptor.

Disclosed herein is a recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95% identical to SEQ ID NO: 642, wherein the mutated VSIV-G envelope glycoprotein comprises the amino acid substitutions K47Q and R354A; and (ii) a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOs: 99 or 100, that binds an antigen expressed on an immune effector cell, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a lentiviral vector encoding a chimeric antigen receptor.

Disclosed herein is a recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95% identical to SEQ ID NO: 642, wherein the mutated VSIV-G envelope glycoprotein comprises the amino acid substitutions K47Q and R354A; (ii) a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 471; and (b) a lentiviral vector encoding a chimeric antigen receptor.

In some embodiments, the one or more mutated viral envelope glycoproteins comprise a rhabdovirus envelope glycoprotein, or one or more paramyxovirus envelope glycoproteins.

In certain embodiments, the one or more mutated viral envelope glycoproteins comprise a vesiculovirus envelope glycoprotein, one or more morbillivirus envelope glycoproteins or one or more henipavirus envelope glycoproteins.

In particular embodiments, the vesiculovirus is selected from the group consisting of: vesicular stomatitis Alagoas virus (VSAV; Alagoas vesiculovirus), Carajás virus (CJSV; Carajas vesiculovirus), Chandipura virus (CHPV; Chandipura vesiculovirus), Cocal virus (COCV; Cocal vesiculovirus), vesicular stomatitis Indiana virus (VSIV; Indiana vesiculovirus), Isfahan virus (ISFV; Isfahan vesiculovirus), Maraba virus (MARAV; Maraba vesiculovirus), Morreton virus (MORV; Morreton vesiculovirus), vesicular stomatitis New

Jersey virus (VSNJV; New Jersey vesiculovirus), and Piry virus (PIRYV; Piry vesiculovirus).

In additional embodiments, the vesiculovirus envelope glycoprotein is a vesiculovirus G protein.

In additional embodiments, the vesiculovirus G protein is a COCV G glycoprotein (COCV-G) or a VSIV G glycoprotein (VSIV-G).

In certain embodiments, the VSIV-G envelope protein comprises one or more of: (a) one or more amino acid substitutions at H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, and R354; (b) an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, and an insertion of GGS between N208 and Y209; or (c) amino acid substitutions at K47 and/or R354; or (d) a deletion of residues 1-8.

In particular embodiments, the VSIV-G envelope protein comprises one or more amino acid substitutions at H8, K47, Y209, and R354.

In particular embodiments, the VSIV-G polypeptide comprises one or more amino acid substitutions at K47, I182, and/or R354 (substitution with any amino acid; a conservation substitution; a disruptive substitution; substitution with D, E, A, G, F, or Q; or substitution with A, G, F, or Q). In particular embodiments, the VSIV-G polypeptide comprises amino acid substitutions at K47, I182, or R354; K47 and I182; K47 and R354; I182 and R354; or at K47, I182, and R354 of an amino acid sequence at least 95% identical to, at least 96% identical to, at least 97% identical to, and least 98% identical to, at least 99% identical to, or identical to, SEQ ID NO: 1.

In particular embodiments, the VSIV-G polypeptide comprises one or more of the following amino acid substitutions: K47A, K47Q, I182E, I182D, R354A, and/or R354Q.

In particular embodiments, the VSIV-G polypeptide comprises the following amino acid substitutions: K47A and I182E; K47A and I182D; K47Q and I182E; K47Q and I182D; I182E and R354A; I182E and R354Q; I182D and R354A; I182D and R354Q; K47A and R354A; K47A and R354Q; K47Q and R354A; K47Q and R354Q; K47A, I182E, and R354A; K47A, I182D, and R354A; K47Q, I182E, and R354A; K47Q, I182D, and R354A; K47A, I182E, and R354Q; K47A, I182D, and R354Q; K47Q, I182E, and R354Q; or K47Q, I182D, and R354Q of an amino acid sequence at least 95% identical to, at least 96% identical

to, at least 97% identical to, and least 98% identical to, at least 99% identical to, or identical to, SEQ ID NO: 1.

In particular embodiments, the VSIV-G envelope protein comprises amino acid substitutions selected from the group consisting of: K47A and R354A; K47A and R354G; K47A and R354F; K47A and R354Q; K47G and R354A; K47G and R354G; K47G and R354F; K47G and R354Q; K47F and R354A; K47F and R354G; K47F and R354F; K47F and R354Q; K47Q and R354A; K47Q and R354G; K47Q and R354F; and K47Q and R354Q.

In certain embodiments, the VSIV-G envelope protein comprises the amino acid sequence set forth in SEQ ID NO: 2 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto, wherein X_1= I, X_2 = A, X_3 = Q, and X_4 = A; X_1= I, X_2 = A, X_3 = Q, and X_4 = G; X_1= I, X_2 = A, X_3 = Q, and X_4 = F; X_1= I, X_2 = A, X_3 = Q, and X_4 = Q; X_1= L, X_2 = A, X_3 = Q, and X_4 = A; X_1= L, X_2 = A, X_3 = Q, and X_4 = G; X_1= L, X_2 = A, X_3 = Q, and X_4 = F; X_1= L, X_2 = A, X_3 = Q, and X_4 = Q; X_1= I, X_2 = A, X_3 = H, and X_4 = A; X_1= I, X_2 = A, X_3 = H, and X_4 = G; X_1= I, X_2 = A, X_3 = H, and X_4 = F; X_1= I, X_2 = A, X_3 = H, and X_4 = Q; X_1= L, X_2 = A, X_3 = H, and X_4 = A; X_1= L, X_2 = A, X_3 = H, and X_4 = G; X_1= L, X_2 = A, X_3 = H, and X_4 = F; X_1= L, X_2 = A, X_3 = H, and X_4 = Q; X_1= I, X_2 = G, X_3 = Q, and X_4 = A; X_1= I, X_2 = G, X_3 = Q, and X_4 = G; X_1= I, X_2 = G, X_3 = Q, and X_4 = F; X_1= I, X_2 = G, X_3 = Q, and X_4 = Q; X_1= L, X_2 = G, X_3 = Q, and X_4 = A; X_1= L, X_2 = G, X_3 = Q, and X_4 = G; X_1= L, X_2 = G, X_3 = Q, and X_4 = F; X_1= L, X_2 = G, X_3 = Q, and X_4 = Q; X_1= I, X_2 = G, X_3 = H, and X_4 = A; X_1= I, X_2 = G, X_3 = H, and X_4 = G; X_1= I, X_2 = G, X_3 = H, and X_4 = F; X_1= I, X_2 = G, X_3 = H, and X_4 = Q; X_1= L, X_2 = G, X_3 = H, and X_4 = A; X_1= L, X_2 = G, X_3 = H, and X_4 = G; X_1= L, X_2 = G, X_3 = H, and X_4 = F; X_1= L, X_2 = G, X_3 = H, and X_4 = Q; X_1= I, X_2 = F, X_3 = Q, and X_4 = A; X_1= I, X_2 = F, X_3 = Q, and X_4 = G; X_1= I, X_2 = F, X_3 = Q, and X_4 = F; X_1= I, X_2 = F, X_3 = Q, and X_4 = Q; X_1= L, X_2 = F, X_3 = Q, and X_4 = A; X_1= L, X_2 = F, X_3 = Q, and X_4 = G; X_1= L, X_2 = F, X_3 = Q, and X_4 = F; X_1= L, X_2 = F, X_3 = Q, and X_4 = Q; X_1= I, X_2 = F, X_3 = H, and X_4 = A; X_1= I, X_2 = F, X_3 = H, and X_4 = G; X_1= I, X_2 = F, X_3 = H, and X_4 = F; X_1= I, X_2 = F, X_3 = H, and X_4 = Q; X_1= L, X_2 = F, X_3 = H, and X_4 = A; X_1= L, X_2 = F, X_3 = H, and X_4 = G; X_1= L, X_2 = F, X_3 = H, and X_4 = F; X_1= L, X_2 = F, X_3 = H, and X_4 = Q; X_1= I, X_2 = Q, X_3 = Q, and X_4 = A; X_1= I, X_2 = Q, X_3 = Q, and X_4 = G; X_1= I, X_2 = Q, X_3 = Q, and X_4 = F; X_1= I, X_2 = Q, X_3 = Q, and X_4 = Q; X_1= L, X_2 = Q, X_3 = Q, and X_4 = A; X_1= L, X_2 = Q, X_3 = Q, and X_4 = G; X_1= L, X_2 = Q, X_3 = Q, and X_4 = F; X_1= L, X_2 = Q, X_3 = Q, and X_4 = Q; X_1= I, X_2 = Q, X_3 = H, and X_4

= A; X_1= I, X_2 = Q, X_3 = H, and X_4 = G; X_1= I, X_2 = Q, X_3 = H, and X_4 = F; X_1= I, X_2 = Q, X_3 = H, and X_4 = Q; X_1= L, X_2 = Q, X_3 = H, and X_4 = A; X_1= L, X_2 = Q, X_3 = H, and X_4 = G; X_1= L, X_2 = Q, X_3 = H, and X_4 = F; and X_1= L, X_2 = Q, X_3 = H, and X_4 = Q.

In some embodiments, the VSIV-G envelope protein comprises the amino acid sequence set forth in any one of SEQ ID NOs: 582-645 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

In particular embodiments, the VSIV-G envelope protein comprises the amino acid sequence set forth in any one of SEQ ID NOs: 630, 634, 638, and 642 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto. In a particular preferred embodiment, the VSIV-G envelope protein comprises the amino acid sequence set forth in SEQ ID NO: 642 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

In additional embodiments, the vesiculovirus G protein is COCV-G.

In some embodiments, the COCV-G envelope protein comprises one or more amino acid substitutions at K47 and/or R354.

In certain embodiments, the COCV-G envelope protein comprises amino acid substitutions selected from the group consisting of: K47A and R354A; K47A and R354G; K47A and R354F; K47A and R354Q; K47G and R354A; K47G and R354G; K47G and R354F; K47G and R354Q; K47F and R354A; K47F and R354G; K47F and R354F; K47F and R354Q; K47Q and R354A; K47Q and R354G; K47Q and R354F; and K47Q and R354Q.

In further embodiments, the COCV-G envelope protein comprises the amino acid sequence set forth in SEQ ID NO: 4 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto, wherein X_1= A and X_2 = A; X_1= A and X_2 = G; X_1= A and X_2 = F; X_1= A and X_2 = Q; X_1= G and X_2 = A; X_1= G and X_2 = G; X_1= G and X_2 = F; X_1= G and X_2 = Q; X_1= F and X_2 = A; X_1= F and X_2 = G; X_1= F and X_2 = F; X_1= F and X_2 = Q; X_1= Q and X_2 = A; X_1= Q and X_2 = G; X_1= Q and X_2 = F; or X_1= A and X_2 = Q.

In particular embodiments, the COCV-G envelope protein comprises the amino acid sequence set forth in any one of SEQ ID NOs: 646-661 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

In certain embodiments, the one or more morbillivirus envelope glycoproteins are measles virus F (MV-F) and measles virus H (MV-H).

In some embodiments, the MV-H protein comprises one or more amino acid substitutions at Y463, R515, S530, and F531.

In additional embodiments, the MV-H protein comprises one or more amino acid substitutions selected from the group consisting of: Y463A, R515A, S530, and F531.

In some embodiments, the MV-H protein comprises the amino acid sequence set forth in SEQ ID NO: 7.

In certain embodiments, the one or more henipavirus envelope glycoproteins are nipah virus F (NiV-F) and nipah virus G (NiV-G).

In particular embodiments, the NiV-G protein comprises one or more amino acid substitutions at E468, W471, Q497, and E500.

In additional embodiments, the NiV-G protein comprises one or more amino acid substitutions selected from the group consisting of: E468A, W471A, Q497A, and E500A.

In particular embodiments, the NiV-G protein comprises the amino acid sequence set forth in SEQ ID NO: 10.

In further embodiments, the antibody or antigen binding fragment thereof is selected from the group consisting of: a Camel Ig, a Llama Ig, an Alpaca Ig, Ig NAR, a Fab′ fragment, a F(ab′)2 fragment, a bispecific Fab dimer (Fab2), a trispecific Fab trimer (Fab3), an Fv, a single chain Fv protein (scFv), a bis-scFv, (scFv)2, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a Fibronectin type III (FN3) domain antibody, a single-domain antibody (sdAb, a camelid VHH, Nanobody), and a centyrin.

In certain embodiments, the antibody or antigen binding fragment thereof binds an antigen expressed on an immune effector cell selected from the group consisting of: the alpha, beta, gamma, or delta chain of the T cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD8α, and CD8β.

In particular embodiments, the antibody or antigen binding fragment thereof comprises (a) a heavy chain variable region (VH) comprising a CDRH1, a CDRH2, and a CDRH3 of an antibody or antigen binding fragment thereof set forth in Table 5; (b) a polypeptide linker; and (c) a light chain variable region (VL) comprising a CDRL1, a CDRL2, and a CDRL3 of an antibody or antigen binding fragment thereof set forth in Table 5.

In additional embodiments, the antibody or antigen binding fragment thereof comprises (a) a heavy chain variable region (VH) of an antibody or antigen binding fragment

thereof set forth in Table 5; (b) a polypeptide linker; and (c) a light chain variable region (VL) of an antibody or antigen binding fragment thereof set forth in Table 5.

In some embodiments, the antibody or antigen binding fragment thereof comprises: (a) a heavy chain variable region (VH) of an antibody or antigen binding fragment thereof set forth in Table 5; (b) a polypeptide linker selected from the group consisting of: (GGGGS)n wherein n = 1, 2, 3, 4 or 5; S(GGGGS)n wherein n = 1, 2, 3, 4 or 5; GEGTSTGSGGSGGSGGAD, GSTSGSGKPGSGEGSTKG and variants thereof comprising an amino acid sequence 95% identical thereto; and (c) the corresponding light chain variable region (VL) of the antibody or antigen binding fragment thereof set forth in Table 5.

In particular embodiments, the antibody or antigen binding fragment thereof comprises the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410.

In particular embodiments, the antibody or antigen binding fragment thereof comprises the amino acid sequence set forth in any one of SEQ ID NOs: 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, and 170.

In further embodiments, the antibody or antigen binding fragment thereof comprises the amino acid sequence set forth in any one of SEQ ID NOs: 99 or 100, 109 or 110, 119 or 120, 129 or 130, 139 or 140, 149 or 150, 159 or 160, and 169 or 170. In a preferred embodiment, the antibody or antigen binding fragment thereof comprises the amino acid sequence set forth in SEQ ID NOs: 99.

In some embodiments, the spacer comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 411-434.

In certain embodiments, the spacer comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 411-413, SEQ ID NOs: 414-423, SEQ ID NOs: 424-427, or SEQ ID NOs: 428-434.

In particular embodiments, the transmembrane domain comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440 or 441.

In some embodiments, the intracellular domain comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 442, 443, 444, 445, 446, 447 or 448.

In particular embodiments, the non-viral membrane-bound tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 455-576. In particular embodiments, the tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 461.

In additional embodiments, the non-viral membrane-bound tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 471-486. In particular embodiments, the tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 471 or 483.

In certain embodiments, the non-viral membrane-bound tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 535-554. In particular embodiments, the tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 537 or 553.

In particular embodiments, the non-viral membrane-bound tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 555-562.

In additional embodiments, the non-viral membrane-bound tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 563 or 564.

In additional embodiments, the non-viral membrane-bound tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 565-576.

In additional embodiments, the non-viral membrane-bound tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in SEQ ID NO: 471 or SEQ ID NO: 553.

In certain embodiments, the particle further comprises one or more secondary non-viral membrane bound tropism polypeptides.

In further embodiments, the one or more secondary non-viral membrane bound tropism polypeptides comprise one or more of CD80, CD86, CD137L, OX40L, and ICOSL or variants thereof.

In particular embodiments, the particle further comprises one or more secondary non-viral membrane-bound tropism polypeptides at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 577-581. In particular embodiments, the one or more secondary non-viral membrane-bound tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 577.

In some embodiments, the recombinant lentiviral vector is engineered or derived from a lentiviral genome of a lentivirus selected from the group consisting of: human immunodeficiency virus 1 (HIV-1); human immunodeficiency virus 2 (HIV-2); visna-maedi virus (VMV); caprine arthritis-encephalitis virus (CAEV); equine infectious anemia virus (EIAV); feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV).

In additional embodiments, the recombinant lentiviral vector further comprises one or more polynucleotides encoding one or more of the following: a signal peptide, a post-transcriptional regulatory element, an insulator element, a selectable marker, and a cell suicide gene.

In certain embodiments, the post-transcriptional regulatory element is a woodchuck hepatitis virus post-transcriptional regulatory element (WPRE) or a hepatitis B virus post-transcriptional regulatory element (HPRE).

In particular embodiments, the promoter is selected from the group consisting of: a β-actin promoter, a cytomegalovirus (CMV) immediate early promoter, a simian virus 40 (SV40) (*e.g.*, early or late) promoter, a Moloney murine leukemia virus (MoMLV) promoter, a Rous sarcoma virus (RSV) promoter, a herpes simplex virus (HSV) (thymidine kinase) promoter, an SV40/CD43 promoter, a spleen focus forming virus (SFFV) promoter, an elongation factor 1-alpha (EFlα) short promoter (intronless), an EFlα long promoter containing an intron, a Ubiquitin C (UBC) promoter, a phosphoglycerate kinase-1 (PGK) promoter, a cytomegalovirus enhancer/chicken β-actin (CAG) promoter, and a myeloproliferative sarcoma virus enhancer, negative control region deleted, dl587rev primer-binding site substituted (MND) U3 promoter.

In further embodiments, the one or more engineered receptors are selected from the group consisting of: a chimeric antigen receptor (CAR), a chimeric costimulatory receptor (CCR), an alpha-beta T cell receptor (αβ TCR), a gamma delta T cell receptor (γδ TCR), a dimerizing agent regulated immunoreceptor complex (DARIC), a chimeric TGF-β receptor (CTBR), and a zetakine receptor.

In certain embodiments, the one or more engineered receptors bind an antigen selected from the group consisting of: alpha folate receptor (FRα), αvβ6 integrin, BAFFR, B cell maturation antigen (BCMA), B7-H3 (CD276), B7-H6, carbonic anhydrase IX (CAIX), CD16, CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD44, CD44v6, CD44v7/8, CD70, CD79A, CD79B, CD123, CD133, CD138, CD171, carcinoembryonic antigen (CEA), claudin 6, (CLDN6), claudin 18 isoform 2 (CLDN18.2), C-type lectin-like molecule-1 (CLL-1), CD2 subset 1 (CS-1), chondroitin sulfate proteoglycan 4 (CSPG4), cutaneous T cell lymphoma-associated antigen 1 (CTAGE1), delta like canonical Notch ligand 3 (DLL3), epidermal growth factor receptor (EGFR), epidermal growth factor receptor variant III (EGFRvIII), epithelial glycoprotein 2 (EGP2), epithelial glycoprotein 40 (EGP40), epithelial cell adhesion molecule (EPCAM), ephrin type-A receptor 2 (EPHA2), erb-b2

receptor tyrosine kinase 4 (ERBB4), fibroblast activation protein (FAP), Fc Receptor Like 5 (FCRL5), fetal acetylcholinesterase receptor (AchR), ganglioside G2 (GD2), ganglioside G3 (GD3), Glypican-3 (GPC3), G Protein-Coupled Receptor Class C Group 5 Member D (GPCR5D), EGFR family including ErbB2 (HER2), HER2 p95, IL-10Rα, IL-13Rα2, Kappa, cancer/testis antigen 2 (LAGE-1A), Lambda, Lewis-Y (LeY), L1 cell adhesion molecule (L1-CAM), melanoma antigen gene (MAGE)-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGEA10, melanoma antigen recognized by T cells 1 (MelanA or MART1), Mesothelin (MSLN), MUC1, MUC16, MHC class I chain related proteins A (MICA), MHC class I chain related proteins B (MICB), neural cell adhesion molecule (NCAM), cancer/testis antigen 1 (NY-ESO-1), placenta-specific 1 (PLAC1), preferentially expressed antigen in melanoma (PRAME), prostate stem cell antigen (PSCA), prostate-specific membrane antigen (PSMA), receptor tyrosine kinase-like orphan receptor 1 (ROR1), SLAMF7, synovial sarcoma, X breakpoint 2 (SSX2), Survivin, TACI, tumor associated glycoprotein 72 (TAG72), tumor endothelial marker 1 (TEM1/CD248), tumor endothelial marker 7-related (TEM7R), transforming growth factor beta 1 (TFGβ1), trophoblast glycoprotein (TPBG), UL16-binding protein (ULBP) 1, ULBP2, ULBP3, ULBP4, ULBP5, ULBP6, vascular endothelial growth factor receptor 2 (VEGFR2), and Wilms tumor 1 (WT-1).

In some embodiments, the one or more engineered receptors bind an antigen selected from the group consisting of: BCMA, CD19, CD20, CD22, CD33, CD38, CD79A, CD79B, GPCR5D, MAGE-A4, MSLN, MUC16, NY-ESO-1, PSCA, PSMA and ROR1.

In particular embodiments, the one or more engineered receptors bind an antigen selected from the group consisting of: BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, and GPCR5D.

In additional embodiments, the one or more engineered receptors bind an antigen selected from the group consisting of: BCMA, CD38, and GPCR5D.

In particular embodiments, the one or more engineered receptors bind an antigen selected from the group consisting of: CD19, CD20, CD22, CD79A, and CD79B.

In certain embodiments, the one or more engineered receptors comprises an extracellular antigen binding domain, a hinge domain, a transmembrane domain, and one or more intracellular signaling domains.

In some embodiments, the one or more engineered antigen receptors comprises an extracellular antigen binding domain selected from the group consisting of: a receptor ectodomain, a ligand, or an antibody or antigen binding fragment thereof selected from the

group consisting of: a Camel Ig, a Llama Ig, an Alpaca Ig, Ig NAR, a Fab′ fragment, a F(ab′)2 fragment, a bispecific Fab dimer (Fab2), a trispecific Fab trimer (Fab3), an Fv, a single chain Fv protein (scFv), a bis-scFv, (scFv)2, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a Fibronectin type III (FN3) domain antibody, a single-domain antibody (sdAb, a camelid VHH, Nanobody), and a centyrin.

In further embodiments, the CAR comprises a hinge domain isolated or derived from a polypeptide selected from the group consisting of: CD4, CD8β, CD8α, CD28, CD134, CD137, CD152, CD278, IgG1, IgG2, IgG3, and IgG4.

In certain embodiments, the CAR comprises a transmembrane domain isolated or derived from a polypeptide selected from the group consisting of: alpha, beta, gamma, or delta chain of the T-cell receptor, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD5, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD152, CD154, CD278, amnionless (AMN), and programmed cell death 1 (PDCD1).

In particular embodiments, the CAR comprises a primary signaling domain isolated or derived from a polypeptide selected from the group consisting of: FcRγ, FcRβ, CD3γ, CD3δ, CD3ε, CD3ζ, CD22, CD79A, CD79B, and CD66d.

In some embodiments, the CAR comprises one or more costimulatory domains isolated or derived from a polypeptide selected from the group consisting of: Toll-like receptor 1 (TLR1), TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, caspase recruitment domain family member 11 (CARD11), CD2, CD7, CD27, CD28, CD30, CD40, CD54 (ICAM), CD83, CD94, CD134 (OX40), CD137 (4-1BB), CD278 (ICOS), DNAX-Activation Protein 10 (DAP10), Linker for activation of T-cells family member 1 (LAT), SH2 Domain-Containing Leukocyte Protein Of 76 kD (SLP76), T cell receptor associated transmembrane adaptor 1 (TRAT1), TNFR2, TNFRS14, TNFRS18, TNFRS25, and zeta chain of T cell receptor associated protein kinase 70 (ZAP70).

In particular embodiments, the CAR comprises an amino acid sequence set forth in any one of SEQ ID NOs: 662, 663, 664, 665, or 666.

In certain embodiments, the one or more engineered receptors further comprises a CCR comprising an extracellular antigen binding domain that binds an antigen different than the antigen bound by the CAR, a hinge domain, a transmembrane domain, and one or more intracellular signaling domains.

In particular embodiments, the one or more engineered receptors comprises a DARIC comprising a DARIC signaling component comprising a multimerization domain, a

transmembrane domain and one or more intracellular signaling domains; and a DARIC binding component comprising an extracellular antigen binding domain, an extracellular antigen binding domain, a transmembrane domain, and optionally one or more intracellular signaling domains.

In further embodiments, the one or more engineered receptors comprises a CTBR comprising (a) a first polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR2, a transmembrane domain, and a first interleukin receptor intracellular signaling domain; (b) a polypeptide cleavage signal; and (c) a second polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR1, a transmembrane domain, and a second interleukin receptor intracellular signaling domain.

In various embodiments, a recombinant particle is contemplated, comprising: (a) a surface comprising (i) one or more mutated viral envelope glycoproteins that retain fusogenic activity and that lack cognate receptor binding activity, wherein the one or more mutated viral envelope glycoproteins comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to any one of SEQ ID NOs: 630, 634, 638, and 642 and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof comprising an amino acid sequence set forth in any one of SEQ ID NOs: 91 and 95, and 99 or 100, that binds an antigen expressed on an immune effector cell, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a therapeutic payload encoding an engineered antigen receptor.

In various embodiments, a recombinant particle is contemplated, comprising: (a) a surface comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642 and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof comprising an amino acid sequence set forth in SEQ ID NO: 99 or 100, that binds an antigen expressed on an immune effector cell, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a lentiviral vector encoding an engineered antigen receptor.

In various embodiments, a recombinant lentiviral particle is contemplated, comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that

comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642 and (ii) a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOs: 99 or 100, that binds an antigen expressed on an immune effector cell, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a therapeutic payload encoding an engineered antigen receptor.

In various embodiments, a recombinant lentiviral particle is contemplated, comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOs: 461, 471, 483, 537, and 553; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor.

In various embodiments, a recombinant lentiviral particle is contemplated, comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 471; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor comprising an amino acid sequence set forth in any one of SEQ ID NOs: 662-666.

In various embodiments, a recombinant lentiviral particle is contemplated, comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 471; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide that comprises

an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor that binds a polypeptide selected from any one of BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, and GPCR5D.

In various embodiments, a recombinant lentiviral particle is contemplated, comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 471; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor that binds BCMA.

In various embodiments, a recombinant lentiviral particle is contemplated, comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 471; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor that binds GPCR5D.

In various embodiments, a recombinant lentiviral particle is contemplated, comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 471; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99%

identical to or identical to SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor that binds CD19.

In additional embodiments, a cell transduced with a particle contemplated herein.

In particular embodiments, the cell is an immune effector cell. Disclosed herein is an immune effector cell transduced in vitro or ex vivo with the recombinant lentiviral particle as defined herein.

In some embodiments, the cell is a T cell, a natural killer (NK) cell, or a natural killer T (NKT) cell.

In certain embodiments, a composition comprising a particle or a cell contemplated herein.

In particular embodiments, a pharmaceutical composition comprises a pharmaceutically acceptable carrier and a particle, a cell, or a composition contemplated herein.

Disclosed herein is a pharmaceutical composition comprising the recombinant lentiviral particle as defined herein or the immune effector cell as defined herein.

In some embodiments, a method of treating, preventing, or ameliorating at least one symptom of a disease, disorder or condition associated therewith in a subject comprises administering to the subject an effective amount of a particle, a cell, a composition, or a pharmaceutical composition contemplated herein.

Disclosed herein is the use of the recombinant lentiviral particle as defined herein, the immune effector cell as defined herein, or the pharmaceutical composition as defined herein in the manufacture of a medicament for treating, preventing, or ameliorating at least one symptom of a disease, disorder or condition associated therewith in a subject. Disclosed herein is the use of the recombinant lentiviral particle as defined herein in the manufacture of a medicament for transducing an immune effector cell in vivo.

In further embodiments, the disease, disorder, or condition is a cancer.

In particular embodiments, the cancer is leukemia selected from the group consisting of: acute lymphocytic leukemia (ALL), an acute myeloid leukemia (AML), a myelodysplastic syndrome (MDS), a plasma cell leukemia (PCL), erythroleukemia, a hairy cell leukemia (HCL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML) and polycythemia vera.

In additional embodiments, the cancer is non-NHL or NHL selected from the group consisting of: diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle-

cell lymphoma (MCL), small lymphocytic lymphoma (SLL), primary mediastinal large B-cell lymphoma, a marginal zone B cell lymphoma (MZL), mucosa-associated lymphatic tissue lymphoma (MALT), Burkitt's lymphoma (BL), immunoblastic large cell lymphoma, centroblastic large cell lymphoma, anaplastic B-cell lymphoma, mycosis fungoides, Sezary syndrome, T-lymphoblastic lymphoma, and anaplastic large-cell lymphoma (ALCL).

In certain embodiments, the cancer is MM selected from the group consisting of: active multiple myeloma, smoldering multiple myeloma, light chain myeloma, non-secretory myeloma, IgD myeloma, IgE myeloma, osteosclerotic myeloma, solitary plasmacytoma of bone, and extramedullary plasmacytoma.

In some embodiments, the cancer is relapsed and/or refractory.

In additional embodiments, the disease, disorder, or condition is an autoimmune disease.

In certain embodiments, the autoimmune disease is systemic lupus erythematosus, rheumatoid arthritis, idiopathic thrombocytopenic purpura, myasthenia gravis, or autoimmune hemolytic anemia.

In some embodiments, a method of transducing an immune effector cell *in vivo*, comprises administering to a subject a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a particle contemplated herein.

In particular embodiments, a method of making the recombinant lentivirus comprises (a) transfecting a host cell with four polynucleotides: a first polynucleotide that encodes lentiviral gag-pol, a second polynucleotide that encodes lentiviral rev, a third polynucleotide that encodes one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides, and a fourth polynucleotide that is a transfer plasmid encoding a recombinant lentiviral vector of any one of the preceding embodiments; and b) culturing the transduced cell for about 1 to 3 days to produce the recombinant lentivirus.

Disclosed herein is a method of making the recombinant lentiviral particle as defined herein comprising (a) transfecting a host cell in vitro with four polynucleotides: a first polynucleotide that encodes lentiviral gag-pol, a second polynucleotide that encodes lentiviral rev, a third polynucleotide that encodes the one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and the one or more non-viral membrane-bound tropism polypeptides, and a fourth polynucleotide

that is a transfer plasmid encoding a recombinant lentiviral vector encoding an engineered antigen receptor; and b) culturing the transduced cell for about 1 to 3 days to produce the particle.

In certain embodiments, a kit comprises a particle contemplated herein, a pharmaceutically acceptable carrier, and instructions for use.

Disclosed herein is a kit comprising the recombinant lentiviral particle as defined herein, a pharmaceutically acceptable carrier, and instructions for use.

BRIEF DESCRIPTION OF SEVERAL VIEWS OF THE DRAWINGS

Figure 1A shows GFP expression (transduction) and CD69 expression (activation) in Jurkat cells targeted with lentiviral particles that have a viral envelope expressing tropism molecules that have T cell specific binding domains and a mutant fusogen.

Figure 1B shows flow cytometry analysis of GFP expression (transduction) and CD69 expression (activation) in PBMCs cells targeted with lentiviral particles that have a viral envelope expressing tropism molecules that have T cell specific binding domains and a mutant fusogen.

Figure 2 shows flow cytometry analysis of GFP expression or CAR expression in HEK293T used to produce lentiviral particles that have a viral envelope expressing (i) tropism molecules that have T cell specific binding domains, a monomeric or dimeric CD8α stalk and a CD8α TM domain and an intracellular domain (ii) a mutant fusogen.

Figure 3A shows a diagram of various tropism molecule stalk architectures experimentally examined in the Examples.

Figure 3B shows tropism molecule expression (measured by anti-CD3 scFv expression) in HEK293T cells used to produce lentiviral particles that have a viral envelope expressing (i) anti-CD3-based tropism molecules and (ii) a mutant fusogen.

Figure 3C shows the transducing units (TU) per nanogram of P24 for lentiviral particles that have anti-CD3-based tropism molecules with various stalk architectures and a mutated fusogen used to transduce Jurkat cells.

Figure 3D shows the transduction specificity for lentiviral particles that express anti-CD3-based tropism molecules with various stalk architectures and a mutated fusogen. Left panel compares on-target transduction in PBMCs to off-target transduction in A549 cells.

Right panel compares on-target transduction in Jurkat cells to off-target transduction in A549 cells.

Figure 4 shows the effects of anti-CD3-based tropism molecule stalk architecture on titer and specificity. Left panel shows the effect of estimated tropism molecule stalk length on titer (TU/ng P24). Right panel shows the effect of estimated tropism molecule stalk length on transduction specificity.

Figure 5A shows the GFP expression (transduction, top panel) and cell count (activation, bottom panel) in PBMCs transduced with lentiviral particles that express anti-CD3-based tropism molecules that have a variety of stalk architectures and a mutant fusogen.

Figure 5B shows the GFP expression (transduction, left panel) in PBMCs transduced with 0.5 ng P24 or 2 ng P24 of lentiviral particles that express anti-CD3-based tropism molecules that have a variety of stalk architectures and a mutant fusogen. Right panel shows the effect of tropism molecule stalk architecture on PBMC transduction compared to Jurkat cell transduction.

Figure 6 shows transduction (top panel) and activation (bottom panel) human T cells in an *in vivo* mouse model. Mice were administered lentiviral particles expressing T cell targeting tropism molecules, a mutant fusogen and a lentiviral vector encoding GFP.

Figure 7A shows the number (left panel) and percentage (right panel) of GFP positive T cells in the blood of mice administered 1 x 10^7 TU, 2.5 x 10^7 TU, 1 x 10^8 TU, or 2.5 x 10^8 TU of lentiviral particles that express (i) T cell targeting tropism molecules (LV 2) or lack T cell targeting tropism molecules (LV 26), (ii) a mutant fusogen and (iii) a lentiviral vector encoding GFP.

Figure 7B shows immunohistochemistry staining in the heart, brain, ovaries, and small intestines of mice administered 1 x 10^7 TU, 2.5 x 10^7 TU, 1 x 10^8 TU, or 2.5 x 10^8 TU of lentiviral particles that express (i) T cell targeting tropism molecules (LV 2) or lack T cell targeting tropism molecules (LV 26), (ii) a mutant fusogen and (iii) a lentiviral vector encoding GFP. The rightmost column shows flow cytometry data of GFP positive T cells in the spleen of these mice at each dose level.

Figure 8 shows that lentiviral particles expressing an anti-CD3-based tropism molecule, a mutant fusogen, and a lentiviral vector encoding an anti-BCMA CAR reduce tumor growth comparable to *ex vivo* manufactured anti-BCMA CAR T cells in an RPMI multiple myeloma mouse model.

Figure 9 shows that lentiviral particles expressing either of two different anti-CD3-based tropism molecules, and a mutant fusogen and a lentiviral vector encoding an anti-BCMA CAR reduce tumor growth comparable to *ex vivo* manufactured anti-BCMA CAR T cells in an Daudi multiple myeloma mouse model.

BRIEF DESCRIPTION OF THE SEQUENCE IDENTIFIERS

SEQ ID NOs: 1-10 set forth amino acid sequences of fusogens.

SEQ ID NOs: 11-410 set forth amino acid sequences of antibodies.

SEQ ID NOs: 411-434 set forth amino acid sequences of spacer domains.

SEQ ID NOs: 435-441 set forth amino acid sequences of transmembrane domains.

SEQ ID NOs: 442-448 set forth amino acid sequences of intracellular domains.

SEQ ID NOs: 449-454 set forth amino acid sequences of signal peptides.

SEQ ID NOs: 455-576 set forth amino acid sequences of non-viral membrane bound tropism polypeptides.

SEQ ID NOs: 577-581 set forth amino acid sequences of secondary tropism polypeptides.

SEQ ID NOs: 582-661 set forth amino acid sequences of fusogens.

SEQ ID NOs: 662-666 set forth amino acid sequences of engineered receptors.

SEQ ID NOs: 667-672 set forth nucleic acid sequences of promoters.

SEQ ID NOs: 673-693 set forth amino acid sequences of polypeptide linkers.

SEQ ID NOs: 694-713 set forth amino acid sequences of viral self-cleaving peptides.

SEQ ID NO: 714 sets forth an amino acid sequence of a lentivirus protease cleavage site.

In the foregoing sequences, X, if present, refers to any amino acid, a specified group of amino acids or the absence of an amino acid.

Throughout the disclosure, the amino acid positions of a fusogen is with reference to the fusogen lacking a signal sequence (*i.e.,* the amino acid sequence after the signal peptide has been cleaved).

DETAILED DESCRIPTION

A. OVERVIEW

The field of *ex vivo* gene therapy is not new and has been evolving for decades. Despite huge potential, *ex vivo* gene therapy has been met with limited success. Moreover, substantial obstacles still plague the field of *ex vivo* gene therapy, obstacles including limited precision and lack of commercial viability are likely among the reasons that it has yet to see widespread adoption in a clinical setting. *In vivo* gene therapy however, is new and offers the potential to deliver life-altering therapies on an unprecedented scale. *In vivo* gene therapy solves the commercial viability issues associated with the astronomical costs associated with manufacturing *ex vivo* gene therapies. But *in vivo* gene therapy comes with its own set of challenges, including potential off-target toxicity, low efficacy, and immunogenicity.

The present disclosure offers solutions to foregoing challenges and others that exist in the field of *in vivo* gene therapy.

The present disclosure generally relates to, in part, to an engineered cell-targeting particle (*e.g.*, a fusosome; an extracellular vesicle, including a microvesicle, an apoptotic body, and an exosome; a lipid nanoparticle; a virus-like particle (VLPs); or a viral particle) that has improved specificity for a desired cell type, *e.g.,* an immune effector cell. Without wishing to be bound by any particular theory, it is contemplated that an engineered cell-targeting particle comprising an efficient fusogen and one or more cell-targeting polypeptides (*i.e.,* tropism polypeptides) increase the on-target delivery of a cargo or payload to a desired cell type and decrease the off-target delivery to undesired cell types. It is further contemplated that particles comprising one or more non-viral tropism polypeptides and a viral envelope glycoprotein that is capable of cell fusion but not cell attachment or cell binding yields an engineered cell-targeting particle that has increased delivery specificity and that efficiently delivers one or more nucleic acids or proteins to a desired cell type.

The disclosure contemplates, in part, recombinant particles with increased specificity for cellular vehicles to enable gene therapy or genome editing applications. Recombinant particles contemplated herein include but are not limited to, a fusosome, an extracellular vesicle, a microvesicle, an apoptotic body, an exosome, a lipid nanoparticle, a virus-like particle (VLPs), or a recombinant viral particle that has a single layer of phospholipid, a phospholipid bilayer, a cell membrane, a capsid, or a viral envelope comprising one or more

membrane-bound viral glycoproteins modified to retain fusogenic activity and decrease, reduce, substantially ablate, ablate, abolish or eliminate cell binding or attachment activity; one or more non-viral membrane-bound tropism polypeptides; and a cargo or payload comprising one or more polynucleotides and/or polypeptides. The recombinant particles may be used for *ex vivo* gene therapy and genome editing but provide substantial advantages for use in *in vivo* gene therapy and genome editing.

The disclosure further contemplates, in part, gene therapy and genome editing compositions comprising a fusosome, an extracellular vesicle, a microvesicle, an apoptotic body, an exosome, a lipid nanoparticle, a virus-like particle (VLPs), or a recombinant viral particle that has a single layer of phospholipid, a phospholipid bilayer, a cell membrane, a capsid, or a viral envelope comprising one or more membrane-bound viral glycoproteins modified to retain fusogenic activity and that lack or substantially lack cell binding or attachment activity and/or cognate receptor binding activity; one or more non-viral membrane-bound tropism polypeptides; and a cargo or payload comprising one or more polynucleotides and/or polypeptides.

The disclosure further contemplates, in part, methods of making the recombinant particles contemplated herein, along with methods of using the particles.

In preferred embodiments, the recombinant particle is a recombinant viral particle, preferably a recombinant retroviral particle, more preferably a recombinant lentiviral particle, and even more preferably, a recombinant HIV-1 based lentiviral particle. In further preferred embodiments, the recombinant particle comprises a polynucleotide payload, preferably a vector, more preferably a viral vector, and even more preferably a retroviral or lentiviral vector.

In particular embodiments, the disclosure contemplates, methods of using a recombinant particle contemplated herein to decrease off-target delivery and increase targeted delivery to an immune effector cell *in vivo*, to increase the specificity of an *in vivo* gene therapy or genome editing composition, to deliver a cargo or payload of one or more polynucleotides and/or polypeptides to an immune effector cell, to treat a wide variety of disorders, diseases and conditions or symptoms associated therewith, including but not limited to cancers, infectious diseases, autoimmune diseases, inflammatory diseases, immunodeficiencies, and monogeneic diseases.

Compositions, pharmaceutical compositions, and kits comprising one or more recombinant particles contemplated herein and methods of making and using the same are also provided in particular embodiments.

Techniques for recombinant (*i.e.*, engineered) DNA, peptide and oligonucleotide synthesis, immunoassays, tissue culture, transformation (*e.g.*, electroporation, lipofection), enzymatic reactions, purification and related techniques and procedures may be generally performed as described in various general and more specific references in microbiology, molecular biology, biochemistry, molecular genetics, cell biology, virology and immunology as cited and discussed throughout the present specification. See, *e.g.*, Sambrook *et al.*, *Molecular Cloning: A Laboratory Manual*, 4th ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.; *Current Protocols in Molecular Biology* (John Wiley and Sons, updated July 2008); *Short Protocols in Molecular Biology: A Compendium of Methods from Current Protocols in Molecular Biology*, Greene Pub. Associates and Wiley-Interscience (2002); Glover, *DNA Cloning: A Practical Approach*, vol. I & II (IRL Press, Oxford Univ. Press USA, 1985); *Current Protocols in Immunology* (Edited by: John E. Coligan, Ada M. Kruisbeek, David H. Margulies, Ethan M. Shevach, Warren Strober 2001 John Wiley & Sons, NY, NY); *Real-Time PCR: Current Technology and Applications*, Edited by Julie Logan, Kirstin Edwards and Nick Saunders, 2009, Caister Academic Press, Norfolk, UK; Anand, *Techniques for the Analysis of Complex Genomes*, (Academic Press, New York, 1992); Guthrie and Fink, *Guide to Yeast Genetics and Molecular Biology* (Academic Press, New York, 1991); *Oligonucleotide Synthesis* (N. Gait, Ed., 1984); *Nucleic Acid the Hybridization* (B. Hames & S. Higgins, Eds., 1985); *Transcription and Translation* (B. Hames & S. Higgins, Eds., 1984); *Animal Cell Culture* (R. Freshney, Ed., 1986); Perbal, *A Practical Guide to Molecular Cloning* (1984); *Next-Generation Genome Sequencing* (Janitz, 2008 Wiley-VCH); *PCR Protocols* (Methods in Molecular Biology) (Park, Ed., 3rd Edition, 2010 Humana Press); *Immobilized Cells and Enzymes* (IRL Press, 1986); the treatise, *Methods in Enzymology* (Academic Press, Inc., N.Y.); *Gene Transfer Vectors for Mammalian Cells* (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); Harlow and Lane, *Antibodies*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1998); *Immunochemical Methods in Cell and Molecular Biology* (Mayer and Walker, eds., Academic Press, London, 1987); *Handbook of Experimental Immunology*, Volumes I-IV (D. M. Weir and CC Blackwell, eds., 1986); Roitt, *Essential Immunology*, 6th Edition, (Blackwell Scientific Publications, Oxford, 1988); *Current Protocols in Immunology* (Q. E.

Coligan, A. M. Kruisbeek, D. H. Margulies, E. M. Shevach and W. Strober, eds., 1991); *Annual Review of Immunology*; as well as monographs in journals such as *Advances in Immunology*.

B. DEFINITIONS

Prior to setting forth this disclosure in more detail, it may be helpful to an understanding thereof to provide definitions of certain terms to be used herein.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which the invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of particular embodiments, preferred embodiments of compositions, methods and materials are described herein. For the purposes of the present disclosure, the following terms are defined below.

The articles "a," "an," and "the" are used herein to refer to one or to more than one (*i.e.,* to at least one, or to one or more) of the grammatical object of the article. By way of example, "an element" means one element or one or more elements.

The use of the alternative (*e.g.*, "or") should be understood to mean either one, both, or any combination of the recited alternatives.

The term "and/or" should be understood to mean either one of, or both of, the alternatives.

As used herein, the term "about" or "approximately" refers to a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by as much as 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2% or 1% to a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length. In one embodiment, the term "about" or "approximately" refers a range of quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length ± 15%, ± 10%, ± 9%, ± 8%, ± 7%, ± 6%, ± 5%, ± 4%, ± 3%, ± 2%, or ± 1% of a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length.

In one embodiment, a range, *e.g.,* 1 to 5, about 1 to 5, or about 1 to about 5, refers to each numerical value encompassed by the range. For example, in one non-limiting and merely illustrative embodiment, the range "1 to 5" is equivalent to the expression 1, 2, 3, 4, 5; or 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, or 5.0; or 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9,

2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, or 5.0.

As used herein, the term "substantially" refers to a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that is 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or higher compared to a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length. In one embodiment, "substantially the same" refers to a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that produces an effect, *e.g.*, a physiological effect, that is approximately the same as a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length. In particular embodiments, "substantially lacks cell binding or cell attachment activity and/or cognate receptor binding activity" or "substantially abates cell binding or cell attachment activity and/or cognate receptor binding activity" refers to the negligible or undetectable or absent cell binding activity or cell attachment activity of a modified membrane-bound viral glycoprotein contemplated herein to bind or attach to its cognate receptor on the surface of a cell compared to the cell binding activity or cell attachment activity of the unmodified membrane-bound viral glycoprotein to bind or attach to its cognate receptor on the surface of the cell.

Throughout this specification, unless the context requires otherwise, the words "comprise", "comprises" and "comprising" will be understood to imply the inclusion of a stated step or element or group of steps or elements but not the exclusion of any other step or element or group of steps or elements. By "consisting of" is meant including, and limited to, whatever follows the phrase "consisting of." Thus, the phrase "consisting of" indicates that the listed elements are required or mandatory and that no other elements may be present. The phrase "consisting essentially of" means including any elements listed after the phrase and other elements that do not interfere with or contribute to the activity or action specified in the disclosure for the listed elements. Thus, the phrase "consisting essentially of" indicates that the listed elements are required or mandatory but that no other elements are present that materially affect the activity or action of the listed elements.

Reference throughout this specification to "one embodiment," "an embodiment," "a particular embodiment," "a related embodiment," "a certain embodiment," "an additional embodiment," or "a further embodiment" or combinations thereof means that a particular feature, structure or characteristic described in connection with the embodiment is included

in at least one embodiment. Thus, the appearances of the foregoing phrases in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. It is also understood that the positive recitation of a feature in one embodiment, serves as a basis for excluding the feature in a particular embodiment.

The terms, "binding domain," "extracellular binding domain," and "extracellular antigen binding domain" are used interchangeably and refers to a domain that enables an engineered receptor, *e.g.,* a chimeric antigen receptor (CAR), a chimeric costimulatory receptor (CCR), an alpha-beta T cell receptor (αβ TCR), a gamma delta T cell receptor (γδ TCR), a dimerizing agent regulated immunoreceptor complex (DARIC), a chimeric TGF-β receptor (CTBR), or a zetakine receptor to specifically bind to a target antigen. The binding domain may be derived either from a natural, synthetic, semi-synthetic, or recombinant source.

An "antibody" refers to a polypeptide that comprises at least a light chain immunoglobulin variable region and/or a heavy chain immunoglobulin variable region, which specifically recognizes and binds one or more epitopes of an antigen.

Antibodies include polyclonal and monoclonal antibodies and antigen binding fragments thereof; murine antibodies, camelid antibodies, and human antibodies, and antigen binding fragments thereof; and chimeric antibodies, an antibody that comprises variable regions from a non-human species and human constant regions, heteroconjugate antibodies, and humanized antibodies, an antibody that comprises complementarity determining regions (CDRs) from a non-human species and human framework and constant regions, and antigen binding fragments thereof.

Murine, chimeric, humanized, and human antibodies comprise two heavy chains and two light chains. Each heavy chain consists of a variable region (VH) and three constant regions (CH1, CH2, CH3), while each light chain consists of a variable region (VL) and a constant region (CL). Mammalian immunoglobulin heavy chains are classified as immunoglobulin (Ig)A, IgD, IgE, IgG, and IgM. Mammalian immunoglobulin light chains are classified as λ or κ.

Light and heavy chain variable regions contain a "framework" region interrupted by three hypervariable regions, also called "complementarity-determining regions" or "CDRs."

The sequences of the framework regions of different light or heavy chains are relatively conserved within a species, such as humans. The framework regions serve to position and align the CDRs in three-dimensional space to bind to an epitope. The CDRs of each chain are numbered sequentially starting from the N-terminus and are also typically identified by the chain in which the particular CDR is located. Heavy chain CDRs are referred to as CDRH1, CDRH2, and CDRH3, and light chain CDRs are referred to as CDRLl, CDRL2, and CDRL3. Although CDRs vary from antibody to antibody, the limited number of amino acid positions within the CDRs directly involved in antigen binding are called specificity determining residues (SDRs).

CDRs can be defined or identified by conventional methods, such as by sequence according to Wu and Kabat, *J Exp Med*. 132(2):211-50 (1970) and Kabat and Wu, *Ann New York Acad Sci*. 190:382–93 (1971), or by structure according to Chothia and Lesk, *J Mol. Biol*. 196(4): 901-917 (1987) and Chothia *et al.*, *Nature.* 342:877–83(1989). Other boundaries defining CDRs overlapping with the Kabat CDRs have been described by Padlan *et al.*, *FASEB J*. 9:133–9 (1995) and MacCallum *et al.*, *J Mol Biol*. 262:732–745 (1996). Additional methods of determining CDRs include the Gelfand numbering system described in Gelfand and Kister, *PNAS USA.* 92:10884–8(1995), Gelfand *et al.*, *Protein Eng*. 11:1015–25 (1998), and Gelfand *et al.*, *PNAS USA*. 93:3675–8 (1996); the Honneger number system described in Honegger and Plückthun, *J Mol Biol*. 309:657–70 (2001); the AbM numbering system described by Abhinandan and Martin, *Mol Immunol*. 45:3832–9 (2008); and the IMGT numbering system described in Giudicelli *et al.*, *Nucleic Acids Res*. 25:206–11 (1997), Lefranc, *Immunol Today* 18:509 (1997), and Lefranc *et al.*, *Dev Comp Immunol*. 27:55–77 (2003). Proprietary and publicly programs that identify CDRs are available, *e.g.*, abYsis (abysis.org/abysis/) and IMGT/V-QUEST (imgt.org/IMGT_vquest).

"VL" or "V_L" refers to the variable region of an immunoglobulin light chain, including that of an antibody, Fv, scFv, dsFv, Fab, or other antigen binding fragment thereof. "VH" or "V_H" refer to the variable region of an immunoglobulin heavy chain, including that of an antibody, Fv, scFv, dsFv, Fab, heavy chain only antibody (hcAb) or other antigen binding fragment thereof.

An "antigen binding fragment" or "antigen binding portion" refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen. An "isolated antibody or antigen binding fragment thereof" refers to an antibody or antigen binding fragment thereof that has been separated from its natural environment and/or that is derived

from a natural, synthetic, semi-synthetic, or recombinant source. Illustrative examples of antigen binding fragments suitable for incorporation into engineered receptors contemplated in particular embodiments herein include, but are not limited to, a Camel Ig, a Llama Ig, an Alpaca Ig, Ig NAR, a Fab' fragment, a F(ab')2 fragment, a bispecific Fab dimer (Fab2), a trispecific Fab trimer (Fab3), an Fv, a single chain Fv protein ("scFv"), a bis-scFv, $(scFv)_2$, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a Fibronectin type III (FN3) domain antibody, a single-domain antibody (sdAb or nanobody, *e.g.*, a camelid VHH or shark VNAR), a centyrin, and other portions of full length antibodies sufficient for antigen binding, and combinations thereof.

A "heavy chain antibody" or "hcAb" refers to an antibody that contains two heavy chain variable domains and no light chains. A "camelid antibody" or "camelid Ig" refers to an hcAb isolated from a Camel, Alpaca, or Llama that consists of a homodimer of a heavy chain variable domain (VHH) and CH2 and CH3 constant domains. An "IgNAR" or "immunoglobulin new antigen receptor" refers to an hcAb isolated from the shark immune repertoire that consists of a homodimer of a variable new antigen receptor (VNAR) domain and five constant new antigen receptor (CNAR) domains.

A "single domain antibody," "sdAb," or "nanobody" as used herein refers to an antibody fragment that contains the smallest known antigen binding unit of the variable region of a heavy chain antibody, *e.g.*, a camelid VHH or shark VNAR. A "humanized VHH" refers to a single domain non-human VHH that has undergone humanization to reduce potential immunogenicity of the antibody in human recipients. A "humanized VNAR" refers to a single domain non-human VNAR that has undergone humanization to reduce potential immunogenicity of the antibody in human recipients.

A "single-chain Fv" or "scFv" antibody fragment comprises the VH and VL domains of an antibody, wherein these domains are present in a single polypeptide chain and in either orientation (*e.g.*, VL-VH or VH-VL). Generally, the scFv polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the scFv to form the desired structure for antigen binding.

The terms "spacer," "spacer domain," or "spacer polypeptide" are used interchangeably and refer to a polypeptide domain or sequence of amino acids in a non-viral membrane-bound tropism polypeptide disposed between an extracellular antigen targeting domain and a transmembrane domain or an ω amino acid, *i.e.,* the amino acid serving as the attachment site of the GPI anchor. A spacer positions the extracellular antigen targeting

domain away from the particle surface to enable proper particle/target cell contact, attachment, or binding. A spacer may be derived either from a natural, synthetic, semi-synthetic, or recombinant source. Illustrative examples of spacer domains include but are not limited to hinge or stalk domains derived, obtained, or isolated from IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3 (*e.g.,* SEQ ID NOs: 411-423), CADHERIN 1 and variants thereof (*e.g.,* SEQ ID NOs: 424-427), CEACAM 5 and variants thereof (*e.g.,* SEQ ID NOs: 428-433), and polypeptide linkers of similar amino acid composition, rigidity, flexibility and/or length.

A "hinge domain," is a polypeptide domain or sequence of amino acids that plays a role in positioning the antigen binding domain away from the effector cell surface to enable proper cell/cell contact, antigen binding and activation. A hinge domain is placed between a binding domain and a transmembrane domain (TM). A hinge domain may be derived either from a natural, synthetic, semi-synthetic, or recombinant source. A hinge domain may be altered by substituting one or more cysteine and/or proline residues in a naturally occurring immunoglobulin hinge domain with one or more other amino acid residues (*e.g.*, one or more serine residues).

A "transmembrane domain" or "TM domain" refers to a hydrophobic portion of polypeptide that anchors the polypeptide to the plasma membrane of the cell. The TM domain may be derived either from a natural, synthetic, semi-synthetic, or recombinant source.

A "glycosylphosphatidylinositol anchor" or "GPI anchor" refers to a moiety comprising a hydrophilic oligosaccharide and a lipophilic fatty acid that attaches a protein to the endoplasmatic reticulum (ER) membrane by a transamidase enzyme complex, the protein subsequently delivered to the outer leaflet of the plasma membrane.

An "intracellular signaling domain" refers to a portion of a polypeptide that participates in transducing the message of effective binding of a target antigen by a receptor expressed on an immune effector cell to the immune effector cell's interior to elicit one or more effector functions (an "effector function" refers to a specialized function of an immune effector cell), *e.g.*, activation, cytokine production, proliferation and cytotoxic activity, including the release of cytotoxic factors, or other cellular responses elicited with antigen binding to the receptor expressed on the immune effector cell. "Intracellular signaling domains" include a polypeptide domain or functional fragment thereof, which transduces an

effector function signal and that directs a cell to perform a specialized function. The term intracellular signaling domain is meant to include any truncated portion of an intracellular signaling domain sufficient to transducing effector function signal.

T cell activation can be said to be mediated by two distinct classes of intracellular signaling domains: primary signaling domains that initiate antigen-dependent primary activation through the TCR (*e.g.*, a TCR/CD3 complex) and costimulatory signaling domains that act in an antigen-independent manner to provide a secondary or costimulatory signal.

A "primary signaling domain" refers to a signaling domain that regulates the primary activation of a TCR complex either in a stimulatory way, or in an inhibitory way. Primary signaling domains that act in a stimulatory manner may contain one or more signaling motifs which are known as immunoreceptor tyrosine-based activation motifs or ITAMs.

A "costimulatory signaling domain" or "costimulatory domain" refers to an intracellular signaling domain of a costimulatory molecule. Costimulatory molecules are cell surface molecules other than antigen receptors or Fc receptors that provide a second signal required for efficient activation and function of T lymphocytes upon binding to antigen.

The terms "individual" and "subject" are often used interchangeably and refer to any animal that exhibits a symptom of a disease, disorder, or condition, *e.g.*, cancer, that can be treated with the recombinant particles, *e.g.,* recombinant retroviral particles or lentiviral particles, gene therapy vectors, compositions, and methods contemplated elsewhere herein. Suitable subjects (*e.g.,* patients) include laboratory animals (*e.g.,* mouse, rat, rabbit, or guinea pig), farm animals, and domestic animals or pets (*e.g.,* cat or dog). Non-human primates and, preferably, human patients, are preferred subjects.

A "patient" refers to a subject that has been diagnosed with a particular disease, disorder, or condition that can be treated with the recombinant particles, *e.g.,* recombinant retroviral particles or lentiviral particles, gene therapy vectors, compositions and methods disclosed elsewhere herein.

"Treatment" or "treating," as used herein includes any beneficial or desirable effect on the symptoms or pathology of a disease or pathological condition and may include even minimal reductions in one or more measurable markers of the disease or condition being treated. Optionally, treatment can include reducing the disease burden or delaying disease progression. "Treatment" may, but does not necessarily, indicate complete eradication or cure of the disease or condition, or associated symptoms thereof.

"Prevent," "prevention," "preventing" and the like, as used herein, indicate an approach for preventing, inhibiting, or reducing the likelihood of occurrence or recurrence of a disease or condition. It also refers to delaying the onset or recurrence of a disease or condition or delaying the occurrence or recurrence of the symptoms of a disease or condition. Prevention includes reducing the intensity, effect, symptoms and/or burden of a disease or condition prior to onset or recurrence of the disease or condition.

"Ameliorating at least one symptom of" as used herein, refers to decreasing one or more symptoms of the disease or condition for which a subject is being treated. In particular embodiments, the disease or condition being treated is a cancer, and the one or more symptoms ameliorated include, but are not limited to, weakness, fatigue, shortness of breath, easy bruising and bleeding, frequent infections, enlarged lymph nodes, distended or painful abdomen (due to enlarged abdominal organs), bone or joint pain, fractures, unplanned weight loss, poor appetite, night sweats, persistent mild fever, and decreased urination (due to impaired kidney function).

Additional definitions are set forth throughout this disclosure.

C. RECOMBINANT PARTICLES

Various particles have been proposed as gene delivery vehicles. The present disclosure contemplates, in part, a recombinant particle engineered to bind to a desired or target cell type and deliver a payload. Recombinant particles comprise a surface and a payload: the surface comprising one or more mutated viral envelope glycoproteins that retain fusogenic activity and substantially lack or lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides engineered to bind a cell, *e.g.,* an immune effector cell; and the payload comprising one or more polynucleotide and/or polypeptides. Suitable recombinant particles for use in particular embodiments contemplated herein include but are not limited to a fusosome; an extracellular vesicle, including a microvesicle, an apoptotic body, and an exosome; a lipid nanoparticle; a virus-like particle (VLPs); or a recombinant viral particle.

In preferred embodiments, a recombinant particle is a recombinant viral particle or recombinant virus. The terms "recombinant viral particle" and "recombinant virus" are used interchangeably.

Recombinant viral particles have been used as a gene delivery platform for treatments of severe genetic diseases and cancer. Illustrative examples of recombinant viral particles

suitable for use in particular embodiments contemplated herein are derived from an adenovirus (Ad), an adeno-associated virus (AAV), a rhabdovirus (*e.g.,* lyssavirus, vesiculovirus), a paramyxovirus (*e.g.,* henipavirus, morbillivirus, respirovirus, rubelavirus), a herpes simplex virus (*e.g.,* HSV-1, HSV-2), vaccinia virus, or a retrovirus (*e.g.*, gammaretrovirus, lentivirus).

Retroviruses are a commonly used tool for gene delivery (Miller, 2000, Nature. 357: 455-460). The term "retrovirus" refers to an enveloped RNA virus that reverse transcribes its genomic RNA into a linear double-stranded DNA copy and subsequently covalently integrates its genomic DNA into a host genome. A recombinant retroviral particle comprises a viral envelope, one or more retroviral proteins, *e.g.,* matrix protein (MA), capsid protein (CA), nucleocapsid protein (NC), reverse transcriptase (RT), and integrase (IN), and a retroviral vector derived or engineered from a retrovirus genome.

Illustrative retroviruses suitable for deriving or engineering recombinant retroviral particles contemplated in particular embodiments herein include but are not limited to an alpharetrovirus, a betaretrovirus, a gammaretrovirus, a deltaretrovirus, an epsilonretrovirus, a spumavirus, and a lentivirus.

Alpharetroviruses include but are not limited to avian leukosis virus, avian carcinoma Mill Hill virus 2, avian myeloblastosis virus, avian myelocytomatosis virus 29, avian sarcoma virus CT10, fujinami sarcoma virus, rous sarcoma virus, UR2 sarcoma virus and Y73 sarcoma virus.

Betaretroviruses include but are not limited to mouse mammary tumor virus, Jaagsiekte sheep retrovirus, langur virus, Mason-Pfizer monkey virus, and squirrel monkey retrovirus (SMRV).

Deltaretroviruses include but are not limited to bovine leukemia virus, primate T-lymphotropic virus 1, primate T-lymphotropic virus 2, primate T-lymphotropic virus 3, and primate T-lymphotropic virus 4.

Epsilonretroviruses include but are not limited to walleye dermal sarcoma virus, walleye epidermal hyperplasia virus 1, and walleye epidermal hyperplasia virus 2.

Gammaretroviruses include but are not limited to baboon endogenous virus (BaEV), chick syncytial virus, feline endogenous virus (*e.g.*, RD114), feline leukemia virus (FeLV), Finkel-Biskis-Jinkins murine sarcoma virus, Gardner-Arnstein feline sarcoma virus, gibbon ape leukemia virus (GALV), guinea pig type-C oncovirus, Hardy-Zuckerman feline sarcoma virus, Harvey murine sarcoma virus, Kirsten murine sarcoma virus, koala retrovirus, murine

leukemia virus (MLV), Moloney murine leukemia virus (MoMLV), Moloney murine sarcoma virus, porcine endogenous virus (PERV), Porcine type-C oncovirus, reticuloendotheliosis virus (REV), Snyder-Theilen feline sarcoma virus, Trager duck spleen necrosis virus, viper retrovirus, xenotropic murine leukemia virus- related virus (XMRV), and woolly monkey sarcoma virus.

Spumaviruses include but are not limited to simian foamy virus, bovine foamy virus, equine foamy virus, feline foamy virus, human foamy virus (HFV), and brown greater galago prosimian foamy virus.

In particular embodiments, a recombinant retroviral particle is derived or engineered from a retrovirus selected from the group consisting of: SMRV, BaEV, RD114, FeLV, GALV, MLV, MoMLV, PERV, REV, XMRV, and HFV.

A "lentivirus" refers to a complex retrovirus. Among retroviruses, lentiviruses are the most efficient at transducing resting or growth-arrested cells. In preferred embodiments, a recombinant retroviral particle is a recombinant lentiviral particle or recombinant lentivirus.

Lentiviruses suitable for deriving or engineering recombinant lentiviruses contemplated in particular embodiments herein include but are not limited to human immunodeficiency virus (HIV), including HIV type 1 (HIV-1) and HIV type 2 (HIV-2); visna-maedi virus (VMV); caprine arthritis-encephalitis virus (CAEV); equine infectious anemia virus (EIAV); feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV).

In particular embodiments, a recombinant lentiviral particle is derived or engineered from an HIV-1 or HIV-2 lentivirus.

D. PARTICLE SURFACE

Recombinant particles engineered to bind to a particular cell type and deliver a payload comprise an outer surface that comprises, expresses, or displays (i) one or more polypeptides that direct the particle to, and allow it to bind or attach to, a desired cell type and (ii) one or more polypeptides that mediate fusion with the cell. In particular embodiments, a recombinant particle selected from the group consisting of a fusosome; a microvesicle, an apoptotic body, and an exosome; a lipid nanoparticle; a virus-like particle (VLPs); or a recombinant viral particle, comprises an outer surface selected from the group consisting of a single layer of phospholipid, a phospholipid bilayer, a cell membrane, a capsid, or a viral envelope.

In particular embodiments, the outer surface of the particle is engineered to express or display one or more mutated viral envelope glycoproteins that retain fusogenic activity and that substantially lack or lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides engineered to bind a specific cell type, *e.g.*, an immune effector cell. Without wishing to be bound by any particular theory, it is contemplated that the viral envelope glycoproteins herein do not contribute to particle tropism. The viral envelope glycoproteins contemplated herein comprise one or more mutations (*e.g.*, amino acid substitution) that substantially reduce or eliminate their native antigen binding activities and/or blind the viral envelope glycoprotein from recognizing and binding or attaching to its cognate receptor expressed on a cell while still retaining the ability to mediate fusion with the cell. In this way, the native tropism activities of viral envelope glycoproteins contemplated herein are substantially extinguished or ablated while the fusion activity is retained or preserved.

Recombinant retroviral or lentiviral particles comprise an outer surface selected from the group consisting of a lipid bilayer, a cell membrane, or a viral envelope comprising polypeptides that mediate virus – cell attachment and fusion; and one or more polynucleotide and/or polypeptide payloads. The outer surface of the retroviral or lentiviral particle is engineered to uncouple or separate particle fusion and tropism activities.

In particular embodiments, the outer surface of the retroviral or lentiviral particle is engineered to express or display one or more non-viral membrane-bound tropism polypeptides that enable selective and/or specific binding of the virus to a desired cell type. The outer surface is also engineered to express or display a viral envelope glycoprotein that mediates virus – cell fusion but that substantially lacks or lacks the ability to bind its cognate receptor. In other words, the viral envelope glycoprotein provides the fusion activity of the recombinant particle and does not provide or contribute to the tropism activity of the particle. Likewise, the non-viral membrane-bound tropism polypeptides provide the tropism activity of the recombinant particle and do not provide or contribute to the fusion activity of the particle. The foregoing engineering strategy enables highly efficient on-target delivery of therapeutic payloads to the desired cell types while minimizing, reducing and/or eliminating delivery to undesired cell types.

In particular embodiments, a recombinant retroviral particle comprises a lipid bilayer, cell membrane, or viral envelope comprising one or more mutated viral envelope glycoproteins that mediate fusion of the viral particle with a cell, but that do not substantially

bind or bind its cognate receptor, and one or more non-viral membrane-bound tropism polypeptides.

In particular embodiments, one or more mutated viral envelope glycoproteins comprise one or more rhabdovirus (*e.g.,* vesiculovirus) envelope glycoproteins or one or more paramyxovirus (*e.g.,* morbillivirus or henipavirus) envelope glycoproteins. In particular embodiments, a mutated viral envelope glycoprotein comprises a heterologous signal peptide.

In particular embodiments, one or more mutated viral envelope glycoproteins comprise one or more rhabdovirus (*e.g.,* vesiculovirus) envelope glycoproteins or one or more paramyxovirus (*e.g.,* morbillivirus or henipavirus) envelope glycoproteins.

In particular embodiments, one or more mutated viral envelope glycoproteins comprise one or more rhabdovirus (*e.g.,* vesiculovirus) envelope glycoproteins and a native or heterologous signal peptide, which is subsequently cleaved.

In particular embodiments, one or more mutated viral envelope glycoproteins comprise one or more paramyxovirus (*e.g.,* morbillivirus or henipavirus) envelope glycoproteins and a native or heterologous signal peptide, which is subsequently cleaved.

Illustrative examples of heterologous signal peptides are set forth in SEQ ID NOs: 449-454.

1. RHABDOVIRUS ENVELOPE GLYCOPROTEINS

The *Rhabdoviridae* family of viruses are negative-sense, single-stranded RNA viruses with a genome of about 10.8–16.1 kb. The prototypic mammalian rhabdoviruses include the rabies virus (RABV) and vesiculoviruses, which cause severe human and animal disease. In particular embodiments, a recombinant particle comprises one or more rhabdovirus envelope glycoproteins modified to substantially ablate or ablate the glycoprotein's ability bind its cognate receptor expressed on a cell while retaining fusogenic activity. The *Rhabdoviridae* family includes cytorhabdoviruses, dichorhaviruses, ephemeroviruses, lyssaviruses, novirhabdoviruses, nucleorhabdoviruses, perhabdoviruses, sigmaviruses, spriviviruses, tibroviruses, tupaviruses, varicosaviruses, and vesiculoviruses, among others.

a. Vesiculovirus Envelope Glycoproteins

Vesiculoviruses use a single glycoprotein to enter a cell: glycoprotein G mediates both cell attachment (tropism) and cell fusion. Glycoprotein G is normally responsible for virus attachment to specific receptors (*e.g.,* low-density lipoprotein receptor (LDL-R) and other members of this receptor family) and fusion between the viral and endosomal membranes. In particular embodiments, a modified vesiculovirus G envelope protein comprises one or more amino acid substitutions that that enable the polypeptide to mediate fusion of the viral particle and a cell but that substantially ablate or ablate the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R.

Illustrative examples of vesiculoviruses suitable for use in particular embodiments from which G glycoproteins can be isolated include, but are not limited to vesicular stomatitis Alagoas virus (VSAV; Alagoas vesiculovirus), Carajás virus (CJSV; Carajas vesiculovirus), Chandipura virus (CHPV; Chandipura vesiculovirus), Cocal virus (COCV; Cocal vesiculovirus), vesicular stomatitis Indiana virus (VSIV, f.k.a. VSV; Indiana vesiculovirus), Isfahan virus (ISFV; Isfahan vesiculovirus), Maraba virus (MARAV; Maraba vesiculovirus), Morreton virus (MORV; Morreton vesiculovirus), vesicular stomatitis New Jersey virus (VSNJV; New Jersey vesiculovirus), and Piry virus (PIRYV; Piry vesiculovirus).

In particular embodiments, a vesiculovirus G envelope protein comprises an amino acid sequence set forth in any one of SEQ ID NOs: 15-322 disclosed in U.S. Patent Application No. 20200216502, each said sequence incorporated by reference herein in its entirety, or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto that enables the polypeptide to mediate fusion of the viral particle with a cell but that substantially ablates or ablates the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R.

In particular embodiments, a vesiculovirus is vesicular stomatitis Indiana virus (VSIV). In particular embodiments, a mutated viral envelope glycoprotein is derived from a VSIV envelope glycoprotein (VSIV-G; *e.g.*, SEQ ID NO: 1: KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPKSHKAIQA DGWMCHASKWVTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPG FPPQSCGYATVTDAEAVIVQVTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHN STTWHSDYKVKGLCDSNLISMDITFFSEDGELSSLGKEGTGFRSNYFAYETGGKA CKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEGSSISAPSQTSVDVSLI

QDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIINGTLKYFETR
YIRVDIAAPILSRMVGMISGTTTERELWDDWAPYEDVEIGPNGVLRTSSGYKFPLY
MIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEG
WFSSWKSSIASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK) or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto comprising one or more modifications that enable the polypeptide to mediate fusion of the viral particle and a cell but that substantially ablate or ablate the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.,* LDL-R. In particular embodiments, a mutated viral envelope glycoprotein is derived from a VSIV-G polypeptide set forth in SEQ ID NO: 1 comprising L47I and/or H80Q amino acid substitutions, such substitutions being present in naturally occurring variants of VSIV.

In particular embodiments, a mutated VSIV-G envelope protein comprises one or more of: one or more amino acid substitutions at H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, and R354 (substitution with any amino acid; a conservation substitution; a disruptive substitution; substitution with D, E, A, G, F, or Q; or substitution with A, G, F, or Q); an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, and an insertion of GGS between N208 and Y209; or a deletion of residues 1-8. In particular embodiments, a VSIV-G envelope protein comprises one or more amino acid substitutions at H8, K47, Y209, and R354. In particular embodiments, a VSIV-G envelope protein comprises one or more amino acid substitutions at H8, K47, Y209, and R354, wherein each substitution can be with A, G, F, or Q. Amino acid positions are with reference to a VSIV-G envelope protein that lacks a signal peptide, *e.g.,* SEQ ID NO: 1. In particular embodiments, a mutated viral envelope glycoprotein is derived from a VSIV-G polypeptide set forth in SEQ ID NO: 1 comprising L47I and/or H80Q amino acid substitutions, such substitutions present in naturally occurring variants of VSIV.

In particular embodiments, a mutated VSIV-G polypeptide comprises one or more amino acid substitutions at K47, I182, and/or R354 (substitution with any amino acid; a conservation substitution; a disruptive substitution; substitution with D, E, A, G, F, or Q; or substitution with A, G, F, or Q). In particular embodiments, a mutated VSIV-G polypeptide comprises amino acid substitutions at K47, I182, or R354; K47 and I182; K47 and R354; I182 and R354; or at K47, I182, and R354 of SEQ ID NO: 1.

In particular embodiments, a mutated VSIV-G polypeptide comprises one or more of the following amino acid substitutions: K47A, K47Q, I182E, I182D, R354A, and/or R354Q. In particular embodiments, a mutated VSIV-G polypeptide comprises the following amino acid substitutions: K47A, K47Q, I182E, I182D, R354A, or R354Q; K47A and I182E; K47A and I182D; K47Q and I182E; K47Q and I182D; I182E and R354A; I182E and R354Q; I182D and R354A; I182D and R354Q; K47A and R354A; K47A and R354Q; K47Q and R354A; K47Q and R354Q; K47A, I182E, and R354A; K47A, I182D, and R354A; K47Q, I182E, and R354A; K47Q, I182D, and R354A; K47A, I182E, and R354Q; K47A, I182D, and R354Q; K47Q, I182E, and R354Q; or K47Q, I182D, and R354Q of SEQ ID NO: 1.

In particular embodiments, a VSIV-G envelope protein comprises one or more amino acid substitutions at K47 and R354 (with reference to a VSIV-G envelope protein that lacks a signal peptide, *e.g.,* SEQ ID NO: 1). In particular embodiments, a VSIV-G envelope protein comprises one or more amino acid substitutions selected from the group consisting of: K47A and R354A; K47A and R354G; K47A and R354F; K47A and R354Q; K47G and R354A; K47G and R354G; K47G and R354F; K47G and R354Q;K47F and R354A; K47F and R354G; K47F and R354F; K47F and R354Q; K47Q and R354A; K47Q and R354G; K47Q and R354F; and K47Q and R354Q. In a preferred embodiment, a VSIV-G envelope comprises the amino acid substitutions K47Q and R354A.

In particular embodiments, a mutated VSIV-G envelope protein comprises an amino acid sequence set forth in SEQ ID NO: 2 (wherein X_1= I, X_2 = A, X_3 = Q, and X_4 = A; X_1= I, X_2 = A, X_3 = Q, and X_4 = G; X_1= I, X_2 = A, X_3 = Q, and X_4 = F; X_1= I, X_2 = A, X_3 = Q, and X_4 = Q; X_1= L, X_2 = A, X_3 = Q, and X_4 = A; X_1= L, X_2 = A, X_3 = Q, and X_4 = G; X_1= L, X_2 = A, X_3 = Q, and X_4 = F; X_1= L, X_2 = A, X_3 = Q, and X_4 = Q; X_1= I, X_2 = A, X_3 = H, and X_4 = A; X_1= I, X_2 = A, X_3 = H, and X_4 = G; X_1= I, X_2 = A, X_3 = H, and X_4 = F; X_1= I, X_2 = A, X_3 = H, and X_4 = Q; X_1= L, X_2 = A, X_3 = H, and X_4 = A; X_1= L, X_2 = A, X_3 = H, and X_4 = G; X_1= L, X_2 = A, X_3 = H, and X_4 = F; X_1= L, X_2 = A, X_3 = H, and X_4 = Q; X_1= I, X_2 = G, X_3 = Q, and X_4 = A; X_1= I, X_2 = G, X_3 = Q, and X_4 = G; X_1= I, X_2 = G, X_3 = Q, and X_4 = F; X_1= I, X_2 = G, X_3 = Q, and X_4 = Q; X_1= L, X_2 = G, X_3 = Q, and X_4 = A; X_1= L, X_2 = G, X_3 = Q, and X_4 = G; X_1= L, X_2 = G, X_3 = Q, and X_4 = F; X_1= L, X_2 = G, X_3 = Q, and X_4 = Q; X_1= I, X_2 = G, X_3 = H, and X_4 = A; X_1= I, X_2 = G, X_3 = H, and X_4 = G; X_1= I, X_2 = G, X_3 = H, and X_4 = F; X_1= I, X_2 = G, X_3 = H, and X_4 = Q; X_1= L, X_2 = G, X_3 = H, and X_4 = A; X_1= L, X_2 = G, X_3 = H, and X_4 = G; X_1= L, X_2 = G, X_3 = H, and X_4 = F; X_1= L, X_2 =

G, X_3 = H, and X_4 = Q; X_1= I, X_2 = F, X_3 = Q, and X_4 = A; X_1= I, X_2 = F, X_3 = Q, and X_4 = G; X_1= I, X_2 = F, X_3 = Q, and X_4 = F; X_1= I, X_2 = F, X_3 = Q, and X_4 = Q; X_1= L, X_2 = F, X_3 = Q, and X_4 = A; X_1= L, X_2 = F, X_3 = Q, and X_4 = G; X_1= L, X_2 = F, X_3 = Q, and X_4 = F; X_1= L, X_2 = F, X_3 = Q, and X_4 = Q; X_1= I, X_2 = F, X_3 = H, and X_4 = A; X_1= I, X_2 = F, X_3 = H, and X_4 = G; X_1= I, X_2 = F, X_3 = H, and X_4 = F; X_1= I, X_2 = F, X_3 = H, and X_4 = Q; X_1= L, X_2 = F, X_3 = H, and X_4 = A; X_1= L, X_2 = F, X_3 = H, and X_4 = G; X_1= L, X_2 = F, X_3 = H, and X_4 = F; X_1= L, X_2 = F, X_3 = H, and X_4 = Q; X_1= I, X_2 = Q, X_3 = Q, and X_4 = A; X_1= I, X_2 = Q, X_3 = Q, and X_4 = G; X_1= I, X_2 = Q, X_3 = Q, and X_4 = F; X_1= I, X_2 = Q, X_3 = Q, and X_4 = Q; X_1= L, X_2 = Q, X_3 = Q, and X_4 = A; X_1= L, X_2 = Q, X_3 = Q, and X_4 = G; X_1= L, X_2 = Q, X_3 = Q, and X_4 = F; X_1= L, X_2 = Q, X_3 = Q, and X_4 = Q; X_1= I, X_2 = Q, X_3 = H, and X_4 = A; X_1= I, X_2 = Q, X_3 = H, and X_4 = G; X_1= I, X_2 = Q, X_3 = H, and X_4 = F; X_1= I, X_2 = Q, X_3 = H, and X_4 = Q; X_1= L, X_2 = Q, X_3 = H, and X_4 = A; X_1= L, X_2 = Q, X_3 = H, and X_4 = G; X_1= L, X_2 = Q, X_3 = H, and X_4 = F; and X_1= L, X_2 = Q, X_3 = H, and X_4 = Q) or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto that mediates fusion of the viral particle and a cell but that substantially ablates or ablates the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R.

Table 1

SEQ ID NO:	AMINO ACID SEQUENCE
2	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAX$_1$QVKMPX$_2$SHKAIQADGWMCHASKW VTTCDFRWYGPKYITX$_3$SIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSEDG ELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEGSS ISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIINGTL KYFETRYIRVDIAAPILSRMVGMISGTTTEX$_4$ELWDDWAPYEDVEIGPNGVLRTSSGYKFPLYMI GHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSSIASF FFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK

In particular embodiments, a mutated VSIV-G envelope protein comprises an amino acid sequence set forth in any one of SEQ ID NOs: 582-645 or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto that mediates fusion of the viral particle and a cell but that substantially ablates or ablates the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R. In particular embodiments, a mutated VSIV-G envelope protein comprises an amino acid sequence set forth in any one of SEQ ID NOs: 630-645 or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto that mediates fusion of the viral particle and a cell but that substantially ablates or ablates the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R. In

particular embodiments, a mutated VSIV-G envelope protein comprises an amino acid sequence set forth in any one of SEQ ID NOs: 630, 634, 638, and 642 or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto that mediates fusion of the viral particle and a cell but that substantially ablates or ablates the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R.

Table 2

SEQ ID NO:	AMINO ACID SEQUENCE
582	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
583	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
584	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
585	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
586	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
587	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN

	GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
588	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
589	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
590	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
591	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
592	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
593	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
594	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK

595	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
596	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
597	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPASHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
598	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
599	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
600	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
601	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
602	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED

	GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
603	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
604	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
605	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
606	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
607	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
608	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
609	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL

	YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
610	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
611	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
612	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
613	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPGSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
614	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
615	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
616	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
617	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPFSHKAIQADGWMCHASKW

	VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
618	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
619	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
620	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
621	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
622	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
623	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
624	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG

	SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
625	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
626	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
627	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
628	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
629	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPFSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
630	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
631	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS

	IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
632	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
633	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
634	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
635	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
636	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
637	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITQSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
638	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
639	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ

	VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
640	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
641	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTAIQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
642	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEAELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
643	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEGELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
644	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEFELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK
645	KFTIVFPHNQKGNWKNVPSNYHYCPSSSDLNWHNDLIGTALQVKMPQSHKAIQADGWMCHASKW VTTCDFRWYGPKYITHSIRSFTPSVEQCKESIEQTKQGTWLNPGFPPQSCGYATVTDAEAVIVQ VTPHHVLVDEYTGEWVDSQFINGKCSNYICPTVHNSTTWHSDYKVKGLCDSNLISMDITFFSED GELSSLGKEGTGFRSNYFAYETGGKACKMQYCKHWGVRLPSGVWFEMADKDLFAAARFPECPEG SSISAPSQTSVDVSLIQDVERILDYSLCQETWSKIRAGLPISPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRVDIAAPILSRMVGMISGTTTEQELWDDWAPYEDVEIGPNGVLRTSSGYKFPL YMIGHGMLDSDLHLSSKAQVFEHPHIQDAASQLPDDESLFFGDTGLSKNPIELVEGWFSSWKSS IASFFFIIGLIIGLFLVLRVGIHLCIKLKHTKKRQIYTDIEMNRLGK

In particular embodiments, a vesiculovirus is cocal virus (COCV). In particular embodiments, a mutated viral envelope glycoprotein is derived from a COCV envelope glycoprotein (COCV-G; *e.g.*, SEQ ID NO: 3:

KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPKTHKAIQA
DGWMCHAAKWITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGF
PPQNCGYATVTDSVAVVVQATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHN
STVWYSDYKVTGLCDATLVDTEITFFSEDGKKESIGKPNTGYRSNYFAYEKGDKV
CKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVGATISAPTQTSVDVSLI
LDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIINGTLKYFETR
YIRIDIDNPIISKMVGKISGSQTERELWTEWFPYEGVEIGPNGILKTPTGYKFPLFMI
GHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFS
SWKSTVVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK) or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto comprising one or more modifications that enable the polypeptide to mediate fusion of the viral particle and a cell but that substantially ablate or ablate the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R. In particular embodiments, a COCV-G envelope protein comprises one or more amino acid substitutions at K47 and/or R354. In particular embodiments, a COCV-G envelope protein comprises one or more amino acid substitutions at K47 and/or R354, wherein each amino acid can be substituted with A, G, F, or Q. In particular embodiments, a COCV-G envelope protein comprises one or more amino acid substitutions at K47 and/or R354 (with reference to a COCV-G envelope protein that lacks a signal peptide, *e.g.,* SEQ ID NO: 3). In particular embodiments, a COCV-G envelope protein comprises one or more amino acid substitutions selected from the group consisting of: K47A and R354A; K47A and R354G; K47A and R354F; K47A and R354Q; K47G and R354A; K47G and R354G; K47G and R354F; K47G and R354Q;K47F and R354A; K47F and R354G; K47F and R354F; K47F and R354Q; K47Q and R354A; K47Q and R354G; K47Q and R354F; and K47Q and R354Q. In particular embodiments, a COCV-G envelope protein comprises an amino acid sequence set forth in SEQ ID NO: 4 (wherein X_1= A and X_2 = A; X_1= A and X_2 = G; X_1= A and X_2 = F; X_1= A and X_2 = Q; X_1= G and X_2 = A; X_1= G and X_2 = G; X_1= G and X_2 = F; X_1= G and X_2 = Q; X_1= F and X_2 = A; X_1= F and X_2 = G; X_1= F and X_2 = F; X_1= F and X_2 = Q; X_1= Q and X_2 = A; X_1= Q and X_2 = G; X_1= Q and X_2 = F; or X_1= A and X_2 = Q) or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto that mediates fusion of the viral particle and a cell but that substantially ablates or ablates the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R.

Table 3

SEQ ID NO	AMINO ACID SEQUENCE
4	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPX$_1$THKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQA TPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSEDGK KESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVGATI SAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIINGTLK YFETRYIRIDIDNPIISKMVGKISGSQTEX$_2$ELWTEWFPYEGVEIGPNGILKTPTGYKFPLFMIG HGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKSTVVTFF FAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK

In particular embodiments, a mutated COCV-G envelope protein comprises an amino acid sequence set forth in any one of SEQ ID NOs: 646-661 or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto that mediates fusion of the viral particle and a cell but that substantially ablates or ablates the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R. In particular embodiments, a mutated COCV-G envelope protein comprises an amino acid sequence set forth in any one of SEQ ID NOs: 658-661 or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto that mediates fusion of the viral particle and a cell but that substantially ablates or ablates the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R. In particular embodiments, a mutated VSIV-G envelope protein comprises an amino acid sequence set forth in SEQ ID NOs: 658 or 661 or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto that mediates fusion of the viral particle and a cell but that substantially ablates or ablates the polypeptide's ability to bind its cognate receptor expressed on a cell, *e.g.*, LDL-R.

Table 4

SEQ ID NO:	AMINO ACID SEQUENCE
646	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPATHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEAELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
647	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPATHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEGELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
648	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPATHKAIQADGWMCHAAKW

	ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEFELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
649	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPATHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEQELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
650	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPGTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEAELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
651	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPGTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEGELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
652	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPGTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEFELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
653	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPGTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEQELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
654	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPFTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEAELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
655	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPFTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG

	ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEGELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
656	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPFTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEFELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
657	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPFTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEQELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
658	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPQTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEAELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
659	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPQTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEGELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
660	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPQTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEFELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK
661	KFSIVFPQSQKGNWKNVPSSYHYCPSSSDQNWHNDLLGITMKVKMPQTHKAIQADGWMCHAAKW ITTCDFRWYGPKYITHSIHSIQPTSEQCKESIKQTKQGTWMSPGFPPQNCGYATVTDSVAVVVQ ATPHHVLVDEYTGEWIDSQFPNGKCETEECETVHNSTVWYSDYKVTGLCDATLVDTEITFFSED GKKESIGKPNTGYRSNYFAYEKGDKVCKMNYCKHAGVRLPSGVWFEFVDQDVYAAAKLPECPVG ATISAPTQTSVDVSLILDVERILDYSLCQETWSKIRSKQPVSPVDLSYLAPKNPGTGPAFTIIN GTLKYFETRYIRIDIDNPIISKMVGKISGSQTEQELWTEWFPYEGVEIGPNGILKTPTGYKFPL FMIGHGMLDSDLHKTSQAEVFEHPHLAEAPKQLPEEETLFFGDTGISKNPVELIEGWFSSWKST VVTFFFAIGVFILLYVVARIVIAVRYRYQGSNNKRIYNDIEMSRFRK

2. PARAMYXOVIRUS ENVELOPE GLYCOPROTEINS

The Paramyxoviridae family of negative-sense single-stranded RNA viruses is known to cause different types of infections in vertebrates. Examples of these infections in

humans include the measles virus, encephalitis, mumps virus, parainfluenza virus, and respiratory syncytial virus. In particular embodiments, a recombinant particle comprises one or more paramyxovirus envelope glycoproteins modified to substantially ablate or ablate the glycoprotein's ability bind its cognate receptor expressed on a cell while retaining fusogenic activity. The Paramyxoviridae family includes morbilliviruses and henipaviruses, among others.

a. Morbillivirus Envelope Glycoproteins

Morbilliviruses use two types of glycoproteins to enter a cell: glycoprotein F (a fusion polypeptide) and glycoprotein H (an attachment protein). Although glycoprotein F mediates fusion and glycoprotein H mediates binding, both H and F glycoproteins are required for viral particle fusion with a cell, glycoprotein H supports glycoprotein F in its membrane fusion function.

Efficient pseudotyping with morbillivirus envelope proteins may be accomplished using glycoprotein F comprising a truncated cytoplasmic portion comprising at least 1 positively charged amino acid residue and no more than 9 consecutive amino acid residues as counted from the N-terminal end of the cytoplasmic portion and glycoprotein H comprising a truncated cytoplasmic portion comprising at least 9 and no more than 19 consecutive amino acid residues as counted from the C-terminal end of the cytoplasmic portion plus an additional methionine at the N-terminus. Moreover, glycoprotein H can be modified to ablate its antigen binding activity.

In particular embodiments, the vector comprises modified morbillivirus F and H viral envelope glycoproteins, wherein glycoprotein H is modified to ablate cell binding activity and both H and F glycoproteins retain the ability to cooperatively mediate cell fusion.

Illustrative examples of morbilliviruses suitable for use in particular embodiments from which F and H glycoproteins can independently be isolated from include but are not limited to canine distemper virus (CDV), cetacean morbillivirus (CeMV), feline morbillivirus (FeMV), measles virus (MV), peste-des-petits-ruminants virus (PPRV), phocine distemper virus (PDV), rinderpest virus (RPV).

In particular embodiments, one or more mutated morbillivirus envelope glycoproteins are derived from measles virus F (MV-F) and measles virus H (MV-H). In particular embodiments, a recombinant particle comprises one or more measles virus viral

envelope glycoproteins modified to lack cell binding activity and retain fusogenic activity. In some embodiments, a recombinant particle comprises a modified MV-F glycoprotein and an MV-H glycoprotein modified to lack cell binding activity and retain fusogenic activity.

In particular embodiments, one or more mutated morbillivirus envelope glycoproteins are derived from measles virus F (MV-F) polypeptide (*e.g.*, SEQ ID NO: 5: QIHWGNLSKIGVVGIGSASYKVMTRSSHQSLVIKLMPNITLLNNCTRVEIAEYRRL LRTVLEPIRDALNAMTQNIRPVQSVASSRRHKRFAGVVLAGAALGVATAAQITA GIALHQSMLNSQAIDNLRASLETTNQAIEAIRQAGQEMILAVQGVQDYINNELIPS MNQLSCDLIGQKLGLKLLRYYTEILSLFGPSLRDPISAEISIQALSYALGGDINKVLE KLGYSGGDLLGILESRGIKARITHVDTESYFIVLSIAYPTLSEIKGVIVHRLEGVSYN IGSQEWYTTVPKYVATQGYLISNFDESSCTFMPEGTVCSQNALYPMSPLLQECLR GSTKSCARTLVSGSFGNRFILSQGNLIANCASILCKCYTTGTIINQDPDKILTYIAAD HCPVVEVNGVTIQVGSRRYPDAVYLHRIDLGPPISLERLDVGTNLGNAIAKLEDA KELLESSDQILRSMKGLSSTSIVYILIAVCLGGLIGIPALICCCRGR) or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto and a measles virus H (MV-H) polypeptide (*e.g.*, SEQ ID NO: 6: MGSRIVINREHLMIDRPYVLLAVLFVMFLSLIGLLAIAGIRLHRAAIYTAEIHKSLST NLDVTNSIEHQVKDVLTPLFKIIGDEVGLRTPQRFTDLVKFISDKIKFLNPDREYDF RDLTWCINPPERIKLDYDQYCADVAAEELMNALVNSTLLETRTTNQFLAVSKGN CSGPTTIRGQFSNMSLSLLDLYLGRGYNVSSIVTMTSQGMYGGTYLVEKPNLSSK RSELSQLSMYRVFEVGVIRNPGLGAPVFHMTNYLEQPVSNDLSNCMVALGELKL AALCHGEDSITIPYQGSGKGVSFQLVKLGVWKSPTDMQSWVPLSTDDPVIDRLYL SSHRGVIADNQAKWAVPTTRTDDKLRMETCFQQACKGKIQALCENPEWAPLKD NRIPSYGVLSVDLSLTVELKIKIASGFGPLITHGSGMDLYKSNHNNVYWLTIPPMK NLALGVINTLEWIPRFKVSPYLFTVPIKEAGGDCHAPTYLPAEVDGDVKLSSNLVI LPGQDLQYVLATYDTSRVEHAVVYYVYSPSRSFSYFYPFRLPIKGVPIELQVECFT WDQKLWCRHFCVLADSESGGHITHSGMVGMGVSCTVTREDGTN) or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto, wherein the MV-H protein lacks cell binding activity and retains fusogenic activity. In particular embodiments, the MV-H polypeptide comprises one or more amino acid substitutions at positions Y463, R515, S530, and F531 of a MV-H polypeptide (*e.g.,* SEQ ID NO 6). In particular embodiments, the MV-H polypeptide comprises one or more of the amino acid substitutions

Y463A, R515A, S530L, and F531S in an MV-H polypeptide (*e.g.*, SEQ ID NO: 7: MGSRIVINREHLMIDRPYVLLAVLFVMFLSLIGLLAIAGIRLHRAAIYTAEIHKSLST NLDVTNSIEHQVKDVLTPLFKIIGDEVGLRTPQRFTDLVKFISDKIKFLNPDREYDF RDLTWCINPPERIKLDYDQYCADVAAEELMNALVNSTLLETRTTNQFLAVSKGN CSGPTTIRGQFSNMSLSLLDLYLGRGYNVSSIVTMTSQGMYGGTYLVEKPNLSSK RSELSQLSMYRVFEVGVIRNPGLGAPVFHMTNYLEQPVSNDLSNCMVALGELKL AALCHGEDSITIPYQGSGKGVSFQLVKLGVWKSPTDMQSWVPLSTDDPVIDRLYL SSHRGVIADNQAKWAVPTTRTDDKLRMETCFQQACKGKIQALCENPEWAPLKD NRIPSYGVLSVDLSLTVELKIKIASGFGPLITHGSGMDLYKSNHNNVYWLTIPPMK NLALGVINTLEWIPRFKVSPALFNVPIKEAGGDCHAPTYLPAEVDGDVKLSSNLVI LPGQDLQYVLATYDTSAVEHAVVYYVYSPSRLSSYFYPFRLPIKGVPIELQVECFT WDQKLWCRHFCVLADSESGGHITHSGMVGMGVSCTVTREDGTN) or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto, wherein the MV-H protein lacks cell binding activity and retains fusogenic activity.

a. Henipavirus Envelope Glycoproteins

Henipaviruses use two types of glycoproteins to enter a cell: glycoprotein F (a fusion polypeptide) and glycoprotein G (an attachment protein). Although glycoprotein F mediates fusion and glycoprotein G mediates binding, both F and G glycoproteins are required for viral particle fusion with a target cell, glycoprotein G supports glycoprotein F in its membrane fusion function.

Efficient pseudotyping with henipavirus envelope proteins may be accomplished using glycoprotein F comprising a truncated cytoplasmic portion comprising at least 6 consecutive amino acid residues as counted from the N-terminal end of the cytoplasmic portion and glycoprotein G comprising a truncated cytoplasmic portion comprising at least 11 to at least 15 consecutive amino acid residues as counted from the C-terminal end of the cytoplasmic portion plus an additional methionine at the N-terminus. Moreover, glycoprotein G can be modified to ablate its antigen binding activity.

In particular embodiments, a recombinant particle comprises henipaviruses F and G viral envelope glycoproteins, wherein glycoprotein G is modified to ablate cell binding activity and both G and F glycoproteins retain the ability to cooperatively mediate cell fusion.

Illustrative examples of henipaviruses suitable for use in particular embodiments from which F and H glycoproteins can independently be isolated from include but are not limited to Cedar virus (CedV; Cedar henipavirus), Kumasi virus (KV; Ghanaian bat henipavirus), Hendra virus (HeV), (MojV; Mojiang henipavirus), and Nipah virus (NiV).

In particular embodiments, one or more mutated henipaviruses envelope glycoproteins are derived from nipah virus F (NiV-F) and nipah virus G (NiV-G). In particular embodiments, a recombinant particle comprises one or more nipah virus viral envelope glycoproteins modified to lack cell binding activity and retain fusogenic activity. In some embodiments, a recombinant particle comprises a modified NiV-F glycoprotein and a NiV-G glycoprotein modified to lack cell binding activity and retain fusogenic activity.

In particular embodiments, one or more mutated henipavirus envelope glycoproteins are derived from a nipah virus F (NiV-F) polypeptide (*e.g.*, SEQ ID NO: 8: LHYEKLSKIGLVKGVTRKYKIKSNPLTKDIVIKMIPNVSNMSQCTGSVMENYKTR LNGILTPIKGALEIYKNNTHDLVGDVRLAGVIMAGVAIGIATAAQITAGVALYEA MKNADNINKLKSSIESTNEAVVKLQETAEKTVYVLTALQDYINTNLVPTIDKISCK QTELSLDLALSKYLSDLLFVFGPNLQDPVSNSMTIQAISQAFGGNYETLLRTLGYA TEDFDDLLESDSITGQIIYVDLSSYYIIVRVYFPILTEIQQAYIQELLPVSFNNDNSEW ISIVPNFILVRNTLISNIEIGFCLITKRSVICNQDYATPMTNNMRECLTGSTEKCPREL VVSSHVPRFALSNGVLFANCISVTCQCQTTGRAISQSGEQTLLMIDNTTCPTAVLG NVIISLGKYLGSVNYNSEGIAIGPPVFTDKVDISSQISSMNQSLQQSKDYIKEAQRL LDTVNPSLISMLSMIILYVLSIASLCIGLITFISFIIVEKKRNT) or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto and a nipah virus G (NiV-G) polypeptide (*e.g.*, SEQ ID NO: 9: MKKINEGLLDSKILSAFNTVIALLGSIVIIVMNIMIIQNYTRSTDNQAVIKDALQGIQ QQIKGLADKIGTEIGPKVSLIDTSSTITIPANIGLLGSKISQSTASINENVNEKCKFTL PPLKIHECNISCPNPLPFREYRPQTEGVSNLVGLPNNICLQKTSNQILKPKLISYTLP VVGQSGTCITDPLLAMDEGYFAYSHLERIGSCSRGVSKQRIIGVGEVLDRGDEVPS LFMTNVWTPPNPNTVYHCSAVYNNEFYYVLCAVSTVGDPILNSTYWSGSLMMT RLAVKPKSNGGGYNQHQLALRSIEKGRYDKVMPYGPSGIKQGDTLYFPAVGFLV RTEFKYNDSNCPITKCQYSKPENCRLSMGIRPNSHYILRSGLLKYNLSDGENPKVV FIEISDQRLSIGSPSKIYDSLGQPVFYQASFSWDTMIKFGDVLTVNPLVVNWRNNT VISRPGQSQCPRFNTCPEICWEGVYNDAFLIDRINWISAGVFLDSNQTAENPVFTV FKDNEILYRAQLASEDTNAQKTITNCFLLKNKIWCISLVEIYDTGDNVIRPKLFAV

KIPEQCT) or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto, wherein the NiV-G polypeptide lacks cell binding activity and retains fusogenic activity. In particular embodiments, the NiV-G polypeptide comprises one or more amino acid substitutions at positions E468, W471, Q497, and E500 of an NiV-G polypeptide (*e.g.*, SEQ ID NO: 9). In particular embodiments, the NiV-G polypeptide comprises one or more of the amino acid substitutions E468A, W471A, Q497A, and E500A in an NiV-G polypeptide (*e.g.*, SEQ ID NO: 10: MKKINEGLLDSKILSAFNTVIALLGSIVIIVMNIMIIQNYTRSTDNQAVIKDALQGIQ QQIKGLADKIGTEIGPKVSLIDTSSTITIPANIGLLGSKISQSTASINENVNEKCKFTL PPLKIHECNISCPNPLPFREYRPQTEGVSNLVGLPNNICLQKTSNQILKPKLISYTLP VVGQSGTCITDPLLAMDEGYFAYSHLERIGSCSRGVSKQRIIGVGEVLDRGDEVPS LFMTNVWTPPNPNTVYHCSAVYNNEFYYVLCAVSTVGDPILNSTYWSGSLMMT RLAVKPKSNGGGYNQHQLALRSIEKGRYDKVMPYGPSGIKQGDTLYFPAVGFLV RTEFKYNDSNCPITKCQYSKPENCRLSMGIRPNSHYILRSGLLKYNLSDGENPKVV FIEISDQRLSIGSPSKIYDSLGQPVFYQASFSWDTMIKFGDVLTVNPLVVNWRNNT VISRPGQSQCPRFNTCPAICAEGVYNDAFLIDRINWISAGVFLDSNATAANPVFTV FKDNEILYRAQLASEDTNAQKTITNCFLLKNKIWCISLVEIYDTGDNVIRPKLFAV KIPEQCT) or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto, wherein the NiV-G polypeptide lacks cell binding activity and retains fusogenic activity.

3. TROPISM POLYPEPTIDES

Recombinant particles contemplated herein comprise one or more tropism polypeptides that govern particle targeting. Without wishing to be bound by any particular theory, it is contemplated that decoupling particle fusion and tropism solves specificity and delivery issues associated with *in vivo* gene therapy and gene editing. In particular embodiments, recombinant particles comprise one or more viral envelope glycoproteins modified to retain cell fusion activity and substantially ablate or ablate native tropism activity and further comprise one or more non-viral membrane-bound tropism polypeptides to support particle targeting. Decoupling particle fusion and tropism activities enables particle on-target delivery to the intended cells and decreases off-target delivery to other cells thereby increasing the safety and efficacy of the therapy.

In particular embodiments, a recombinant particle contemplated herein comprises an outer surface comprising, expressing, or displaying one or more non-viral membrane bound tropism polypeptides. A "tropism polypeptide" is a polypeptide that binds one or more antigens on a desired cell type. A "non-viral membrane bound tropism polypeptide" is a polypeptide that binds one or more antigens on a desired cell type; that is not native to, or derived from, either in whole or in part, a virus.

In particular embodiments, a recombinant particle comprises an outer surface comprising one or more mutated viral envelope glycoproteins that mediate fusion of the particle with a cell but that do not bind its cognate receptor expressed on a cell, and one or more non-viral membrane-bound tropism polypeptides that direct the particle to bind a specific antigen expressed on a cell, *e.g.,* an immune effector cell. In particular embodiments, a recombinant particle contemplated herein comprises an outer surface comprising, expressing or displaying a primary non-viral membrane bound tropism polypeptide and optionally, a secondary non-viral membrane bound tropism polypeptide.

In particular embodiments, a recombinant particle, *e.g.,* retroviral or lentiviral particle, comprises a lipid bilayer, cell membrane, or viral envelope comprising one or more mutated viral envelope glycoproteins that mediate fusion of the viral particle with a cell but that do not bind its cognate receptor expressed on a cell, and one or more non-viral membrane-bound tropism polypeptides, *e.g.,* a primary and optionally a secondary non-viral membrane bound tropism polypeptide, that direct the particle to bind one or more specific antigens expressed on a cell, *e.g.,* an immune effector cell.

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an extracellular antigen targeting domain, a spacer polypeptide, a transmembrane domain or GPI anchor, and optionally an intracellular domain. In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an intracellular domain of no more than one, two, three, four, five, six, seven, eight, nine, or ten amino acids.

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 455-576.

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, and 486.

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, and 554.

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 555, 556, 557, 558, 559, 560, 561, and 562.

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 563, 564, 564, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, and 576.

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an amino acid sequence set forth in SEQ ID NO: 471 and SEQ ID NO: 472.

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an amino acid sequence set forth in SEQ ID NO: 553 and SEQ ID NO: 554.

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an amino acid sequence set forth in SEQ ID NO: 563 and SEQ ID NO: 564.

a. Extracellular Antigen Targeting Domain

Recombinant particles contemplated in particular embodiments comprise a detargeted fusogen and one or more non-viral membrane bound tropism polypeptides that comprise an extracellular antigen targeting domain that binds one or more antigens specifically or selectively expressed on a particular cell type, *e.g.,* an immune effector cell. As used herein, an "extracellular antigen targeting domain" (also referred to as an "extracellular targeting domain," "antigen targeting domain," or "targeting domain") refers to any naturally occurring, synthetic, semi-synthetic, or recombinantly produced binding partner that binds a biological molecule or target antigen expressed or displayed on the surface of a cell. In particular embodiments, an extracellular antigen targeting domain binds an antigen expressed on a desired or specified cell type. In some embodiments, expression of the antigen is specific to the cell. In preferred embodiments, an extracellular antigen targeting domain binds an antigen expressed on an immune effector cell.

In various embodiments, a non-viral membrane bound tropism polypeptide comprises one or more extracellular targeting domains selected from the group consisting of:

an antibody, a ligand (*e.g.*, cytokines, chemokines, or cell surface associated ligands), a receptor ectodomain (*e.g.*, c-Met, EGFR), or an aptamer.

In particular embodiments, an extracellular antigen targeting domain comprises an antibody or antigen binding fragment thereof that binds an antigen expressed on the surface of a cell, *e.g.,* an immune effector cell. In certain embodiments, an extracellular antigen targeting domain comprises an antibody or antigen binding fragment thereof selected from the group consisting of: a Camel Ig, a Llama Ig, an Alpaca Ig, Ig NAR, a Fab' fragment, a F(ab')2 fragment, a bispecific Fab dimer (Fab2), a trispecific Fab trimer (Fab3), an Fv, a single chain Fv protein (scFv), a bis-scFv, $(scFv)_2$, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein (dsFv), a Fibronectin type III (FN3) domain antibody, a single-domain antibody (sdAb or nanobody, *e.g.*, a camelid VHH or shark VNAR), and a centyrin; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain that binds an antigen expressed on an immune effector cell selected from the group consisting of: alpha, beta, gamma, or delta chain of the T-cell receptor, CD1a, CD1b, CD1c, CD2, CD3δ, CD3ε CD3γ, CD4, CD5, CD6, CD7, CD8α, CD8β, CD11a, CD11b, CD11c, CD25, CD26, CD27, CD28, CD30, CD35, CD37, CD38, CD39, CD43, CD45RO, CD45RA, CD45RB, CD45RAB, CD45RBC, CD45ABC, CD49a, CD49f, CD49d, CD56, CD57, CD62L, CD69, CD70, CD73, CD74, CDw75, CDw76, CD80 (B7-1), CD83, CDw84, CD86 (B7-2), CD89, CD94, CD95, CD96, CD98, CD99, CD100, CDw101, CD102, CD103, CD104, CDw108, CDw121a (IL-1RI), CD122 (IL-2Rβ), CDw124(IL-4R), CDw127 (IL-7R), CDw128 (IL-8R), CD134, CD137, CD152 (CTLA-4), CD154 (CD40L), CD161, CD183, CD184, CD185, CD193, CD194, CD195, CD196, CD197, CD223 (LAG-3), CD244 (SlamF4), CD270 (TNFRSF14; HVEM), CD272 (BTLA-4), CD273 (PD-L2), CD274 (PD-L1), CD278 (ICOS), CD279, CD300, CD357 (TNFRSF18; GITR), CMRF35, CCR10, IL-2Rγ, IL-10R, IL-12R, IL-13Rα1, P2RX7, Sca-1, SlamF6, TIGIT, TIM-3,TNRF2, and TNFRS25; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain that binds an antigen expressed on an immune effector cell selected from the group consisting of: the alpha, beta, gamma, or delta

chain of the T cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD7, CD8α, and CD8β; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an scFv, a murine scFv, a humanized scFv, a human scFv, or one or more VHH or VNAR single domain antibodies that binds an antigen expressed on an immune effector cell selected from the group consisting of: the alpha, beta, gamma, or delta chain of the T cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD7, CD8α, and CD8β; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof. Illustrative examples of anti-CD3ε antibodies or antigen binding fragments thereof suitable for use in particular embodiments contemplated herein include but are not limited to scFvs or other antigen binding fragments isolated from OKT3, UCHT1, YTH12.5, and TR66, and variants thereof, having at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or at least 99% identity thereto.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising a CDRH1, a CDRH2, and a CDRH3 and a CDRL1, a CDRL2, and a CDRL3 of an antibody or antigen binding fragment thereof set forth in Table 5; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising: CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 12-14, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 16-18; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 22-24, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 26-28; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 32-34, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 36-38; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 42-44, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 46-48; CDRH1, CDRH2, and CDRH3 amino acid

sequences set forth in SEQ ID NOs: 52-54, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 56-58; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 62-64, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 66-68; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 72-74, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 76-78; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 82-84, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 86-88; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 92-94, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 96-98; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 102-104, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 106-108; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 112-114, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 116-118; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 122-124, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 126-128; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 132-134, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 136-138; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 142-144, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 146-148; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 152-154, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 156-158; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 162-164, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 166-168; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 172-174, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 176-178; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 182-184, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 186-188; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 192-194, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 196-198; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 202-204, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 206-208; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 212-214, and CDRL1, CDRL2, and CDRL3 amino acid

sequences set forth in SEQ ID NOs: 216-218; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 222-224, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 226-228; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 232-234, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 236-238; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 242-244, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 246-248; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 252-254, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 256-258; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 262-264, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 266-268; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 272-274, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 276-278; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 282-284, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 286-288; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 292-294, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 296-298; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 302-304, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 306-308; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 312-314, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 316-318; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 322-324, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 326-328; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 332-334, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 336-338; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 342-344, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 346-348; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 352-354, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 356-358; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 362-364, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 366-368; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 372-374, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 376-378; CDRH1, CDRH2, and CDRH3 amino acid

sequences set forth in SEQ ID NOs: 382-384, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 386-388; CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 392-394, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 396-398; or CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 402-404, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 406-408; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 92-94, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 96-98; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 102-104, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 106-108; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 112-114, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 116-118; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 122-124, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 126-128; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or

antigen binding fragment thereof comprising CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 132-134, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 136-138; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 142-144, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 146-148; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 152-154, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 156-158; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising CDRH1, CDRH2, and CDRH3 amino acid sequences set forth in SEQ ID NOs: 162-164, and CDRL1, CDRL2, and CDRL3 amino acid sequences set forth in SEQ ID NOs: 166-168; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising a heavy chain variable (VH) domain and a light chain variable (VL) domain of an antibody or antigen binding fragment thereof set forth in Table 5; a polypeptide linker disposed between the VH domain and the VL domain; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain. In particular embodiments the polypeptide linker is selected from the group consisting of: $(GGGGS)_n$ wherein n = 1, 2, 3, 4 or 5; $S(GGGGS)_n$ wherein n = 1, 2, 3, 4 or 5; GEGTSTGSGGSGGSGGAD, GSTSGSGKPGSGEGSTKG and variants thereof comprising an amino acid sequence at least 90% identical thereto.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising: a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 11 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 15; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 21 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 25; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 31 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 35; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 41 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 45; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 51 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 55; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 61 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 65; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 71 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 75; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 81 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 85; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 91 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 95; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 101 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 105; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 111 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 115; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 121 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 125; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 131 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 135; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 141 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 145; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 151 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 155; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 161 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 165; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 171 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 175; a VH domain comprising

an amino acid sequence set forth in SEQ ID NO: 181 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 185; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 191 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 195; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 201 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 205; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 211 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 215; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 221 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 225; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 231 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 235; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 241 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 245; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 251 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 255; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 261 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 265; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 271 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 275; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 281 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 285; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 291 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 295; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 301 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO:305; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 311 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 315; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 321 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 325; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 331 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 335; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 341 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 345; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 351 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 355; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 361

and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 365; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 371 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 375; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 381 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 385; a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 391 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 395; or a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 401 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO:405; a polypeptide linker disposed between the VH domain and the VH domain; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain. In particular embodiments the polypeptide linker is selected from the group consisting of: $(GGGGS)_n$ wherein n = 1, 2, 3, 4 or 5; $S(GGGGS)_n$ wherein n = 1, 2, 3, 4 or 5; GEGTSTGSGGSGGSGGAD, GSTSGSGKPGSGEGSTKG and variants thereof comprising an amino acid sequence at least 90% identical thereto.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising: a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 91 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 95; a polypeptide linker disposed between the VH domain and the VL domain; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising: a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 101 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 105; a polypeptide linker disposed between the VH domain and the VL domain; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising: a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 111 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 115; a polypeptide linker disposed between the VH domain and the

VL domain; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising: a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 121 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 125; a polypeptide linker disposed between the VH domain and the VL domain; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising: a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 131 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 135; a polypeptide linker disposed between the VH domain and the VL domain; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising: a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 141 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 145; a polypeptide linker disposed between the VH domain and the VL domain; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising: a VH domain comprising an amino acid sequence set forth in SEQ ID NO: 151 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 155; a polypeptide linker disposed between the VH domain and the VL domain; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising: or a VH domain comprising an amino acid

sequence set forth in SEQ ID NO: 161 and a VL domain comprising an amino acid sequence set forth in SEQ ID NO: 165; a polypeptide linker disposed between the VH domain and the VL domain; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments the polypeptide linker is selected from the group consisting of: $(GGGGS)_n$ wherein n = 1, 2, 3, 4 or 5; $S(GGGGS)_n$ wherein n = 1, 2, 3, 4 or 5; GEGTSTGSGGSGGSGGAD, GSTSGSGKPGSGEGSTKG and variants thereof comprising an amino acid sequence at least 90% identical thereto.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof set forth in Table 5; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 79. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 80. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 89. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 90. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 99. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an

extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 100. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 109. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 110. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 119. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 120. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 129. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 130. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 139. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 140. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 149. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 150. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 159. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 160. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 169. In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising the amino acid sequence set forth in SEQ ID NO: 170.

Table 5

Ab ID	SEQ ID NO	ID	AMINO ACID SEQUENCE
CD3.1	11	VH	QVQLLESGAELARPGASVKMSCKASGYTFTRYTMHWVKQRPGQG LEWIGYINPSRGYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTS EDSAVYYCAGYYDDHYCLDYWGQGTLVTVSS
	12	CDRH1	RYTMH
	13	CDRH2	YINPSRGYTNYNQKFKD
	14	CDRH3	YYDDHYCLDY
	15	VL	DIVMTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPK RWIYDTSKLASGVPAHFRGSGSGTSYSLTISGMEAEDAATYYCQ QWSSNPFTFGSGTKLEIK
	16	CDRL1	SASSSVSYMN
	17	CDRL2	DTSKLAS
	18	CDRL3	QQWSSNPFT
	19	scFv	QVQLLESGAELARPGASVKMSCKASGYTFTRYTMHWVKQRPGQG LEWIGYINPSRGYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTS EDSAVYYCAGYYDDHYCLDYWGQGTLVTVSSGGGGSGGGGSGGG GSDIVMTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTS PKRWIYDTSKLASGVPAHFRGSGSGTSYSLTISGMEAEDAATYY CQQWSSNPFTFGSGTKLEIKS
	20	scFv	DIVMTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPK RWIYDTSKLASGVPAHFRGSGSGTSYSLTISGMEAEDAATYYCQ QWSSNPFTFGSGTKLEIKGGGGSGGGGSGGGGSQVQLLESGAEL ARPGASVKMSCKASGYTFTRYTMHWVKQRPGQGLEWIGYINPSR GYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTSEDSAVYYCAGY YDDHYCLDYWGQGTLVTVS
CD3.2	21	VH	QVQLQQSGAELARPGASVKMSCKASGYTFTRYTMHWVKQRPGQG LEWIGYINPSRGYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTS EDSAVYYCARYYDDHYCLDYWGQGTTLTVSSS
	22	CDRH1	RYTMH
	23	CDRH2	YINPSRGYTNYNQKFKD
	24	CDRH3	YYDDHYCLDY
	25	VL	QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPK RWIYDTSKLASGVPAHFRGSGSGTSYSLTISGMEAEDAATYYCQ QWSSNPFTFGSGTKLEIN
	26	CDRL1	SASSSVSYMN
	27	CDRL2	DTSKLAS
	28	CDRL3	QQWSSNPFT
	29	scFv	QVQLQQSGAELARPGASVKMSCKASGYTFTRYTMHWVKQRPGQG LEWIGYINPSRGYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTS EDSAVYYCARYYDDHYCLDYWGQGTTLTVSSSGGGGSGGGGSGG GGSQIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGT SPKRWIYDTSKLASGVPAHFRGSGSGTSYSLTISGMEAEDAATY YCQQWSSNPFTFGSGTKLEIN
	30	scFv	QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPK RWIYDTSKLASGVPAHFRGSGSGTSYSLTISGMEAEDAATYYCQ QWSSNPFTFGSGTKLEINGGGGSGGGGSGGGGSQVQLQQSGAEL ARPGASVKMSCKASGYTFTRYTMHWVKQRPGQGLEWIGYINPSR GYTNYNQKFKDKATLTTDKSSSTAYMQLSSLTSEDSAVYYCARY YDDHYCLDYWGQGTTLTVSSS
CD3.3	31	VH	QVQLQQSGAELARPGASVKMSCKASGYTFTSYTMHWVKQRPGQG LEWIGYINPSSGYTKYNQKFKDKATLTADKSSSTAYMQLSSLTS EDSAVYYCARWQDYDVYFDYWGQGTTLTVSS
	32	CDRH1	SYTMH
	33	CDRH2	YINPSSGYTKYNQKFKD
	34	CDRH3	WQDYDVYFDY
	35	VL	QIVLSQSPAILSASPGEKVTMTCRASSSVSYMHWYQQKPGSSPK PWIYATSNLASGVPARFSGSGSGTSYSLTISRVEAEDAATYYCQ

			QWSSNPPTFGGGTKLETK
	36	CDRL1	RASSSVSYMH
	37	CDRL2	ATSNLAS
	38	CDRL3	QQWSSNPPT
	39	scFv	QVQLQQSGAELARPGASVKMSCKASGYTFTSYTMHWVKQRPGQG LEWIGYINPSSGYTKYNQKFKDKATLTADKSSSTAYMQLSSLTS EDSAVYYCARWQDYDVYFDYWGQGTTLTVSSGGGGSGGGGSGGG GSQIVLSQSPAILSASPGEKVTMTCRASSSVSYMHWYQQKPGSS PKPWIYATSNLASGVPARFSGSGSGTSYSLTISRVEAEDAATYY CQQWSSNPPTFGGGTKLETK
	40	scFv	QIVLSQSPAILSASPGEKVTMTCRASSSVSYMHWYQQKPGSSPK PWIYATSNLASGVPARFSGSGSGTSYSLTISRVEAEDAATYYCQ QWSSNPPTFGGGTKLETGGGGSGGGGSGGGGSQVQLQQSGAELA RPGASVKMSCKASGYTFTSYTMHWVKQRPGQGLEWIGYINPSSG YTKYNQKFKDKATLTADKSSSTAYMQLSSLTSEDSAVYYCARWQ DYDVYFDYWGQGTTLTVSS
CD3.4	41	VH	EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKN LEWMGLINPYKGVSTYNQKFKDKATLTVDKSSSTAYMELLSLTS EDSAVYYCARSGYYGDSDWYFDVWGAGTTVTVSS
	42	CDRH1	GYTMN
	43	CDRH2	LINPYKGVSTYNQKFKD
	44	CDRH3	SGYYGDSDWYFDV
	45	VL	DIQMTQTTSSLSASLGDRVTISCRASQDIRNYLNWYQQKPDGTV KLLIYYTSRLHSGVPSKFSGSGSGTDYSLTISNLEQEDIATYFC QQGNTLPWTFAGGTKLEIK
	46	CDRL1	RASQDIRNYLN
	47	CDRL2	YTSRLHS
	48	CDRL3	QQGNTLPWT
	49	scFv	EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKN LEWMGLINPYKGVSTYNQKFKDKATLTVDKSSSTAYMELLSLTS EDSAVYYCARSGYYGDSDWYFDVWGAGTTVTVSSGGGGSGGGGS GGGGSDIQMTQTTSSLSASLGDRVTISCRASQDIRNYLNWYQQK PDGTVKLLIYYTSRLHSGVPSKFSGSGSGTDYSLTISNLEQEDI ATYFCQQGNTLPWTFAGGTKLEIK
	50	scFv	DIQMTQTTSSLSASLGDRVTISCRASQDIRNYLNWYQQKPDGTV KLLIYYTSRLHSGVPSKFSGSGSGTDYSLTISNLEQEDIATYFC QQGNTLPWTFAGGTKLEIKGGGGSGGGGSGGGGSEVQLQQSGPE LVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWMGLINPY KGVSTYNQKFKDKATLTVDKSSSTAYMELLSLTSEDSAVYYCAR SGYYGDSDWYFDVWGAGTTVTVSS
CD3.5	51	VH	QVQLQQSAAELARPGASVKMSCKASGYTFTRYTMQWVKQRPGQG LEWIGYINPSSGYIGYSQKFKDKTTLTADKSSSTAYMQLSSLTS EDSAVYYCARSKVYYDYDVYSMDYWGQGTSVTVSS
	52	CDRH1	RYTMQ
	53	CDRH2	YINPSSGYIGYSQKFKD
	54	CDRH3	SKVYYDYDVYSMDY
	55	VL	QIILTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPK RWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQ QWSSNPLTFGAGTKLELK
	56	CDRL1	SASSSVSYMH
	57	CDRL2	DTSKLA
	58	CDRL3	QQWSSNPLT
	59	scFv	QVQLQQSAAELARPGASVKMSCKASGYTFTRYTMQWVKQRPGQG LEWIGYINPSSGYIGYSQKFKDKTTLTADKSSSTAYMQLSSLTS EDSAVYYCARSKVYYDYDVYSMDYWGQGTSVTVSSGGGGSGGGG SGGGGSQIILTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQK SGTSPKRWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDA ATYYCQQWSSNPLTFGAGTKLELK

	60	scFv	QIILTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPK RWIYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQ QWSSNPLTFGAGTKLELKGGGGSGGGGSGGGGSQVQLQQSAAEL ARPGASVKMSCKASGYTFTRYTMQWVKQRPGQGLEWIGYINPSS GYIGYSQKFKDKTTLTADKSSSTAYMQLSSLTSEDSAVYYCARS KVYYDYDVYSMDYWGQGTSVTVSS
CD3.6	61	VH	QVQLQQSGAELARPGASVKMSCKASGYTFISYTMHWVKQRPGQG LEWIGYINPRSGYTHYNQKLKDKATLTADKSSSSAYMQLSSLTS EDSAVYYCARSAYYDYDGFAYWGQGTLVTVSA
	62	CDRH1	SYTMH
	63	CDRH2	YINPRSGYTHYNQKLKD
	64	CDRH3	SAYYDYDGFAY
	65	VL	QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYKQKSGTSPK RWTYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQ QWSSNPPTFGSGTKLEIK
	66	CDRL1	SASSSVSYMN
	67	CDRL2	DTSKLAS
	68	CDRL3	QQWSSNPPT
	69	scFv	QVQLQQSGAELARPGASVKMSCKASGYTFISYTMHWVKQRPGQG LEWIGYINPRSGYTHYNQKLKDKATLTADKSSSSAYMQLSSLTS EDSAVYYCARSAYYDYDGFAYWGQGTLVTVSAGGGGSGGGGSGG GGSQIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYKQKSGT SPKRWTYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATY YCQQWSSNPPTFGSGTKLEIK
	70	scFv	QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYKQKSGTSPK RWTYDTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQ QWSSNPPTFGSGTKLEIKGGGGSGGGGSGGGGSQVQLQQSGAEL ARPGASVKMSCKASGYTFISYTMHWVKQRPGQGLEWIGYINPRS GYTHYNQKLKDKATLTADKSSSSAYMQLSSLTSEDSAVYYCARS AYYDYDGFAYWGQGTLVTVSA
CD3.7	71	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFISYTMHWVRQAPGQG LEWMGYINPRSGYTHYNQKLKDKATLTADKSASTAYMELSSLRS EDTAVYYCARSAYYDYDGFAYWGQGTLVTVSS
	72	CDRH1	SYTMH
	73	CDRH2	YINPRSGYTHYNQKLKD
	74	CDRH3	SAYYDYDGFAY
	75	VL	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPK RLIYDTSKLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ QWSSNPPTFGGGTKVEIK
	76	CDRL1	SASSSVSYMN
	77	CDRL2	DTSKLAS
	78	CDRL3	QQWSSNPPT
	79	scFv	QVQLVQSGAEVKKPGASVKVSCKASGYTFISYTMHWVRQAPGQG LEWMGYINPRSGYTHYNQKLKDKATLTADKSASTAYMELSSLRS EDTAVYYCARSAYYDYDGFAYWGQGTLVTVSSGGGGSGGGGSGG GGSDIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGK APKRLIYDTSKLASGVPSRFSGSGSGTDFTLTISSLQPEDFATY YCQQWSSNPPTFGGGTKVEIK
	80	scFv	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPK RLIYDTSKLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQ QWSSNPPTFGGGTKVEIKGGGGSGGGGSGGGGSQVQLVQSGAEV KKPGASVKVSCKASGYTFISYTMHWVRQAPGQGLEWMGYINPRS GYTHYNQKLKDKATLTADKSASTAYMELSSLRSEDTAVYYCARS AYYDYDGFAYWGQGTLVTVSS
CD3.8	81	VH	EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKDRFTISRDDSQSILYLQMNNL KTEDTAMYYCVRHGNFGNSYVSWFAYWGQGTLVTVSS
	82	CDRH1	TYAMN

	83	CDRH2	RIRSKYNNYATYYADSVKD
	84	CDRH3	HGNFGNSYVSWFAY
	85	VL	QAVVTQESALTTSPGETVTLTCRSSTGAVTTSNYANWVQEKPDH LFTGLIGGTNKRAPGVPARFSGSLIGDKAALTITGAQTEDEAIY FCALWYSNLWVFGGGTKLTVL
	86	CDRL1	RSSTGAVTTSNYAN
	87	CDRL2	GTNKRAP
	88	CDRL3	ALWYSNLWV
	89	scFv	EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKDRFTISRDDSQSILYLQMNNL KTEDTAMYYCVRHGNFGNSYVSWFAYWGQGTLVTVSS GGGGSGGGGSGGGGSQAVVTQESALTTSPGETVTLTCRSSTGAV TTSNYANWVQEKPDHLFTGLIGGTNKRAPGVPARFSGSLIGDKA ALTITGAQTEDEAIYFCALWYSNLWVFGGGTKLTVL
	90	scFv	QAVVTQESALTTSPGETVTLTCRSSTGAVTTSNYANWVQEKPDH LFTGLIGGTNKRAPGVPARFSGSLIGDKAALTITGAQTEDEAIY FCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESG GGLVQPKGSLKLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIR SKYNNYATYYADSVKDRFTISRDDSQSILYLQMNNLKTEDTAMY YCVRHGNFGNSYVSWFAYWGQGTLVTVSS
CD3.9	91	VH	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYDDHYCLDYWGQGTTVTVSS
	92	CDRH1	RYTMH
	93	CDRH2	YINPSRGYTNYADSVKG
	94	CDRH3	YYDDHYCLDY
	95	VL	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIK
	96	CDRL1	RASQSVSYMN
	97	CDRL2	DTSKVAS
	98	CDRL3	QQWSSNPLT
	99	scFv	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGGSGGGGSGG GGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGK APKRWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATY YCQQWSSNPLTFGGGTKVEIK
	100	scFv	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDVQLVQSGAE VKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPS RGYTNYADSVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCAR YYDDHYCLDYWGQGTTVTVSS
CD3.10	101	VH	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYDDPYCLDYWGQGTTVTVSS
	102	CDRH1	RYTMH
	103	CDRH2	YINPSRGYTNYADSVKG
	104	CDRH3	YYDDPYCLDY
	105	VL	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIK
	106	CDRL1	RASQSVSYMN
	107	CDRL2	DTSKVAS
	108	CDRL3	QQWSSNPLT
	109	scFv	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS

			EDTATYYCARYYDDPYCLDYWGQGTTVTVSSSGGGGSGGGGSGG GGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGK APKRWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATY YCQQWSSNPLTFGGGTKVEIK
	110	scFv	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDVQLVQSGAE VKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPS RGYTNYADSVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCAR YYDDPYCLDYWGQGTTVTVSS
CD3.11	111	VH	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYNDQYCLDYWGQGTTVTVSSS
	112	CDRH1	RYTMH
	113	CDRH2	YINPSRGYTNYADSVKG
	114	CDRH3	YYNDQYCLDY
	115	VL	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIK
	116	CDRL1	RASQSVSYMN
	117	CDRL2	DTSKVAS
	118	CDRL3	QQWSSNPLT
	119	scFv	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYNDQYCLDYWGQGTTVTVSSSSGGGGSGGGGSG GGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPG KAPKRWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAAT YYCQQWSSNPLTFGGGTKVEIK
	120	scFv	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDVQLVQSGAE VKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPS RGYTNYADSVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCAR YYNDQYCLDYWGQGTTVTVSSS
CD3.12	121	VH	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYDAHNCLDYWGQGTTVTVSS
	122	CDRH1	RYTMH
	123	CDRH2	YINPSRGYTNYADSVKG
	124	CDRH3	YYDAHNCLDY
	125	VL	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIK
	126	CDRL1	RASQSVSYMN
	127	CDRL2	DTSKVAS
	128	CDRL3	QQWSSNPLT
	129	scFv	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYDAHNCLDYWGQGTTVTVSSSGGGGSGGGGSGG GGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGK APKRWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATY YCQQWSSNPLTFGGGTKVEIK
	130	scFv	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDVQLVQSGAE VKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPS RGYTNYADSVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCAR YYDAHNCLDYWGQGTTVTVSS

CD3.13	131	VH	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYSDDHYCLDYWGQGTTVTVSS
	132	CDRH1	RYTMH
	133	CDRH2	YINPSRGYTNYADSVKG
	134	CDRH3	YSDDHYCLDY
	135	VL	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIK
	136	CDRL1	RASQSVSYMN
	137	CDRL2	DTSKVAS
	138	CDRL3	QQWSSNPLT
	139	scFv	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYSDDHYCLDYWGQGTTVTVSSSGGGGSGGGGSGG GGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGK APKRWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATY YCQQWSSNPLTFGGGTKVEIK
	140	scFv	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDVQLVQSGAE VKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPS RGYTNYADSVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCAR YSDDHYCLDYWGQGTTVTVSS
CD3.14	141	VH	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYSDDRYCLDYWGQGTTVTVSS
	142	CDRH1	RYTMH
	143	CDRH2	YINPSRGYTNYADSVKG
	144	CDRH3	YSDDRYCLDY
	145	VL	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIK
	146	CDRL1	RASQSVSYMN
	147	CDRL2	DTSKVAS
	148	CDRL3	QQWSSNPLT
	149	scFv	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYSDDRYCLDYWGQGTTVTVSSSGGGGSGGGGSGG GGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGK APKRWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATY YCQQWSSNPLTFGGGTKVEIK
	150	scFv	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDVQLVQSGAE VKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPS RGYTNYADSVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCAR YSDDRYCLDYWGQGTTVTVSS
CD3.15	151	VH	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYDDNYCLDYWGQGTTVTVSSS
	152	CDRH1	RYTMH
	153	CDRH2	YINPSRGYTNYADSVKG
	154	CDRH3	YYDDNYCLDY
	155	VL	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIK
	156	CDRL1	RASQSVSYMN

	157	CDRL2	DTSKVAS
	158	CDRL3	QQWSSNPLT
	159	scFv	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYDDNYCLDYWGQGTTVTVSSSSGGGGSGGGGSG GGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPG KAPKRWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAAT YYCQQWSSNPLTFGGGTKVEIK
	160	scFv	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDVQLVQSGAE VKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPS RGYTNYADSVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCAR YYDDNYCLDYWGQGTTVTVSSS
CD3.16	161	VH	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYDDQYCLDYWGQGTTVTVSS
	162	CDRH1	RYTMH
	163	CDRH2	YINPSRGYTNYADSVKG
	164	CDRH3	YYDDQYCLDY
	165	VL	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIK
	166	CDRL1	RASQSVSYMN
	167	CDRL2	DTSKVAS
	168	CDRL3	QQWSSNPLT
	169	scFv	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQG LEWIGYINPSRGYTNYADSVKGRFTITTDKSTSTAYMELSSLRS EDTATYYCARYYDDQYCLDYWGQGTTVTVSSSGGGGSGGGGSGG GGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGK APKRWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATY YCQQWSSNPLTFGGGTKVEIK
	170	scFv	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPK RWIYDTSKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQ QWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDVQLVQSGAE VKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPS RGYTNYADSVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCAR YYDDQYCLDYWGQGTTVTVSS
CD3.17	171	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFPMAWVRQAPGKG LEWVSTISTSGGRTYYRDSVKGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCAKFRQYSGGFDYWGQGTLVTVSS
	172	CDRH1	SFPMA
	173	CDRH2	TISTSGGRTYYRDSVKG
	174	CDRH3	FRQYSGGFDY
	175	VL	DIQLTQPNSVSTSLGSTVKLSCTLSSGNIENNYVHWYQLYEGRS PTTMIYDDDKRPDGVPDRFSGSIDRSSNSAFLTIHNVAIEDEAI YFCHSYVSSFNVFGGGTKLTVL
	176	CDRL1	TLSSGNIENNYVH
	177	CDRL2	DDDKRPD
	178	CDRL3	HSYVSSFNV
	179	scFv	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFPMAWVRQAPGKG LEWVSTISTSGGRTYYRDSVKGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCAKFRQYSGGFDYWGQGTLVTVSSGGGGSGGGGSGGG GSDIQLTQPNSVSTSLGSTVKLSCTLSSGNIENNYVHWYQLYEG RSPTTMIYDDDKRPDGVPDRFSGSIDRSSNSAFLTIHNVAIEDE AIYFCHSYVSSFNVFGGGTKLTVL
	180	scFv	DIQLTQPNSVSTSLGSTVKLSCTLSSGNIENNYVHWYQLYEGRS PTTMIYDDDKRPDGVPDRFSGSIDRSSNSAFLTIHNVAIEDEAI

			YFCHSYVSSFNVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLLES GGGLVQPGGSLRLSCAASGFTFSSFPMAWVRQAPGKGLEWVSTI STSGGRTYYRDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYY CAKFRQYSGGFDYWGQGTLVTVSS
CD3.18	181	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSL RAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVSS
	182	CDRH1	TYAMN
	183	CDRH2	RIRSKYNNYATYYADSVKD
	184	CDRH3	HGNFGNSYVSWFAY
	185	VL	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQ APRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVL
	186	CDRL1	RSSTGAVTTSNYAN
	187	CDRL2	GTNKRAP
	188	CDRL3	ALWYSNLWV
	189	scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSL RAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVSSGGGGSGG GGSGGGGSQAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYAN WVQQKPGQAPRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNLWVFGGGTKLTVL
	190	scFv	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQ APRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVSRIR SKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVY YCARHGNFGNSYVSWFAYWGQGTMVTVSS
CD3.19	191	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSL RAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVSS
	192	CDRH1	TYAMN
	193	CDRH2	RIRSKYNNYATYYADSVKD
	194	CDRH3	HGNFGNSYVSWFAY
	195	VL	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWFQQKPGQ APRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVL
	196	CDRL1	RSSTGAVTTSNYAN
	197	CDRL2	GTNKRAP
	198	CDRL3	ALWYSNLWV
	199	scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSL RAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVSSGGGGSGG GGSGGGGSQAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYAN WFQQKPGQAPRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNLWVFGGGTKLTVL
	200	scFv	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWFQQKPGQ APRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVSRIR SKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVY YCARHGNFGNSYVSWFAYWGQGTMVTVSS
CD3.20	201	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSL RAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVSS
	202	CDRH1	TYAMN
	203	CDRH2	RIRSKYNNYATYYADSVKD
	204	CDRH3	HGNFGNSYVSWFAY

	205	VL	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQ APRGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVL
	206	CDRL1	RSSTGAVTTSNYAN
	207	CDRL2	GTNKRAP
	208	CDRL3	ALWYSNLWV
	209	scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSL RAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVSSGGGGSGG GGSGGGGSQAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYAN WVQQKPGQAPRGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNLWVFGGGTKLTVL
	210	scFv	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQ APRGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVARIR SKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVY YCARHGNFGNSYVSWFAYWGQGTMVTVSS
CD3.21	211	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTMVTVSS
	212	CDRH1	TYAMN
	213	CDRH2	RIRSKYNNYATYYADSVKD
	214	CDRH3	HGNFGNSYVSW
	215	VL	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWFQQKPGQ APRGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVL
	216	CDRL1	RSSTGAVTTSNYAN
	217	CDRL2	GTNKRAP
	218	CDRL3	ALWYSNLWV
	219	scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTMVTVSSGGGGSGG GGSGGGGSQAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYAN WFQQKPGQAPRGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNLWVFGGGTKLTVL
	220	scFv	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWFQQKPGQ APRGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVARIR SKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVY YCVRHGNFGNSYVSWFAYWGQGTMVTVSS
CD3.22	221	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTMVTVSS
	222	CDRH1	TYAMN
	223	CDRH2	RIRSKYNNYATYYADSVKD
	224	CDRH3	HGNFGNSYVSWFAY
	225	VL	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWYQQKPGQ APRGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVL
	226	CDRL1	RSSTGAVTTSNYAN
	227	CDRL2	GTNKRAP
	228	CDRL3	ALWYSNLWV
	229	scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTMVTVSSGGGGSGG GGSGGGGSQAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYAN

			WYQQKPGQAPRGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNLWVFGGGTKLTVL
	230	scFv	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWYQQKPGQ APRGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIR SKYNNYATYYADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVY YCVRHGNFGNSYVSWFAYWGQGTMVTVSS
CD3.23	231	VH	QVQLVESGGGVVQPGRSLRLSCAASGFKFSGYGMHWVRQAPGKG LEWVAVIWYDGSKKYYVDSVKGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCARQMGYWHFDLWGRGTLVTVSS
	232	CDRH1	GYGMH
	233	CDRH2	VIWYDGSKKYYVDSVKG
	234	CDRH3	QMGYWHFDL
	235	VL	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC QQRSNWPPLTFGGGTKVEIKR
	236	CDRL1	RASQSVSSYLA
	237	CDRL2	DASNRAT
	238	CDRL3	QQRSNWPPLT
	239	scFv	QVQLVESGGGVVQPGRSLRLSCAASGFKFSGYGMHWVRQAPGKG LEWVAVIWYDGSKKYYVDSVKGRFTISRDNSKNTLYLQMNSLRA EDTAVYYCARQMGYWHFDLWGRGTLVTVSSGGGGSGGGGSGGGG SEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQA PRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYY CQQRSNWPPLTFGGGTKVEIKR
	240	scFv	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAP RLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYC QQRSNWPPLTFGGGTKVEIKRGGGGSGGGGSGGGGSQVQLVESG GGVVQPGRSLRLSCAASGFKFSGYGMHWVRQAPGKGLEWVAVIW YDGSKKYYVDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARQMGYWHFDLWGRGTLVTVSS
CD3.24	241	VH	QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKG LEWIGYINPSRGYTNYNQKVKDRFTISRDNSKNTAFLQMDSLRP EDTGVYFCARYYDDHYCLDYWGQGTPVTVSS
	242	CDRH1	RYTMH
	243	CDRH2	YINPSRGYTNYNQKVKD
	244	CDRH3	YYDDHYCLDY
	245	VL	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPK RWIYDTSKLASGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQ QWSSNPFTFGQGTKLQIT
	246	CDRL1	SASSSVSYMN
	247	CDRL2	DTSKLAS
	248	CDRL3	QQWSSNPFT
	249	scFv	QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKG LEWIGYINPSRGYTNYNQKVKDRFTISRDNSKNTAFLQMDSLRP EDTGVYFCARYYDDHYCLDYWGQGTPVTVSSGGGGSGGGGSGGG GSDIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKA PKRWIYDTSKLASGVPSRFSGSGSGTDYTFTISSLQPEDIATYY CQQWSSNPFTFGQGTKLQIT
	250	scFv	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPK RWIYDTSKLASGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQ QWSSNPFTFGQGTKLQITGGGGSGGGGSGGGGSQVQLVQSGGGV VQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGYINPSR GYTNYNQKVKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARY YDDHYCLDYWGQGTPVTVSS
CD3.25	251	VH	EVQLLEQSGAELVRPGTSVKISCKASGYAFTNYWLGWVKQRPGH GLEWIGDIFPGSGNIHYNEKFKGKATLTADKSSSTAYMQLSSLT

			FEDSAVYFCARLRNWDEPMDYWGQGTTVTVSS
	252	CDRH1	NYWLG
	253	CDRH2	DIFPGSGNIHYNEKFKG
	254	CDRH3	LRNWDEPMDY
	255	VL	ELVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQ KPGQPPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAED LAVYYCQNDYSYPLTFGAGTKLEIK
	256	CDRL1	KSSQSLLNSGNQKNYLT
	257	CDRL2	WASTRES
	258	CDRL3	QNDYSYPLT
	259	scFv	EVQLLEQSGAELVRPGTSVKISCKASGYAFTNYWLGWVKQRPGH GLEWIGDIFPGSGNIHYNEKFKGKATLTADKSSSTAYMQLSSLT FEDSAVYFCARLRNWDEPMDYWGQGTTVTVSSGGGGSGGGGSGG GGSELVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTW YQQKPGQPPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQ AEDLAVYYCQNDYSYPLTFGAGTKLEIK
	260	scFv	ELVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQ KPGQPPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAED LAVYYCQNDYSYPLTFGAGTKLEIKGGGGSGGGGSGGGGSEVQL LEQSGAELVRPGTSVKISCKASGYAFTNYWLGWVKQRPGHGLEW IGDIFPGSGNIHYNEKFKGKATLTADKSSSTAYMQLSSLTFEDS AVYFCARLRNWDEPMDYWGQGTTVTVSS
CD3.26	261	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYAASVKGRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSWFAYWGQGTLVTVSS
	262	CDRH1	TYAMN
	263	CDRH2	RIRSKYNNYATYYAASVKG
	264	CDRH3	HGNFGNSYVSWFAY
	265	VL	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQ APRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVL
	266	CDRL1	RSSTGAVTTSNYAN
	267	CDRL2	GTNKRAP
	268	CDRL3	ALWYSNLWV
	269	scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYAASVKGRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSWFAYWGQGTLVTVSSGGGGSGG GGSGGGGSQTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYAN WVQQKPGQAPRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNLWVFGGGTKLTVL
	270	scFv	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQ APRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIR SKYNNYATYYAASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVY YCARHGNFGNSYVSWFAYWGQGTLVTVSS
CD3.27	271	VH	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVSS
	272	CDRH1	TYAMN
	273	CDRH2	RIRSKYNNYATYYADSVKG
	274	CDRH3	HGNFGNSYVSWFAY
	275	VL	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQ AFRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGAQPEDEAEY YCALWYSNLWVFGGGTKLTVL
	276	CDRL1	GSSTGAVTTSNYAN
	277	CDRL2	GTNKRAP
	278	CDRL3	ALWYSNLWV

	279	scFv	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVSSGGGGSGG GGSGGGGSQAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYAN WVQEKPGQAFRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGA QPEDEAEYYCALWYSNLWVFGGGTKLTVL
	280	scFv	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQ AFRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGAQPEDEAEY YCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLLESG GGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVSRIR SKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVY YCVRHGNFGNSYVSWFAYWGQGTLVTVSS
CD3.28	281	VH	EVQLLESGGGLVQPGGSLRLSCAASGFQFSSYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHTTFPSSYVSYYGYWGQGTLVTVSS
	282	CDRH1	SYAMN
	283	CDRH2	RIRSKYNNYATYYADSVKG
	284	CDRH3	HTTFPSSYVSYYGY
	285	VL	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQ AFRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGAQPEDEAEY YCALWYSNLWVFGGGTKLTVL
	286	CDRL1	GSSTGAVTTSNYAN
	287	CDRL2	GTNKRAP
	288	CDRL3	ALWYSNLWV
	289	scFv	EVQLLESGGGLVQPGGSLRLSCAASGFQFSSYAMNWVRQAPGKG LEWVSRIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHTTFPSSYVSYYGYWGQGTLVTVSSGGGGSGG GGSGGGGSQAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYAN WVQEKPGQAFRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGA QPEDEAEYYCALWYSNLWVFGGGTKLTVL
	290	scFv	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQ AFRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGAQPEDEAEY YCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLLESG GGLVQPGGSLRLSCAASGFQFSSYAMNWVRQAPGKGLEWVSRIR SKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVY YCVRHTTFPSSYVSYYGYWGQGTLVTVSS
CD3.29	291	VH	QVQLVQSGAEVKKPGASVKVSCKASGYSFTGYTMNWVRQAPGQG LEWMGLINPYNSDTNYAQKLQGRVTMTTDTSTSTAYMELRSLRS DDTAVYYCARVALRVALDYWGQGTLVTVSS
	292	CDRH1	GYTMN
	293	CDRH2	LINPYNSDTNYAQKLQG
	294	CDRH3	VALRVALDY
	295	VL	DIQMTQSPSSLSASVGDRVTITCKASQNVATHVGWYQQKPGKAP KRLIYSASYRYSGVPSRFSGSGSGTEFTLTISNLQPEDFATYYC QQYNRYPYTFGQGTKLEIK
	296	CDRL1	KASQNVATHVG
	297	CDRL2	SASYRYS
	298	CDRL3	QQYNRYPYT
	299	scFv	QVQLVQSGAEVKKPGASVKVSCKASGYSFTGYTMNWVRQAPGQG LEWMGLINPYNSDTNYAQKLQGRVTMTTDTSTSTAYMELRSLRS DDTAVYYCARVALRVALDYWGQGTLVTVSSGGGGSGGGGSGGGG SDIQMTQSPSSLSASVGDRVTITCKASQNVATHVGWYQQKPGKA PKRLIYSASYRYSGVPSRFSGSGSGTEFTLTISNLQPEDFATYY CQQYNRYPYTFGQGTKLEIK
	300	scFv	DIQMTQSPSSLSASVGDRVTITCKASQNVATHVGWYQQKPGKAP KRLIYSASYRYSGVPSRFSGSGSGTEFTLTISNLQPEDFATYYC QQYNRYPYTFGQGTKLEIKGGGGSGGGGSGGGGSQVQLVQSGAE VKKPGASVKVSCKASGYSFTGYTMNWVRQAPGQGLEWMGLINPY NSDTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR

			VALRVALDYWGQGTLVTVSS
CD3.30	301	VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKG LEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTALYYCAKDSRGYGDYRLGGAYWGQGTLVTVSS
	302	CDRH1	DYAMH
	303	CDRH2	GISWNSGSIGYADSVKG
	304	CDRH3	DSRGYGDYRLGGAY
	305	VL	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAP RLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYC QQYNNWPWTFGQGTKVEIK
	306	CDRL1	RASQSVSSNLA
	307	CDRL2	GASTRAT
	308	CDRL3	QQYNNWPWT
	309	scFv	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKG LEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTALYYCAKDSRGYGDYRLGGAYWGQGTLVTVSSGGGGSGGGG SGGGGSEIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQ KPGQAPRLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSED FAVYYCQQYNNWPWTFGQGTKVEIK
	310	scFv	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAP RLLIYGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYC QQYNNWPWTFGQGTKVEIKGGGGSGGGGSGGGGSEVQLVESGGG LVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWN SGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAK DSRGYGDYRLGGAYWGQGTLVTVSS
CD3.31	311	VH	EVQLVQSGAEVKKPGASVKVSCKASGFSFTNYYVHWMRQAPGQG LEWMGWISPGSDNTKYNEKFKGRVTMTRDTSISTAYMELSRLRS DDTAVYYCARDDYGNYYFDYWGQGTTVTVSS
	312	CDRH1	NYYVH
	313	CDRH2	WISPGSDNTKYNEKFKG
	314	CDRH3	DDYGNYYFDY
	315	VL	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSRTRKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCKQSYILRTFGGGTKVEIK
	316	CDRL1	KSSQSLLNSRTRKNYLA
	317	CDRL2	WASTRES
	318	CDRL3	KQSYILRT
	319	scFv	EVQLVQSGAEVKKPGASVKVSCKASGFSFTNYYVHWMRQAPGQG LEWMGWISPGSDNTKYNEKFKGRVTMTRDTSISTAYMELSRLRS DDTAVYYCARDDYGNYYFDYWGQGTTVTVSSGGGGSGGGGSGGG GSDIVMTQSPDSLAVSLGERATINCKSSQSLLNSRTRKNYLAWY QQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQA EDVAVYYCKQSYILRTFGGGTKVEIK
	320	scFv	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSRTRKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCKQSYILRTFGGGTKVEIKGGGGSGGGGSGGGGSEVQLV QSGAEVKKPGASVKVSCKASGFSFTNYYVHWMRQAPGQGLEWMG WISPGSDNTKYNEKFKGRVTMTRDTSISTAYMELSRLRSDDTAV YYCARDDYGNYYFDYWGQGTTVTVSS
CD3.32	321	VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKG LEWVSGISWNSGSKGYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTALYYCAKYGSGYGKFYHYGLDVWGQGTTVTVSS
	322	CDRH1	DYSMH
	323	CDRH2	GISWNSGSKGYADSVKG
	324	CDRH3	YGSGYGKFYHYGLDV
	325	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSYSTPPITFGQGTRLEIK

	326	CDRL1	RASQSISSYLN
	327	CDRL2	AASSLQS
	328	CDRL3	QQSYSTPPIT
	329	scFv	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKG LEWVSGISWNSGSKGYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTALYYCAKYGSGYGKFYHYGLDVWGQGTTVTVSSGGGGSGGG GSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQ QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQQSYSTPPITFGQGTRLEIK
	330	scFv	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSYSTPPITFGQGTRLEIKGGGGSGGGGSGGGGSEVQLVESGG GLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISW NSGSKGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCA KYGSGYGKFYHYGLDVWGQGTTVTVSS
CD3.33	331	VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKG LEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTALYYCAKYGSGYGKFYYYGMDVWGQGTTVTVSS
	332	CDRH1	DYSMH
	333	CDRH2	GISWNSGSIGYADSVKG
	334	CDRH3	YGSGYGKFYYYGMDV
	335	VL	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSYSTPPITFGQGTRLEIK
	336	CDRL1	RASQSISSYLN
	337	CDRL2	AASSLQS
	338	CDRL3	QQSYSTPPIT
	339	scFv	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKG LEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRA EDTALYYCAKYGSGYGKFYYYGMDVWGQGTTVTVSSGGGGSGGG GSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQ QKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPE DFATYYCQQSYSTPPITFGQGTRLEIK
	340	scFv	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAP KLLIYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYC QQSYSTPPITFGQGTRLEIKGGGGSGGGGSGGGGSEVQLVESGG GLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISW NSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCA KYGSGYGKFYYYGMDVWGQGTTVTVSS
CD3.34	341	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSYFAYWGQGTTVTVSS
	342	CDRH1	TYAMN
	343	CDRH2	RIRSKYNNYATYYADSVKG
	344	CDRH3	HGNFGNSYVSYFAY
	345	VL	EIVVTQSPATLSVSPGERATLSCRSSTGAVTESNYANWVQEKPG QAFRGLIGGANKRAPGVPARFSGSLSGDEATLTISSLQSEDFAV YYCALFYSNTWVFGQGTKLEIK
	346	CDRL1	RSSTGAVTESNYAN
	347	CDRL2	GANKRAP
	348	CDRL3	ALFYSNTWV
	349	scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSL RAEDTAVYYCVRHGNFGNSYVSYFAYWGQGTTVTVSSGGGGSGG GGSGGGGSEIVVTQSPATLSVSPGERATLSCRSSTGAVTESNYA NWVQEKPGQAFRGLIGGANKRAPGVPARFSGSLSGDEATLTISS LQSEDFAVYYCALFYSNTWVFGQGTKLEIK
	350	scFv	EIVVTQSPATLSVSPGERATLSCRSSTGAVTESNYANWVQEKPG

			QAFRGLIGGANKRAPGVPARFSGSLSGDEATLTISSLQSEDFAV YYCALFYSNTWVFGQGTKLEIKGGGGSGGGGSGGGGSEVQLVES GGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARI RSKYNNYATYYADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAV YYCVRHGNFGNSYVSYFAYWGQGTTVTVSS
CD3.35	351	VH	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNL KTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSS
	352	CDRH1	KYAMN
	353	CDRH2	RIRSKYNNYATYYADSVKD
	354	CDRH3	HGNFGNSYISYWAY
	355	VL	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQ APRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCVLWYSNRWVFGGGTKLTVL
	356	CDRL1	GSSTGAVTSGNYPN
	357	CDRL2	GTKFLAP
	358	CDRL3	VLWYSNRWV
	359	scFv	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKG LEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNL KTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVSSGGGGSGG GGSGGGGSQTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPN WVQQKPGQAPRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCVLWYSNRWVFGGGTKLTVL
	360	scFv	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQ APRGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCVLWYSNRWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIR SKYNNYATYYADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVY YCVRHGNFGNSYISYWAYWGQGTLVTVSS
CD3.36	361	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMTWVRQAPGKG LEWVAFIRNRARGYTSDHNPSVKGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCARDRPSYYVLDYWGQGTTVTVSS
	362	CDRH1	DYYMT
	363	CDRH2	FIRNRARGYTSDHNPSVKG
	364	CDRH3	DRPSYYVLDY
	365	VL	DIVMTQSPDSLAVSLGERATINCKSSQSLFNVRSRKNYLAWYQQ KPGQPPKLLISWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCKQSYDLFTFGSGTKLEIK
	366	CDRL1	KSSQSLFNVRSRKNYLA
	367	CDRL2	WASTRES
	368	CDRL3	KQSYDLFT
	369	scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMTWVRQAPGKG LEWVAFIRNRARGYTSDHNPSVKGRFTISRDNAKNSLYLQMNSL RAEDTAVYYCARDRPSYYVLDYWGQGTTVTVSSGGGGSGGGGSG GGGSDIVMTQSPDSLAVSLGERATINCKSSQSLFNVRSRKNYLA WYQQKPGQPPKLLISWASTRESGVPDRFSGSGSGTDFTLTISSL QAEDVAVYYCKQSYDLFTFGSGTKLEIK
	370	scFv	DIVMTQSPDSLAVSLGERATINCKSSQSLFNVRSRKNYLAWYQQ KPGQPPKLLISWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCKQSYDLFTFGSGTKLEIKGGGGSGGGGSGGGGSEVQLV ESGGGLVQPGGSLRLSCAASGFTFSDYYMTWVRQAPGKGLEWVA FIRNRARGYTSDHNPSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARDRPSYYVLDYWGQGTTVTVSS
CD3.37	371	VH	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYAASVKGRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSWFAYWGQGTLVTVSS
	372	CDRH1	TYAMN
	373	CDRH2	RIRSKYNNYATYYAASVKG

	374	CDRH3	HGNFGNSYVSWFAY
	375	VL	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQ APRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVL
	376	CDRL1	RSSTGAVTTSNYAN
	377	CDRL2	GTNKRAP
	378	CDRL3	ALWYSNLWV
	379	scFv	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKG LEWVARIRSKYNNYATYYAASVKGRFTISRDDSKNSLYLQMNSL KTEDTAVYYCARHGNFGNSYVSWFAYWGQGTLVTVSSGGGGSGG GGSGGGGSQTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYAN WVQQKPGQAPRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGV QPEDEAEYYCALWYSNLWVFGGGTKLTVL
	380	scFv	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQ APRGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEY YCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGSEVQLVESG GGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIR SKYNNYATYYAASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVY YCARHGNFGNSYVSWFAYWGQGTLVTVSS
CD3.38	381	VH	QVQLVQSGAEVKKPGASVKVSCKASGFNIKDYYMHWVRQAPGQR LEWMGWIDLENANTIYDAKFQGRVTITRDTSASTAYMELSSLRS EDTAVYYCARDAYGRYFYDVWGQGTLVTVSS
	382	CDRH1	DYYMH
	383	CDRH2	WIDLENANTIYDAKFQG
	384	CDRH3	DAYGRYFYDV
	385	VL	DIVMTQSPDSLAVSLGERATINCKSSQSLLNARTGKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCKQSYSRRTFGGGTKVE IK
	386	CDRL1	KSSQSLLNARTGKNYLA
	387	CDRL2	WASTRES
	388	CDRL3	KQSYSRRT
	389	scFv	QVQLVQSGAEVKKPGASVKVSCKASGFNIKDYYMHWVRQAPGQR LEWMGWIDLENANTIYDAKFQGRVTITRDTSASTAYMELSSLRS EDTAVYYCARDAYGRYFYDVWGQGTLVTVSSGGGGSGGGGSGGG GSDIVMTQSPDSLAVSLGERATINCKSSQSLLNARTGKNYLAWY QQKPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQA EDVAVYYCKQSYSRRTFGGGTKVEIK
	390	scFv	DIVMTQSPDSLAVSLGERATINCKSSQSLLNARTGKNYLAWYQQ KPGQPPKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAED VAVYYCKQSYSRRTFGGGTKVEIKGGGGSGGGGSGGGGSQVQLV QSGAEVKKPGASVKVSCKASGFNIKDYYMHWVRQAPGQRLEWMG WIDLENANTIYDAKFQGRVTITRDTSASTAYMELSSLRSEDTAV YYCARDAYGRYFYDVWGQGTLVTVSS
CD3.39	391	VH	QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKG LEWIGYINPSRGYTNYNQKVKDRFTISRDNSKNTAFLQMDSLRP EDTGVYFCARYYDDHYCLDYWGQGTPVTVSS
	392	CDRH1	RYTMH
	393	CDRH2	YINPSRGYTNYNQKVKD
	394	CDRH3	YYDDHYCLDY
	395	VL	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPK RWIYDTSKLASGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQ QWSSNPFTFGQGTKLQIT
	396	CDRL1	SASSSVSYMN
	397	CDRL2	DTSKLAS
	398	CDRL3	QQWSSNPFT
	399	scFv	QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKG LEWIGYINPSRGYTNYNQKVKDRFTISRDNSKNTAFLQMDSLRP EDTGVYFCARYYDDHYCLDYWGQGTPVTVSSGGGGSGGGGSGGG

			GSDIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKA PKRWIYDTSKLASGVPSRFSGSGSGTDYTFTISSLQPEDIATYY CQQWSSNPFTFGQGTKLQIT
	400	scFv	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPK RWIYDTSKLASGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQ QWSSNPFTFGQGTKLQITGGGGSGGGGSGGGGSQVQLVQSGGGV VQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGYINPSR GYTNYNQKVKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARY YDDHYCLDYWGQGTPVTVSS
CD3.40	401	VH	QVQLVQSGPEVKKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQG LEWIGYINPSSAYTNYNQKFKDRVTITADKSTSTAYMELSSLRS EDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSS
	402	CDRH1	RSTMH
	403	CDRH2	YINPSSAYTNYNQKFKD
	404	CDRH3	PQVHYDYNGFPY
	405	VL	DIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPK RWIYDSSKLASGVPSRFSGSGSGTEYTLTISSLQPDDFATYYCQ QWSRNPPTFGGGTKVEIKR
	406	CDRL1	SASSSVSYMN
	407	CDRL2	DSSKLAS
	408	CDRL3	QQWSRNPPT
	409	scFv	QVQLVQSGPEVKKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQG LEWIGYINPSSAYTNYNQKFKDRVTITADKSTSTAYMELSSLRS EDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSSGGGGSGGGGSG GGGSDIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPG KAPKRWIYDSSKLASGVPSRFSGSGSGTEYTLTISSLQPDDFAT YYCQQWSRNPPTFGGGTKVEIKR
	410	scFv	DIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPK RWIYDSSKLASGVPSRFSGSGSGTEYTLTISSLQPDDFATYYCQ QWSRNPPTFGGGTKVEIKRGGGGSGGGGSGGGGSQVQLVQSGPE VKKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQGLEWIGYINPS SAYTNYNQKFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCAR PQVHYDYNGFPYWGQGTLVTVSS

b. Spacer

Non-viral membrane-bound tropism polypeptides contemplated in particular embodiments comprise a spacer domain. In particular embodiments, a spacer domain impacts the manufacturability of the particle, the expression of the tropism polypeptide and the on-target/off-target cell binding profile of the tropism polypeptide. Without wishing to be bound to any particular theory, it is contemplated that in particular embodiments, disposing the extracellular targeting domains of the one or more non-viral membrane bound tropism polypeptides a particular distance from a particle surface (*e.g.*, lipid bilayer, cell membrane, or envelope) out-competes the host cell derived membrane proteins and leads to increased targeting specificity of the vector. Increased vector specificity should correspond to efficacy at lower vector doses, which corresponds to increased safety. Lower doses also lead to manufacturing cost advantages and efficiencies, which has been an insurmountable obstacle for current *ex vivo* gene therapies.

In particular embodiments, a particle comprises a non-viral membrane bound tropism polypeptide that comprises a spacer domain of about 12 nm in length, about 13 nm in length, about 14 nm in length, about 15 nm in length, about 16 nm in length, about 17 nm in length, about 18 nm in length, about 19 nm in length, about 20 nm in length, about 21 nm in length, about 22 nm in length, about 23 nm in length, about 24 nm in length, about 25 nm in length, about 26 nm in length, about 27 nm in length, about 28 nm in length, about 29 nm in length, about 30 nm in length, about 31 nm in length, about 32 nm in length, about 33 nm in length, about 34 nm in length, about 35 nm in length, about 36 nm in length, about 37 nm in length, about 38 nm in length, about 39 nm in length, about 40 nm in length, about 41 nm in length, about 42 nm in length, about 43 nm in length, about 44 nm in length, about 45 nm in length, about 46 nm in length, about 47 nm in length, about 48 nm in length, about 49 nm in length, about 50 nm in length, about 51 nm in length, about 52 nm in length, about 53 nm in length, about 54 nm in length, or about 55 nm in length, wherein the targeting domain is disposed about 12 nm to about 25 nm, about 13 nm to about 20 nm, or about 12 nm, about 13, nm, about 14 nm, about 15 nm, about 16 nm, about 17 nm, about 18 nm, about 19 nm, or about 20 nm from the vector surface.

In particular embodiments, a particle comprises a non-viral membrane bound tropism polypeptide that comprises a spacer domain about 12 nm in length to about 20 nm in length, wherein the extracellular antigen targeting domain is disposed at least about 12 nm, about 13, nm, about 14 nm, about 15 nm, about 16 nm, about 17 nm, about 18 nm, about 19 nm, or about 20 nm from the particle surface.

In particular embodiments, a particle comprises a tropism polypeptide that comprises a spacer comprising a hinge or stalk polypeptide about 12 nm in length, about 13 nm in length, about 14 nm in length, about 15 nm in length, about 16 nm in length, about 17 nm in length, about 18 nm in length, about 19 nm in length, or about 20 nm in length, wherein the targeting domain is disposed about 12 nm to about 20 nm from the particle surface.

In particular embodiments, a spacer comprises one, two, three, four, five, six, seven, eight, nine, ten or more domains are linked together to achieve the desired length and distance to dispose the extracellular targeting domain from the particle surface. The following table lists exemplary spacers domains based on hinge or stalk polypeptides and their predicted lengths.

Table 6

Spacer	Est. Length	SEQUENCE

SEQ ID NO	(nm)	
411	13	CD8α
423	17	CD45RO del.d2-d3
422	21	CD45RO del.d3
415	25	CD45RO
419	30	CD45RA
416	35	CD45RAB
424	5	ECAD.5
425	10	ECAD.4-5
426	15	ECAD.3-5
427	20	ECAD.2-5
431	8	CEACAM.A3
430	16	CEACAM.A2
428	24	CEACAM.A1
434	4	CEACAM.B3
433	12	CEACAM.B2
432	20	CEACAM.B1

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain; a spacer comprising a hinge or stalk domain derived, obtained, or isolated from PDGFR, IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3, CADHERIN 1 (E-CADHERIN; ECAD), CEACAM 5, variants thereof, an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto, and polypeptide linkers of similar amino acid composition and lengths; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3; a VH and VL; and/or an scFv set forth in Table 5; a spacer comprising a hinge or stalk domain derived, obtained, or isolated from PDGFR, IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3, CADHERIN 1, CEACAM 5, or variants thereof; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110,

119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer comprising a hinge or stalk domain derived, obtained, or isolated from PDGFR, IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3, CADHERIN 1, CEACAM 5, or variants thereof; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer comprising a hinge or stalk domain derived, obtained, or isolated from PDGFR, IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3, CADHERIN 1, CEACAM 5, or variants thereof; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, and 170; a spacer comprising a hinge or stalk domain derived, obtained, or isolated from PDGFR, IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3, CADHERIN 1, CEACAM 5, or variants thereof; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411-413, SEQ ID NOs: 414-

423, SEQ ID NOs: 424-427, and SEQ ID NOs: 428-434; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, a VH and VL, and/or an scFv set forth in Table 5; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, and SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3; a VH and VL; and/or an scFv set forth in Table 5; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 423, and 428; a transmembrane domain or GPI anchor, and optionally an intracellular domain

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, and SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200,

209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434, and amino acid sequences at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, and 170; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434, and amino acid sequences at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, and 170; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 423, 428, and amino acid sequences at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto; a transmembrane domain or GPI anchor, and optionally an intracellular domain.

Table 7

SEQ ID NO:	AMINO ACID SEQUENCE
411	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACD
412	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAAD

413	TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFAXD
414	SPTPSPTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSL DNASAFNTTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDVPGERST ASTFPTDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASETTTLSPSGSAVISTTT IATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNNEVHNLTECKNASVS ISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIETFTCDTQNITYRFQCGN MIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGEPQIIFCRSEAAHQGVI TWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAA MCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCD FRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSK
415	SPTPSPTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAK LNVNENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVE KADTTICLKWKNIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFT NASKIIKTDFGSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIK YDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRP PRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHS TSYNSK
416	SPTPSPTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSL DNASAFNTTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDAYLNASE TTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCT NNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIET FTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGE PQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLS LHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEV EAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSK
417	SPTPSPTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSL DNASAFNTTDVPGERSTASTFPTDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNAS ETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTC TNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIE TFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPG EPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVL SLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLE VEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSK
418	SPTPSPTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDVPGERSTAS TFPTDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASETTTLSPSGSAVISTTTIA TTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNNEVHNLTECKNASVSIS HNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIETFTCDTQNITYRFQCGNMI FDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGEPQIIFCRSEAAHQGVITW NPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMC HFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFR VKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSK
419	SPTPSPTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSL DNASAFNTTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFT AKLNVNENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQ VEKADTTICLKWKNIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHK FTNASKIIKTDFGSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNL IKYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKC RPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILH HSTSYNSK
420	SPTPSPTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDAYLNASETT TLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNN EVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIETFT CDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGEPQ IIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLH AYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVEA GNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSK
421	SPTPSPTDVPGERSTASTFPTDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASET TTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTN NEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIETF

	TCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGEP QIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSL HAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVE AGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSK
422	SPTPSPTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAK LNVNENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVE KADTTICLKWKNIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFT NASKIIKTDFGSPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESHK NCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSK
423	SPTPSPTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAK LNVNENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPSQVWNMTVSMTSDN SMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPG EPFILHHSTSYNSK
424	APIPEPRTIFFCERNPKPQVINIIDADLPPNTSPFTAELTHGASANWTIQYNDPTQESIILKPK MALEVGDYKINLKLMDNQNKDQVTTLEVSVCDCEGAAGVCRKAQPVEAGLQIPA
425	APIFVPPEKRVEVSEDFGVGQEITSYTAQEPDTFMEQKITYRIWRDTANWLEINPDTGAISTRA ELDREDFEHVKNSTYTALIIATDNGSPVATGTGTLLLILSDVNDNAPIPEPRTIFFCERNPKPQ VINIIDADLPPNTSPFTAELTHGASANWTIQYNDPTQESIILKPKMALEVGDYKINLKLMDNQN KDQVTTLEVSVCDCEGAAGVCRKAQPVEAGLQIPA
426	NPPIFNPTTYKGQVPENEANVVITTLKVTDADAPNTPAWEAVYTILNDDGGQFVVTTNPVNNDG ILKTAKGLDFEAKQQYILHVAVTNVVPFEVSLTTSTATVTVDVLDVNEAPIFVPPEKRVEVSED FGVGQEITSYTAQEPDTFMEQKITYRIWRDTANWLEINPDTGAISTRAELDREDFEHVKNSTYT ALIIATDNGSPVATGTGTLLLILSDVNDNAPIPEPRTIFFCERNPKPQVINIIDADLPPNTSPF TAELTHGASANWTIQYNDPTQESIILKPKMALEVGDYKINLKLMDNQNKDQVTTLEVSVCDCEG AAGVCRKAQPVEAGLQIPA
427	PEFTQEVFKGSVMEGALPGTSVMEVTATDADDDVNTYNAAIAYTILSQDPELPDKNMFTINRNT GVISVVTTGLDRESFPTYTLVVQAADLQGEGLSTTATAVITVTDTNDNPPIFNPTTYKGQVPEN EANVVITTLKVTDADAPNTPAWEAVYTILNDDGGQFVVTTNPVNNDGILKTAKGLDFEAKQQYI LHVAVTNVVPFEVSLTTSTATVTVDVLDVNEAPIFVPPEKRVEVSEDFGVGQEITSYTAQEPDT FMEQKITYRIWRDTANWLEINPDTGAISTRAELDREDFEHVKNSTYTALIIATDNGSPVATGTG TLLLILSDVNDNAPIPEPRTIFFCERNPKPQVINIIDADLPPNTSPFTAELTHGASANWTIQYN DPTQESIILKPKMALEVGDYKINLKLMDNQNKDQVTTLEVSVCDCEGAAGVCRKAQPVEAGLQI PA
428	ELPKPSISSNNSKPVEDKDAVAFTCEPETQDATYLWWVNNQSLPVSPRLQLSNGNRTLTLFNVT RNDTASYKCETQNPVSARRSDSVILNVLYGPDAPTISPLNTSYRSGENLNLSCHAASNPPAQYS WFVNGTFQQSTQELFIPNITVNNSGSYTCQAHNSDTGLNRTTVTTITVYAEPPKPFITSNNSNP VEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRNDVGPYECGIQNE LSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWLIDGNIQQHTQEL FISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSNNSKPVEDKDAVAFTCEPE AQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDARAYVCGIQNSVSANRSDPVTLDVL YGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYA CFVSNLATGRNNSIVKSITVS
429	ELPKPSISSNNSKPVEDKDAVAFTCEPETQDATYLWWVNNQSLPVSPRLQLSNGNRTLTLFNVT RNDTASYKCETQNPVSARRSDSVILNVLYGPDAPTISPLNTSYRSGENLNLSCHAASNPPAQYS WFVNGTFQQSTQELFIPNITVNNSGSYTCQAHNSDTGLNRTTVTTITVYAEPPKPFITSNNSNP VEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRNDVGPYECGIQNE LSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWLIDGNIQQHTQEL FISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSNNSKPVEDKDAVAFTCEPE AQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDARAYVCGIQNSVSANRSDPVTLDVL YGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYA CFVSNLATGRNNSIVKSITVSA
430	PKPFITSNNSNPVEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRN DVGPYECGIQNELSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWL IDGNIQQHTQELFISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSNNSKPVE DKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDARAYVCGIQNSVS ANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFI AKITPNNNGTYACFVSNLATGRNNSIVKSITVSA
431	AELPKPSISSNNSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNV TRNDARAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQY

	SWRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVSA
432	PDAPTISPLNTSYRSGENLNLSCHAASNPPAQYSWFVNGTFQQSTQELFIPNITVNNSGSYTCQ AHNSDTGLNRTTVTTITVYAEPPKPFITSNNSNPVEDEDAVALTCEPEIQNTTYLWWVNNQSLP VSPRLQLSNDNRTLTLLSVTRNDVGPYECGIQNELSVDHSDPVILNVLYGPDDPTISPSYTYYR PGVNLSLSCHAASNPPAQYSWLIDGNIQQHTQELFISNITEKNSGLYTCQANNSASGHSRTTVK TITVSAELPKPSISSNNSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTL TLFNVTRNDARAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASN PSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVSA
433	PDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWLIDGNIQQHTQELFISNITEKNSGLYTCQ ANNSASGHSRTTVKTITVSAELPKPSISSNNSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLP VSPRLQLSNGNRTLTLFNVTRNDARAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYL SGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNSIVK SITVSA
434	PDTPIISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYACF VSNLATGRNNSIVKSITVSA

c. Transmembrane Domain

Non-viral membrane-bound tropism polypeptides contemplated in particular embodiments comprise an extracellular antigen targeting domain that binds an antigen expressed on an immune effector cell; a spacer polypeptide; a transmembrane domain and optionally, an intracellular domain.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain that binds an antigen expressed on an immune effector cell; a spacer polypeptide; a transmembrane domain derived, obtained, or isolated from a polypeptide selected from the group consisting of: alpha, beta, gamma, or delta chain of the T-cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD5, CD7, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD40, CD45, CD64, CD80, CD86, CD95, CD 134, CD137, CD152, CD154, CD200R, CD223, CD235a, CD244, CD270, CD272, CD273, CD274, CD278, CD279, CD300, CD357, TNRF2, TNFRS14, TNFRS25, TLR2, TLR4, TLR5, TIM1, SlamFl, SlamF5, SlamF6, and an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain; a spacer comprising a hinge or stalk domain derived, obtained, or isolated from PDGFR, IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3, CADHERIN 1, CEACAM 5, variants thereof, and polypeptide linkers of similar amino acid composition and lengths; a

transmembrane domain derived, obtained, or isolated from a polypeptide selected from the group consisting of: alpha, beta, gamma, or delta chain of the T-cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD5, CD7, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD40, CD45, CD64, CD80, CD86, CD95, CD 134, CD137, CD152, CD154, CD200R, CD223, CD235a, CD244, CD270, CD272, CD273, CD274, CD278, CD279, CD300, CD357, PDGFR, TNRF2, TNFRS14, TNFRS25, TLR2, TLR4, TLR5, TIM1, SlamFl, SlamF5, SlamF6, and an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, a VH and VL, and/or an scFv set forth in Table 5; a spacer comprising a hinge or stalk domain derived, obtained, or isolated from PDGFR, IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3, CADHERIN 1, CEACAM 5, or variants thereof; a transmembrane domain derived, obtained, or isolated from a polypeptide selected from the group consisting of: alpha, beta, gamma, or delta chain of the T-cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD5, CD7, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD40, CD45, CD64, CD80, CD86, CD95, CD 134, CD137, CD152, CD154, CD200R, CD223, CD235a, CD244, CD270, CD272, CD273, CD274, CD278, CD279, CD300, CD357, PDGFR, TNRF2, TNFRS14, TNFRS25, TLR2, TLR4, TLR5, TIM1, SlamFl, SlamF5, SlamF6, and an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290,

299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer comprising a hinge or stalk domain derived, obtained, or isolated from PDGFR, IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3, CADHERIN 1, CEACAM 5, or variants thereof; a transmembrane domain derived, obtained, or isolated from a polypeptide selected from the group consisting of: alpha, beta, gamma, or delta chain of the T-cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD5, CD7, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD40, CD45, CD64, CD80, CD86, CD95, CD 134, CD137, CD152, CD154, CD200R, CD223, CD235a, CD244, CD270, CD272, CD273, CD274, CD278, CD279, CD300, CD357, PDGFR, TNRF2, TNFRS14, TNFRS25, TLR2, TLR4, TLR5, TIM1, SlamFl, SlamF5, SlamF6, and an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer comprising a hinge or stalk domain derived, obtained, or isolated from PDGFR, IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3, CADHERIN 1, CEACAM 5, or variants thereof; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440, and 441 and an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or

antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, and 170; a spacer comprising a hinge or stalk domain derived, obtained, or isolated from PDGFR, IgG1, IgG2, IgG4, CD2, CD3, CD4, CD8α, CD8β, CD28, CD45ABC, CD45RO, CD45RAB, CD45RAC, CD45RBC, CD45RA, CD45RB, CD45RC, CD45del-d3, CD45del-d2-d3, CADHERIN 1, CEACAM 5, or variants thereof; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440, and 441, and an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411-413, SEQ ID NOs: 414-423, SEQ ID NOs: 424-427, and SEQ ID NOs: 428-434; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440, and 441; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, a VH and VL, and/or an scFv set forth in Table 5; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, and SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440, and 441; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200,

209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, and SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440, and 441; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, and SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440, and 441, and an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, or at least 99% identical thereto; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, and 170; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 423, and 428; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 437 and 439; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

Table 8

SEQ ID NO:	AMINO ACID SEQUENCE
435	VMSVATIVIVDICITGGLLLLVYYWS
436	MALIVLGGVAGLLLFIGLGIFF
437	IYIWAPLAGTCGVLLLSLVITLYC
438	FWVLVVVGGVLACYSLLVTVAFIIFWV
439	ALIAFLAFLIIVTSIALLVVL
440	ILGILGGILALLILILLLLLF
441	IISFFLALTSTALLFLLFFLTLRFSVV

In particular embodiments, a non-viral membrane-bound tropism polypeptide comprises a transmembrane domain and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids. In preferred embodiments, an intracellular domain comprises, consists essentially of, or consists of one, two, three, four, five, or six of the amino acids set forth in any one of SEQ ID NOs: 442, 443, 444, 445, 446, 447, and 448.

Table 9

SEQ ID NO:	AMINO ACID SEQUENCE
442	KNRKA
443	CVRC
444	NHRNR
445	RSKRS
446	YKIYD
447	LRRRA
448	KRGRK

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an extracellular antigen targeting domain, a spacer polypeptide, and a GPI anchor. A "GPI anchor" or "glycosylphosphatidylinositol anchor" refers to a posttranslational modification that anchors a non-viral membrane bound tropism polypeptide in the outer leaflet of a lipid bilayer, a cell membrane, or a viral envelope of a recombinant particle contemplated herein. A GPI anchor is a complex structure comprising a phosphoethanolamine linker, glycan core, and phospholipid tail. In particular embodiments, a nascently translated non-viral membrane-bound tropism polypeptide comprises a GPI attachment signal peptide at its C-terminus. The signal peptide is recognized by GPI transamidase, which cleaves and replaces it with a preassembled GPI by transamidation at an amino acid termed the ω site amino acid thereby generating a GPI anchored non-viral membrane-bound tropism polypeptide.

In particular embodiments, a non-viral membrane bound tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 455-576. In

particular preferred embodiments, a non-viral membrane bound tropism polypeptide comprises an amino acid sequence set forth in any one of SEQ ID NOs: 461, 471, 483, 537, and 553.

Table 10

SEQ ID NO:	AMINO ACID SEQUENCE
455	QVQLLESGAELARPGASVKMSCKASGYTFTRYTMHWVKQRPGQGLEWIGYINPSRGYTNYNQ KFKDKATLTTDKSSSTAYMQLSSLTSEDSAVYYCAGYYDDHYCLDYWGQGTLVTVSSGGGGS GGGGSGGGGSDIVMTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPKRWIYDTSK LASGVPAHFRGSGSGTSYSLTISGMEAEDAATYYCQQWSSNPFTFGSGTKLEIKSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
456	DIVMTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPKRWIYDTSKLASGVPAHFR GSGSGTSYSLTISGMEAEDAATYYCQQWSSNPFTFGSGTKLEIKSGGGGSGGGGSGGGGSQV QLLESGAELARPGASVKMSCKASGYTFTRYTMHWVKQRPGQGLEWIGYINPSRGYTNYNQKF KDKATLTTDKSSSTAYMQLSSLTSEDSAVYYCAGYYDDHYCLDYWGQGTLVTVSTTTPAPRP PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
457	QVQLQQSGAELARPGASVKMSCKASGYTFTRYTMHWVKQRPGQGLEWIGYINPSRGYTNYNQ KFKDKATLTTDKSSSTAYMQLSSLTSEDSAVYYCARYYDDHYCLDYWGQGTTLTVSSSGGGG SGGGGSGGGGSQIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPKRWIYDTS KLASGVPAHFRGSGSGTSYSLTISGMEAEDAATYYCQQWSSNPFTFGSGTKLEINTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
458	QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYQQKSGTSPKRWIYDTSKLASGVPAHFR GSGSGTSYSLTISGMEAEDAATYYCQQWSSNPFTFGSGTKLEINGGGGSGGGGSGGGGSQVQ LQQSGAELARPGASVKMSCKASGYTFTRYTMHWVKQRPGQGLEWIGYINPSRGYTNYNQKFK DKATLTTDKSSSTAYMQLSSLTSEDSAVYYCARYYDDHYCLDYWGQGTTLTVSSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
459	QVQLQQSGAELARPGASVKMSCKASGYTFTSYTMHWVKQRPGQGLEWIGYINPSSGYTKYNQ KFKDKATLTADKSSSTAYMQLSSLTSEDSAVYYCARWQDYDVYFDYWGQGTTLTVSSGGGGS GGGGSGGGGSQIVLSQSPAILSASPGEKVTMTCRASSSVSYMHWYQQKPGSSPKPWIYATSN LASGVPARFSGSGSGTSYSLTISRVEAEDAATYYCQQWSSNPPTFGGGTKLETKTTTPAPRP PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
460	QIVLSQSPAILSASPGEKVTMTCRASSSVSYMHWYQQKPGSSPKPWIYATSNLASGVPARFS GSGSGTSYSLTISRVEAEDAATYYCQQWSSNPPTFGGGTKLETGGGGSGGGGSGGGGSQVQL QQSGAELARPGASVKMSCKASGYTFTSYTMHWVKQRPGQGLEWIGYINPSSGYTKYNQKFKD KATLTADKSSSTAYMQLSSLTSEDSAVYYCARWQDYDVYFDYWGQGTTLTVSSTTTPAPRPP TPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
461	EVQLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWMGLINPYKGVSTYNQ KFKDKATLTVDKSSSTAYMELLSLTSEDSAVYYCARSGYYGDSDWYFDVWGAGTTVTVSSGG GGSGGGGSGGGGSDIQMTQTTSSLSASLGDRVTISCRASQDIRNYLNWYQQKPDGTVKLLIY YTSRLHSGVPSKFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPWTFAGGTKLEIKTTTP APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVIT LYC
462	DIQMTQTTSSLSASLGDRVTISCRASQDIRNYLNWYQQKPDGTVKLLIYYTSRLHSGVPSKF SGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPWTFAGGTKLEIKGGGGSGGGGSGGGGSEV QLQQSGPELVKPGASMKISCKASGYSFTGYTMNWVKQSHGKNLEWMGLINPYKGVSTYNQKF KDKATLTVDKSSSTAYMELLSLTSEDSAVYYCARSGYYGDSDWYFDVWGAGTTVTVSSTTTP APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVIT LYC
463	QVQLQQSAAELARPGASVKMSCKASGYTFTRYTMQWVKQRPGQGLEWIGYINPSSGYIGYSQ KFKDKTTLTADKSSSTAYMQLSSLTSEDSAVYYCARSKVYYDYDVYSMDYWGQGTSVTVSSG GGGSGGGGSGGGGSQIILTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIY DTSKLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSNPLTFGAGTKLELKTTTP APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVIT LYC

464	QIILTQSPAIMSASPGEKVTMTCSASSSVSYMHWYQQKSGTSPKRWIYDTSKLASGVPARFS GSGSGTSYSLTISSMEAEDAATYYCQQWSSNPLTFGAGTKLELKGGGGSGGGGSGGGGSQVQ LQQSAAELARPGASVKMSCKASGYTFTRYTMQWVKQRPGQGLEWIGYINPSSGYIGYSQKFK DKTTLTADKSSSTAYMQLSSLTSEDSAVYYCARSKVYYDYDVYSMDYWGQGTSVTVSSTTTP APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVIT LYC
465	QVQLQQSGAELARPGASVKMSCKASGYTFISYTMHWVKQRPGQGLEWIGYINPRSGYTHYNQ KLKDKATLTADKSSSSAYMQLSSLTSEDSAVYYCARSAYYDYDGFAYWGQGTLVTVSAGGGG SGGGGSGGGGSQIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYKQKSGTSPKRWTYDTS KLASGVPARFSGSGSGTSYSLTISSMEAEDAATYYCQQWSSNPPTFGSGTKLEIKTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
466	QIVLTQSPAIMSASPGEKVTMTCSASSSVSYMNWYKQKSGTSPKRWTYDTSKLASGVPARFS GSGSGTSYSLTISSMEAEDAATYYCQQWSSNPPTFGSGTKLEIKGGGGSGGGGSGGGGSQVQ LQQSGAELARPGASVKMSCKASGYTFISYTMHWVKQRPGQGLEWIGYINPRSGYTHYNQKLK DKATLTADKSSSSAYMQLSSLTSEDSAVYYCARSAYYDYDGFAYWGQGTLVTVSATTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
467	QVQLVQSGAEVKKPGASVKVSCKASGYTFISYTMHWVRQAPGQGLEWMGYINPRSGYTHYNQ KLKDKATLTADKSASTAYMELSSLRSEDTAVYYCARSAYYDYDGFAYWGQGTLVTVSSGGGG SGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRLIYDTS KLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQWSSNPPTFGGGTKVEIKTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
468	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQKPGKAPKRLIYDTSKLASGVPSRFS GSGSGTDFTLTISSLQPEDFATYYCQQWSSNPPTFGGGTKVEIKGGGGSGGGGSGGGGSQVQ LVQSGAEVKKPGASVKVSCKASGYTFISYTMHWVRQAPGQGLEWMGYINPRSGYTHYNQKLK DKATLTADKSASTAYMELSSLRSEDTAVYYCARSAYYDYDGFAYWGQGTLVTVSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
469	EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKDRFTISRDDSQSILYLQMNNLKTEDTAMYYCVRHGNFGNSYVSWFAYWGQGTLVTVS SGGGGSGGGGSGGGGSQAVVTQESALTTSPGETVTLTCRSSTGAVTTSNYANWVQEKPDHLF TGLIGGTNKRAPGVPARFSGSLIGDKAALTITGAQTEDEAIYFCALWYSNLWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
470	QAVVTQESALTTSPGETVTLTCRSSTGAVTTSNYANWVQEKPDHLFTGLIGGTNKRAPGVPA RFSGSLIGDKAALTITGAQTEDEAIYFCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGS EVQLVESGGGLVQPKGSLKLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKDRFTISRDDSQSILYLQMNNLKTEDTAMYYCVRHGNFGNSYVSWFAYWGQGTLVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
471	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
472	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
473	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDPYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
474	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDPYCLDYWGQGTTVTVSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
475	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD

	SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYNDQYCLDYWGQGTTVTVSSSSGGG GSGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDT SKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKTTTPAP RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLY C
476	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYNDQYCLDYWGQGTTVTVSSSTTTPAP RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLY C
477	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDAHNCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
478	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDAHNCLDYWGQGTTVTVSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
479	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYSDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
480	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYSDDHYCLDYWGQGTTVTVSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
481	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYSDDRYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
482	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYSDDRYCLDYWGQGTTVTVSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
483	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDNYCLDYWGQGTTVTVSSSSGGG GSGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDT SKVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKTTTPAP RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLY C
484	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDNYCLDYWGQGTTVTVSSSTTTPAP RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLY C
485	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDQYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
486	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS

	GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDQYCLDYWGQGTTVTVSSTTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
487	EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFPMAWVRQAPGKGLEWVSTISTSGGRTYYRD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKFRQYSGGFDYWGQGTLVTVSSGGGGS GGGGSGGGGSDIQLTQPNSVSTSLGSTVKLSCTLSSGNIENNYVHWYQLYEGRSPTTMIYDD DKRPDGVPDRFSGSIDRSSNSAFLTIHNVAIEDEAIYFCHSYVSSFNVFGGGTKLTVLTTTP APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVIT LYC
488	DIQLTQPNSVSTSLGSTVKLSCTLSSGNIENNYVHWYQLYEGRSPTTMIYDDDKRPDGVPDR FSGSIDRSSNSAFLTIHNVAIEDEAIYFCHSYVSSFNVFGGGTKLTVLGGGGSGGGGSGGGG SEVQLLESGGGLVQPGGSLRLSCAASGFTFSSFPMAWVRQAPGKGLEWVSTISTSGGRTYYR DSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKFRQYSGGFDYWGQGTLVTVSSTTTP APRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVIT LYC
489	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVSRIRSKYNNYATYY ADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVS SGGGGSGGGGSGGGGSQAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAP RGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
490	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAPRGLIGGTNKRAPGTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGS EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVSRIRSKYNNYATYY ADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
491	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVSRIRSKYNNYATYY ADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVS SGGGGSGGGGSGGGGSQAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWFQQKPGQAP RGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
492	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWFQQKPGQAPRGLIGGTNKRAPGTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGS EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVSRIRSKYNNYATYY ADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
493	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVS SGGGGSGGGGSGGGGSQAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAP RGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
494	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAPRGLIGGTNKRAPWTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGS EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVYYCARHGNFGNSYVSWFAYWGQGTMVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
495	EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTMVTVS SGGGGSGGGGSGGGGSQAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWFQQKPGQAP RGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
496	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWFQQKPGQAPRGLIGGTNKRAPWTPA

	RFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGS EVQLVESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTMVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
497	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTMVTVS SGGGGSGGGGSGGGGSQAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWYQQKPGQAP RGLIGGTNKRAPWTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
498	QAVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWYQQKPGQAPRGLIGGTNKRAPWTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGS EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKDRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTMVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
499	QVQLVESGGGVVQPGRSLRLSCAASGFKFSGYGMHWVRQAPGKGLEWVAVIWYDGSKKYYVD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARQMGYWHFDLWGRGTLVTVSSGGGGSG GGGSGGGGSEIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASN RATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPLTFGGGTKVEIKRTTTPAP RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLY C
500	EIVLTQSPATLSLSPGERATLSCRASQSVSSYLAWYQQKPGQAPRLLIYDASNRATGIPARF SGSGSGTDFTLTISSLEPEDFAVYYCQQRSNWPPLTFGGGTKVEIKRGGGGSGGGGSGGGGS QVQLVESGGGVVQPGRSLRLSCAASGFKFSGYGMHWVRQAPGKGLEWVAVIWYDGSKKYYVD SVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARQMGYWHFDLWGRGTLVTVSSTTTPAP RPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLY C
501	QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGYINPSRGYTNYNQ KVKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYCLDYWGQGTPVTVSSGGGGS GGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSK LASGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFGQGTKLQITTTTPAPRP PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
502	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFS GSGSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFGQGTKLQITGGGGSGGGGSGGGGSQVQ LVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGYINPSRGYTNYNQKVK DRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYCLDYWGQGTPVTVSSTTTPAPRP PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
503	EVQLLEQSGAELVRPGTSVKISCKASGYAFTNYWLGWVKQRPGHGLEWIGDIFPGSGNIHYN EKFKGKATLTADKSSSTAYMQLSSLTFEDSAVYFCARLRNWDEPMDYWGQGTTVTVSSGGGG SGGGGSGGGGSELVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPK LLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPLTFGAGTKLEIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLS LVITLYC
504	ELVMTQSPSSLTVTAGEKVTMSCKSSQSLLNSGNQKNYLTWYQQKPGQPPKLLIYWASTRES GVPDRFTGSGSGTDFTLTISSVQAEDLAVYYCQNDYSYPLTFGAGTKLEIKGGGGSGGGGSG GGGSEVQLLEQSGAELVRPGTSVKISCKASGYAFTNYWLGWVKQRPGHGLEWIGDIFPGSGN IHYNEKFKGKATLTADKSSSTAYMQLSSLTFEDSAVYFCARLRNWDEPMDYWGQGTTVTVSS TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLS LVITLYC
505	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY AASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARHGNFGNSYVSWFAYWGQGTLVTVS SGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAP RGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
506	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAPRGLIGGTNKRAPGTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGS

	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY AASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARHGNFGNSYVSWFAYWGQGTLVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
507	EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVSRIRSKYNNYATYY ADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVS SGGGGSGGGGSGGGGSQAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQAF RGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGAQPEDEAEYYCALWYSNLWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
508	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQAFRGLIGGTNKRAPGTPA RFSGSLLGGKAALTLSGAQPEDEAEYYCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGS EVQLLESGGGLVQPGGSLRLSCAASGFTFSTYAMNWVRQAPGKGLEWVSRIRSKYNNYATYY ADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGNSYVSWFAYWGQGTLVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
509	EVQLLESGGGLVQPGGSLRLSCAASGFQFSSYAMNWVRQAPGKGLEWVSRIRSKYNNYATYY ADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHTTFPSSYVSYYGYWGQGTLVTVS SGGGGSGGGGSGGGGSQAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQAF RGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGAQPEDEAEYYCALWYSNLWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
510	QAVVTQEPSLTVSPGGTVTLTCGSSTGAVTTSNYANWVQEKPGQAFRGLIGGTNKRAPGTPA RFSGSLLGGKAALTLSGAQPEDEAEYYCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGS EVQLLESGGGLVQPGGSLRLSCAASGFQFSSYAMNWVRQAPGKGLEWVSRIRSKYNNYATYY ADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHTTFPSSYVSYYGYWGQGTLVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
511	QVQLVQSGAEVKKPGASVKVSCKASGYSFTGYTMNWVRQAPGQGLEWMGLINPYNSDTNYAQ KLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARVALRVALDYWGQGTLVTVSSGGGGSG GGGSGGGGSDIQMTQSPSSLSASVGDRVTITCKASQNVATHVGWYQQKPGKAPKRLIYSASY RYSGVPSRFSGSGSGTEFTLTISNLQPEDFATYYCQQYNRYPYTFGQGTKLEIKTTTPAPRP PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
512	DIQMTQSPSSLSASVGDRVTITCKASQNVATHVGWYQQKPGKAPKRLIYSASYRYSGVPSRF SGSGSGTEFTLTISNLQPEDFATYYCQQYNRYPYTFGQGTKLEIKGGGGSGGGGSGGGGSQV QLVQSGAEVKKPGASVKVSCKASGYSFTGYTMNWVRQAPGQGLEWMGLINPYNSDTNYAQKL QGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCARVALRVALDYWGQGTLVTVSSTTTPAPRP PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
513	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGSIGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDSRGYGDYRLGGAYWGQGTLVTVSSG GGGSGGGGSGGGGSEIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLI YGASTRATGIPARFSGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPWTFGQGTKVEIKTTT PAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVI TLYC
514	EIVMTQSPATLSVSPGERATLSCRASQSVSSNLAWYQQKPGQAPRLLIYGASTRATGIPARF SGSGSGTEFTLTISSLQSEDFAVYYCQQYNNWPWTFGQGTKVEIKGGGGSGGGGSGGGGSEV QLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGSIGYADSV KGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKDSRGYGDYRLGGAYWGQGTLVTVSSTTT PAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVI TLYC
515	EVQLVQSGAEVKKPGASVKVSCKASGFSFTNYYVHWMRQAPGQGLEWMGWISPGSDNTKYNE KFKGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARDDYGNYYFDYWGQGTTVTVSSGGGGS GGGGSGGGGSDIVMTQSPDSLAVSLGERATINCKSSQSLLNSRTRKNYLAWYQQKPGQPPKL LIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQSYILRTFGGGTKVEIKTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLV ITLYC
516	DIVMTQSPDSLAVSLGERATINCKSSQSLLNSRTRKNYLAWYQQKPGQPPKLLIYWASTRES GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQSYILRTFGGGTKVEIKGGGGSGGGGSGG GGSEVQLVQSGAEVKKPGASVKVSCKASGFSFTNYYVHWMRQAPGQGLEWMGWISPGSDNTK

	YNEKFKGRVTMTRDTSISTAYMELSRLRSDDTAVYYCARDDYGNYYFDYWGQGTTVTVSSTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLV ITLYC
517	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSKGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYGSGYGKFYHYGLDVWGQGTTVTVSS GGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIKT TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSL VITLYC
518	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIKGGGGSGGGGSGGGGSE VQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSKGYADS VKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYGSGYGKFYHYGLDVWGQGTTVTVSST TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSL VITLYC
519	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSIGYAD SVKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYGSGYGKFYYYGMDVWGQGTTVTVSS GGGGSGGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLL IYAASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIKT TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSL VITLYC
520	DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRF SGSGSGTDFTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIKGGGGSGGGGSGGGGSE VQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSIGYADS VKGRFTISRDNAKNSLYLQMNSLRAEDTALYYCAKYGSGYGKFYYYGMDVWGQGTTVTVSST TTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSL VITLYC
521	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGNSYVSYFAYWGQGTTVTVS SGGGGSGGGGSGGGGSEIVVTQSPATLSVSPGERATLSCRSSTGAVTESNYANWVQEKPGQA FRGLIGGANKRAPGVPARFSGSLSGDEATLTISSLQSEDFAVYYCALFYSNTWVFGQGTKLE IKTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL LSLVITLYC
522	EIVVTQSPATLSVSPGERATLSCRSSTGAVTESNYANWVQEKPGQAFRGLIGGANKRAPGVP ARFSGSLSGDEATLTISSLQSEDFAVYYCALFYSNTWVFGQGTKLEIKGGGGSGGGGSGGGG SEVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATY YADSVKGRFTISRDDSKNTLYLQMNSLRAEDTAVYYCVRHGNFGNSYVSYFAYWGQGTTVTV SSTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLL LSLVITLYC
523	EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVS SGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAP RGLIGGTKFLAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
524	QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGNYPNWVQQKPGQAPRGLIGGTKFLAPGTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCVLWYSNRWVFGGGTKLTVLGGGGSGGGGSGGGGS EVQLVESGGGLVQPGGSLKLSCAASGFTFNKYAMNWVRQAPGKGLEWVARIRSKYNNYATYY ADSVKDRFTISRDDSKNTAYLQMNNLKTEDTAVYYCVRHGNFGNSYISYWAYWGQGTLVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
525	EVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMTWVRQAPGKGLEWVAFIRNRARGYTSDH NPSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDRPSYYVLDYWGQGTTVTVSSGGG GSGGGGSGGGGSDIVMTQSPDSLAVSLGERATINCKSSQSLFNVRSRKNYLAWYQQKPGQPP KLLISWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQSYDLFTFGSGTKLEIK TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLS LVITLYC
526	DIVMTQSPDSLAVSLGERATINCKSSQSLFNVRSRKNYLAWYQQKPGQPPKLLISWASTRES GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQSYDLFTFGSGTKLEIKGGGGSGGGGSGG

	GGSEVQLVESGGGLVQPGGSLRLSCAASGFTFSDYYMTWVRQAPGKGLEWVAFIRNRARGYT SDHNPSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDRPSYYVLDYWGQGTTVTVSS TTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLS LVITLYC
527	EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY AASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARHGNFGNSYVSWFAYWGQGTLVTVS SGGGGSGGGGSGGGGSQTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAP RGLIGGTNKRAPGTPARFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTV LTTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
528	QTVVTQEPSLTVSPGGTVTLTCRSSTGAVTTSNYANWVQQKPGQAPRGLIGGTNKRAPGTPA RFSGSLLGGKAALTLSGVQPEDEAEYYCALWYSNLWVFGGGTKLTVLGGGGSGGGGSGGGGS EVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGKGLEWVARIRSKYNNYATYY AASVKGRFTISRDDSKNSLYLQMNSLKTEDTAVYYCARHGNFGNSYVSWFAYWGQGTLVTVS STTTPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLL SLVITLYC
529	QVQLVQSGAEVKKPGASVKVSCKASGFNIKDYYMHWVRQAPGQRLEWMGWIDLENANTIYDA KFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCARDAYGRYFYDVWGQGTLVTVSSGGGGS GGGGSGGGGSDIVMTQSPDSLAVSLGERATINCKSSQSLLNARTGKNYLAWYQQKPGQPPKL LIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQSYSRRTFGGGTKVEIKTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLV ITLYC
530	DIVMTQSPDSLAVSLGERATINCKSSQSLLNARTGKNYLAWYQQKPGQPPKLLIYWASTRES GVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCKQSYSRRTFGGGTKVEIKGGGGSGGGGSGG GGSQVQLVQSGAEVKKPGASVKVSCKASGFNIKDYYMHWVRQAPGQRLEWMGWIDLENANTI YDAKFQGRVTITRDTSASTAYMELSSLRSEDTAVYYCARDAYGRYFYDVWGQGTLVTVSSTT TPAPRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLV ITLYC
531	QVQLVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGYINPSRGYTNYNQ KVKDRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYCLDYWGQGTPVTVSSGGGGS GGGGSGGGGSDIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSK LASGVPSRFSGSGSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFGQGTKLQITTTTPAPRP PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
532	DIQMTQSPSSLSASVGDRVTITCSASSSVSYMNWYQQTPGKAPKRWIYDTSKLASGVPSRFS GSGSGTDYTFTISSLQPEDIATYYCQQWSSNPFTFGQGTKLQITGGGGSGGGGSGGGGSQVQ LVQSGGGVVQPGRSLRLSCKASGYTFTRYTMHWVRQAPGKGLEWIGYINPSRGYTNYNQKVK DRFTISRDNSKNTAFLQMDSLRPEDTGVYFCARYYDDHYCLDYWGQGTPVTVSSTTTPAPRP PTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYC
533	QVQLVQSGPEVKKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQ KFKDRVTITADKSTSTAYMELSSLRSEDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSSGGG GSGGGGSGGGGSDIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRWIYDS SKLASGVPSRFSGSGSGTEYTLTISSLQPDDFATYYCQQWSRNPPTFGGGTKVEIKRTTTPA PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITL YC
534	DIQMTQSPSTLSASVGDRVTMTCSASSSVSYMNWYQQKPGKAPKRWIYDSSKLASGVPSRFS GSGSGTEYTLTISSLQPDDFATYYCQQWSRNPPTFGGGTKVEIKRGGGGSGGGGSGGGGSQV QLVQSGPEVKKPGSSVKVSCKASGYTFSRSTMHWVRQAPGQGLEWIGYINPSSAYTNYNQKF KDRVTITADKSTSTAYMELSSLRSEDTAVYYCARPQVHYDYNGFPYWGQGTLVTVSSTTTPA PRPPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITL YC
535	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASSPTPS PTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSLDNA SAFNTTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDVPGERSTA STFPTDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASETTTLSPSGSAVISTT TIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNNEVHNLTECKNA SVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIETFTCDTQNITYR

	FQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGEPQIIFCRSE AAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLHAYIIA KVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNT LVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSKALIAFLAFLIIV TSIALLVVLYKIYD
536	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASSPTPS PTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSLDNA SAFNTTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDVPGERSTA STFPTDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASETTTLSPSGSAVISTT TIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNNEVHNLTECKNA SVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIETFTCDTQNITYR FQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGEPQIIFCRSE AAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLHAYIIA KVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNT LVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSKALIAFLAFLIIV TSIALLVVLYKIYD
537	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASSPTPS PTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNV NENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEK ADTTICLKWKNIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKF TNASKIIKTDFGSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKN LIKYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMH VKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGE PFILHHSTSYNSKALIAFLAFLIIVTSIALLVVLYKIYD
538	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASSPTPS PTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNV NENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEK ADTTICLKWKNIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKF TNASKIIKTDFGSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKN LIKYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMH VKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGE PFILHHSTSYNSKALIAFLAFLIIVTSIALLVVLYKIYD
539	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASSPTPS PTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSLDNA SAFNTTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDAYLNASET TTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTC TNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKN IETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDF GSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKP YTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNG PHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYN SKALIAFLAFLIIVTSIALLVVLYKIYD
540	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASSPTPS PTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSLDNA

	SAFNTTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDAYLNASET TTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTC TNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKN IETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDF GSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKP YTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNG PHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYN SKALIAFLAFLIIVTSIALLVVLYKIYD
541	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASSPTPS PTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSLDNA SAFNTTDVPGERSTASTFPTDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASE TTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNT CTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWK NIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTD FGSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLK PYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRN GPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSY NSKALIAFLAFLIIVTSIALLVVLYKIYD
542	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASSPTPS PTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSLDNA SAFNTTDVPGERSTASTFPTDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASE TTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNT CTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWK NIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTD FGSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLK PYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRN GPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSY NSKALIAFLAFLIIVTSIALLVVLYKIYD
543	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASSPTPS PTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDVPGERSTASTFP TDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASETTTLSPSGSAVISTTTIAT TPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNNEVHNLTECKNASVSI SHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIETFTCDTQNITYRFQCG NMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGEPQIIFCRSEAAHQ GVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLHAYIIAKVQR NGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRN ESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSKALIAFLAFLIIVTSIA LLVVLYKIYD
544	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASSPTPS PTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDVPGERSTASTFP TDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASETTTLSPSGSAVISTTTIAT TPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNNEVHNLTECKNASVSI SHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIETFTCDTQNITYRFQCG NMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPGEPQIIFCRSEAAHQ GVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKYVLSLHAYIIAKVQR NGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRN ESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSKALIAFLAFLIIVTSIA

	LLVVLYKIYD
545	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASSPTPS PTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSLDNA SAFNTTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTA KLNVNENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCT QVEKADTTICLKWKNIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYN NHKFTNASKIIKTDFGSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLN LDKNLIKYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSD NSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGD YPGEPFILHHSTSYNSKALIAFLAFLIIVTSIALLVVLYKIYD
546	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASSPTPS PTGLTTAKMPSVPLSSDPLPTHTTAFSPASTFERENDFSETTTSLSPDNTSTQVSPDSLDNA SAFNTTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTA KLNVNENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCT QVEKADTTICLKWKNIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYN NHKFTNASKIIKTDFGSPGEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLN LDKNLIKYDLQNLKPYTKYVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSD NSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGD YPGEPFILHHSTSYNSKALIAFLAFLIIVTSIALLVVLYKIYD
547	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASSPTPS PTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDAYLNASETTTLS PSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNNE VHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIETF TCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPG EPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKY VLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHER YHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSKAL IAFLAFLIIVTSIALLVVLYKIYD
548	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASSPTPS PTGVSSVQTPHLPTHADSQTPSAGTDTQTFSGSAANAKLNPTPGSNAISDAYLNASETTTLS PSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNNE VHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIETF TCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSPG EPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTKY VLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHER YHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSKAL IAFLAFLIIVTSIALLVVLYKIYD
549	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASSPTPS PTDVPGERSTASTFPTDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASETTTL SPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNN EVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIET FTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSP GEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTK YVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHE

	RYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSKA LIAFLAFLIIVTSIALLVVLYKIYD
550	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASSPTPS PTDVPGERSTASTFPTDPVSPLTTTLSLAHHSSAALPARTSNTTITANTSDAYLNASETTTL SPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNVNENVECGNNTCTNN EVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEKADTTICLKWKNIET FTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKFTNASKIIKTDFGSP GEPQIIFCRSEAAHQGVITWNPPQRSFHNFTLCYIKETEKDCLNLDKNLIKYDLQNLKPYTK YVLSLHAYIIAKVQRNGSAAMCHFTTKSAPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHE RYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSKA LIAFLAFLIIVTSIALLVVLYKIYD
551	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASSPTPS PTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNV NENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEK ADTTICLKWKNIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKF TNASKIIKTDFGSPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNE SHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSKALIAFLAFLIIVTSIAL LVVLYKIYD
552	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASSPTPS PTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNV NENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPGVEKFQLHDCTQVEK ADTTICLKWKNIETFTCDTQNITYRFQCGNMIFDNKEIKLENLEPEHEYKCDSEILYNNHKF TNASKIIKTDFGSPPSQVWNMTVSMTSDNSMHVKCRPPRDRNGPHERYHLEVEAGNTLVRNE SHKNCDFRVKDLQYSTDYTFKAYFHNGDYPGEPFILHHSTSYNSKALIAFLAFLIIVTSIAL LVVLYKIYD
553	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASSPTPS PTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNV NENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPSQVWNMTVSMTSDNS MHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYP GEPFILHHSTSYNSKALIAFLAFLIIVTSIALLVVLYKIYD
554	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASSPTPS PTDAYLNASETTTLSPSGSAVISTTTIATTPSKPTCDEKYANITVDYLYNKETKLFTAKLNV NENVECGNNTCTNNEVHNLTECKNASVSISHNSCTAPDKTLILDVPPSQVWNMTVSMTSDNS MHVKCRPPRDRNGPHERYHLEVEAGNTLVRNESHKNCDFRVKDLQYSTDYTFKAYFHNGDYP GEPFILHHSTSYNSKALIAFLAFLIIVTSIALLVVLYKIYD
555	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASAPIPE PRTIFFCERNPKPQVINIIDADLPPNTSPFTAELTHGASANWTIQYNDPTQESIILKPKMAL EVGDYKINLKLMDNQNKDQVTTLEVSVCDCEGAAGVCRKAQPVEAGLQIPAILGILGGILAL LILILLLLLFLRRRA
556	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV

	QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASAPIPE PRTIFFCERNPKPQVINIIDADLPPNTSPFTAELTHGASANWTIQYNDPTQESIILKPKMAL EVGDYKINLKLMDNQNKDQVTTLEVSVCDCEGAAGVCRKAQPVEAGLQIPAILGILGGILAL LILILLLLLFLRRRA
557	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASAPIFV PPEKRVEVSEDFGVGQEITSYTAQEPDTFMEQKITYRIWRDTANWLEINPDTGAISTRAELD REDFEHVKNSTYTALIIATDNGSPVATGTGTLLLILSDVNDNAPIPEPRTIFFCERNPKPQV INIIDADLPPNTSPFTAELTHGASANWTIQYNDPTQESIILKPKMALEVGDYKINLKLMDNQ NKDQVTTLEVSVCDCEGAAGVCRKAQPVEAGLQIPAILGILGGILALLILILLLLLFLRRRA
558	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASAPIFV PPEKRVEVSEDFGVGQEITSYTAQEPDTFMEQKITYRIWRDTANWLEINPDTGAISTRAELD REDFEHVKNSTYTALIIATDNGSPVATGTGTLLLILSDVNDNAPIPEPRTIFFCERNPKPQV INIIDADLPPNTSPFTAELTHGASANWTIQYNDPTQESIILKPKMALEVGDYKINLKLMDNQ NKDQVTTLEVSVCDCEGAAGVCRKAQPVEAGLQIPAILGILGGILALLILILLLLLFLRRRA
559	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASNPPIF NPTTYKGQVPENEANVVITTLKVTDADAPNTPAWEAVYTILNDDGGQFVVTTNPVNNDGILK TAKGLDFEAKQQYILHVAVTNVVPFEVSLTTSTATVTVDVLDVNEAPIFVPPEKRVEVSEDF GVGQEITSYTAQEPDTFMEQKITYRIWRDTANWLEINPDTGAISTRAELDREDFEHVKNSTY TALIIATDNGSPVATGTGTLLLILSDVNDNAPIPEPRTIFFCERNPKPQVINIIDADLPPNT SPFTAELTHGASANWTIQYNDPTQESIILKPKMALEVGDYKINLKLMDNQNKDQVTTLEVSV CDCEGAAGVCRKAQPVEAGLQIPAILGILGGILALLILILLLLLFLRRRA
560	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASNPPIF NPTTYKGQVPENEANVVITTLKVTDADAPNTPAWEAVYTILNDDGGQFVVTTNPVNNDGILK TAKGLDFEAKQQYILHVAVTNVVPFEVSLTTSTATVTVDVLDVNEAPIFVPPEKRVEVSEDF GVGQEITSYTAQEPDTFMEQKITYRIWRDTANWLEINPDTGAISTRAELDREDFEHVKNSTY TALIIATDNGSPVATGTGTLLLILSDVNDNAPIPEPRTIFFCERNPKPQVINIIDADLPPNT SPFTAELTHGASANWTIQYNDPTQESIILKPKMALEVGDYKINLKLMDNQNKDQVTTLEVSV CDCEGAAGVCRKAQPVEAGLQIPAILGILGGILALLILILLLLLFLRRRA
561	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASPEFTQ EVFKGSVMEGALPGTSVMEVTATDADDDVNTYNAAIAYTILSQDPELPDKNMFTINRNTGVI SVVTTGLDRESFPTYTLVVQAADLQGEGLSTTATAVITVTDTNDNPPIFNPTTYKGQVPENE ANVVITTLKVTDADAPNTPAWEAVYTILNDDGGQFVVTTNPVNNDGILKTAKGLDFEAKQQY ILHVAVTNVVPFEVSLTTSTATVTVDVLDVNEAPIFVPPEKRVEVSEDFGVGQEITSYTAQE PDTFMEQKITYRIWRDTANWLEINPDTGAISTRAELDREDFEHVKNSTYTALIIATDNGSPV ATGTGTLLLILSDVNDNAPIPEPRTIFFCERNPKPQVINIIDADLPPNTSPFTAELTHGASA NWTIQYNDPTQESIILKPKMALEVGDYKINLKLMDNQNKDQVTTLEVSVCDCEGAAGVCRKA QPVEAGLQIPAILGILGGILALLILILLLLLFLRRRA
562	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASPEFTQ EVFKGSVMEGALPGTSVMEVTATDADDDVNTYNAAIAYTILSQDPELPDKNMFTINRNTGVI SVVTTGLDRESFPTYTLVVQAADLQGEGLSTTATAVITVTDTNDNPPIFNPTTYKGQVPENE

	ANVVITTLKVTDADAPNTPAWEAVYTILNDDGGQFVVTTNPVNNDGILKTAKGLDFEAKQQY ILHVAVTNVVPFEVSLTTSTATVTVDVLDVNEAPIFVPPEKRVEVSEDFGVGQEITSYTAQE PDTFMEQKITYRIWRDTANWLEINPDTGAISTRAELDREDFEHVKNSTYTALIIATDNGSPV ATGTGTLLLILSDVNDNAPIPEPRTIFFCERNPKPQVINIIDADLPPNTSPFTAELTHGASA NWTIQYNDPTQESIILKPKMALEVGDYKINLKLMDNQNKDQVTTLEVSVCDCEGAAGVCRKA QPVEAGLQIPAILGILGGILALLILILLLLLFLRRRA
563	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASPELPK PSISSNNSKPVEDKDAVAFTCEPETQDATYLWWVNNQSLPVSPRLQLSNGNRTLTLFNVTRN DTASYKCETQNPVSARRSDSVILNVLYGPDAPTISPLNTSYRSGENLNLSCHAASNPPAQYS WFVNGTFQQSTQELFIPNITVNNSGSYTCQAHNSDTGLNRTTVTTITVYAEPPKPFITSNNS NPVEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRNDVGPYECG IQNELSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWLIDGNIQ QHTQELFISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSNNSKPVEDKDA VAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDARAYVCGIQNSVSAN RSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFI AKITPNNNGTYACFVSNLATGRNNSIVKSITVSKALIAFLAFLIIVTSIALLVVLYKIYD
564	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASPELPK PSISSNNSKPVEDKDAVAFTCEPETQDATYLWWVNNQSLPVSPRLQLSNGNRTLTLFNVTRN DTASYKCETQNPVSARRSDSVILNVLYGPDAPTISPLNTSYRSGENLNLSCHAASNPPAQYS WFVNGTFQQSTQELFIPNITVNNSGSYTCQAHNSDTGLNRTTVTTITVYAEPPKPFITSNNS NPVEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRNDVGPYECG IQNELSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWLIDGNIQ QHTQELFISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSNNSKPVEDKDA VAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDARAYVCGIQNSVSAN RSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFI AKITPNNNGTYACFVSNLATGRNNSIVKSITVSKALIAFLAFLIIVTSIALLVVLYKIYD
565	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASPELPK PSISSNNSKPVEDKDAVAFTCEPETQDATYLWWVNNQSLPVSPRLQLSNGNRTLTLFNVTRN DTASYKCETQNPVSARRSDSVILNVLYGPDAPTISPLNTSYRSGENLNLSCHAASNPPAQYS WFVNGTFQQSTQELFIPNITVNNSGSYTCQAHNSDTGLNRTTVTTITVYAEPPKPFITSNNS NPVEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRNDVGPYECG IQNELSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWLIDGNIQ QHTQELFISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSNNSKPVEDKDA VAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDARAYVCGIQNSVSAN RSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFI AKITPNNNGTYACFVSNLATGRNNSIVKSITVSA
566	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASPELPK PSISSNNSKPVEDKDAVAFTCEPETQDATYLWWVNNQSLPVSPRLQLSNGNRTLTLFNVTRN DTASYKCETQNPVSARRSDSVILNVLYGPDAPTISPLNTSYRSGENLNLSCHAASNPPAQYS WFVNGTFQQSTQELFIPNITVNNSGSYTCQAHNSDTGLNRTTVTTITVYAEPPKPFITSNNS NPVEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRNDVGPYECG IQNELSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWLIDGNIQ QHTQELFISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSNNSKPVEDKDA VAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDARAYVCGIQNSVSAN RSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFI AKITPNNNGTYACFVSNLATGRNNSIVKSITVSA
567	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD

	SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASPPKPF ITSNNSNPVEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRNDV GPYECGIQNELSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWL IDGNIQQHTQELFISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSNNSKP VEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDARAYVCGIQ NSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQH TQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVSA
568	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASPPKPF ITSNNSNPVEDEDAVALTCEPEIQNTTYLWWVNNQSLPVSPRLQLSNDNRTLTLLSVTRNDV GPYECGIQNELSVDHSDPVILNVLYGPDDPTISPSYTYYRPGVNLSLSCHAASNPPAQYSWL IDGNIQQHTQELFISNITEKNSGLYTCQANNSASGHSRTTVKTITVSAELPKPSISSNNSKP VEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRNDARAYVCGIQ NSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQH TQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVSA
569	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASAELPK PSISSNNSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRN DARAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYS WRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVSA
570	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASAELPK PSISSNNSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSNGNRTLTLFNVTRN DARAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNLSCHSASNPSPQYS WRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVSA
571	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASPDAPT ISPLNTSYRSGENLNLSCHAASNPPAQYSWFVNGTFQQSTQELFIPNITVNNSGSYTCQAHN SDTGLNRTTVTTITVYAEPPKPFITSNNSNPVEDEDAVALTCEPEIQNTTYLWWVNNQSLPV SPRLQLSNDNRTLTLLSVTRNDVGPYECGIQNELSVDHSDPVILNVLYGPDDPTISPSYTYY RPGVNLSLSCHAASNPPAQYSWLIDGNIQQHTQELFISNITEKNSGLYTCQANNSASGHSRT TVKTITVSAELPKPSISSNNSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSN GNRTLTLFNVTRNDARAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNL SCHSASNPSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVS A
572	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASPDAPT ISPLNTSYRSGENLNLSCHAASNPPAQYSWFVNGTFQQSTQELFIPNITVNNSGSYTCQAHN SDTGLNRTTVTTITVYAEPPKPFITSNNSNPVEDEDAVALTCEPEIQNTTYLWWVNNQSLPV SPRLQLSNDNRTLTLLSVTRNDVGPYECGIQNELSVDHSDPVILNVLYGPDDPTISPSYTYY RPGVNLSLSCHAASNPPAQYSWLIDGNIQQHTQELFISNITEKNSGLYTCQANNSASGHSRT TVKTITVSAELPKPSISSNNSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPVSPRLQLSN GNRTLTLFNVTRNDARAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSYLSGANLNL SCHSASNPSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNSIVKSITVS A
573	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG

	SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASPDDPT ISPSYTYYRPGVNLSLSCHAASNPPAQYSWLIDGNIQQHTQELFISNITEKNSGLYTCQANN SASGHSRTTVKTITVSAELPKPSISSNNSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPV SPRLQLSNGNRTLTLFNVTRNDARAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSY LSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNS IVKSITVSA
574	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASPDDPT ISPSYTYYRPGVNLSLSCHAASNPPAQYSWLIDGNIQQHTQELFISNITEKNSGLYTCQANN SASGHSRTTVKTITVSAELPKPSISSNNSKPVEDKDAVAFTCEPEAQNTTYLWWVNGQSLPV SPRLQLSNGNRTLTLFNVTRNDARAYVCGIQNSVSANRSDPVTLDVLYGPDTPIISPPDSSY LSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSNLATGRNNS IVKSITVSA
575	DVQLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYAD SVKGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSSGGGG SGGGGSGGGGSDIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTS KVASGVPARFSGSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKASPDTPI ISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSN LATGRNNSIVKSITVSA
576	DIVLTQSPATLSLSPGERATLSCRASQSVSYMNWYQQKPGKAPKRWIYDTSKVASGVPARFS GSGSGTDYSLTINSLEAEDAATYYCQQWSSNPLTFGGGTKVEIKSGGGGSGGGGSGGGGSDV QLVQSGAEVKKPGASVKVSCKASGYTFTRYTMHWVRQAPGQGLEWIGYINPSRGYTNYADSV KGRFTITTDKSTSTAYMELSSLRSEDTATYYCARYYDDHYCLDYWGQGTTVTVSSASPDTPI ISPPDSSYLSGANLNLSCHSASNPSPQYSWRINGIPQQHTQVLFIAKITPNNNGTYACFVSN LATGRNNSIVKSITVSA

d. Additional Tropism Polypeptides

Recombinant particles contemplated herein comprise at least one non-viral membrane-bound tropism polypeptide. In particular embodiments, it may be preferred, and in some cases necessary or advantageous, to engineer a recombinant particle that comprises at least one additional non-viral membrane-bound tropism polypeptide. In some embodiments, a recombinant particle comprises two non-viral membrane-bound tropism polypeptides. In some embodiments, a recombinant particle comprises three non-viral membrane-bound tropism polypeptides.

In particular embodiments, a recombinant particle comprises a lipid bilayer, cell membrane, or viral envelope comprising one or more mutated viral envelope glycoproteins that mediate fusion of the viral particle with a cell but that do not bind its cognate receptor expressed on a cell, and at least two non-viral membrane-bound tropism polypeptides, *e.g.,* a primary and/or secondary non-viral membrane bound tropism polypeptide, that direct the particle to bind one or more specific antigens expressed on a desired cell type, *e.g.,* an immune effector cell. In preferred embodiments, the recombinant particle is a recombinant viral particle, *e.g.,* a retroviral or lentiviral particle.

In particular embodiments, wherein a recombinant particle comprises at least two non-viral membrane-bound tropism polypeptides, each non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain that binds an antigen expressed on an immune effector cell; a spacer polypeptide, a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a recombinant particle comprises at least two non-viral membrane-bound tropism polypeptides, one non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain that binds an antigen expressed on an immune effector cell including but not limited to the alpha, beta, gamma, or delta chain of the T cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD8α, and CD8β; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain; and another non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain that an antigen expressed on an immune effector cell including but not limited to the alpha or beta chain of a TCR, CD28, CD134 (OX40), CD137 (4-1BB), and CD278 (ICOS); a spacer polypeptide, a transmembrane domain or GPI anchor; and optionally an intracellular domain.

In particular embodiments, a recombinant particle comprises at least two non-viral membrane-bound tropism polypeptides, one non-viral membrane-bound tropism polypeptide comprises an extracellular antigen targeting domain that binds an antigen expressed on an immune effector cell including but not limited to the alpha, beta, gamma, or delta chain of the T cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD8α, and CD8β; a spacer polypeptide; a transmembrane domain or GPI anchor; and optionally an intracellular domain; and another non-viral membrane bound tropism polypeptide comprises all or part of a costimulatory molecule including but not limited to CD80, CD86, OX40L, 4-1BBL, and ICOSL or a functional fragment thereof. In particular embodiments, the functional fragment is a CD80, CD86, OX40L, 4-1BBL, and ICOSL comprising a C-terminal truncation that results in a cytoplasmic domain of about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids or more). In particular embodiments, the functional fragment comprises, consists essentially of, or consists of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581.

In particular embodiments, a recombinant particle comprises a first non-viral membrane-bound tropism polypeptide comprising an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising a

CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, and CDRL3, a VH and VL, and/or an scFv set forth in Table 5; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, and SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440, and 441; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids; and a second non-viral membrane bound tropism polypeptide comprising, consisting essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581.

In particular embodiments, a recombinant particle comprising a first non-viral membrane-bound tropism polypeptide comprising an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, and SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440, and 441; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids; and a second non-viral membrane bound tropism polypeptide comprising, consisting essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581.

In particular embodiments, a recombinant particle comprising a non-viral membrane-bound tropism polypeptide comprising an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350,

359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410; a spacer polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, and SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440, and 441; and optionally, an intracellular domain of no more than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids; and a second non-viral membrane bound tropism polypeptide comprising, consisting essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581.

In particular embodiments, a recombinant particle comprising a non-viral membrane-bound tropism polypeptide comprising an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, and 170; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 412, and 413, SEQ ID NOs: 414, 415, 416, 417, 418, 419, 420, 421, 422, and 423, SEQ ID NOs: 424, 425, 426, and 427, and SEQ ID NOs: 428, 429, 430, 431, 432, 433, and 434; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440, and 441; and optionally, an intracellular domain comprising, consisting essentially of, or consisting of one, two, three, four, five, or six of the amino acids set forth in any one of SEQ ID NOs: 442, 443, 444, 445, 446, 447 and 448; and a second non-viral membrane bound tropism polypeptide comprising, consisting essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581.

In particular embodiments, a recombinant particle comprising a non-viral membrane-bound tropism polypeptide comprising an extracellular antigen targeting domain comprising an anti-CD3ε antibody or antigen binding fragment thereof comprising the amino acid sequence set forth in any one of SEQ ID NOs: 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, and 170; a spacer comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 411, 423, and 428; a transmembrane domain comprising an amino acid sequence set forth in any one of SEQ ID NOs: 437 and 439; and optionally, an intracellular domain comprising, consisting essentially of, or consisting of one, two, three, four, five, or six of the amino acids set forth in any one of SEQ ID NOs 444 and 446; and a second non-viral membrane bound tropism polypeptide comprising, consisting

essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581.

In particular embodiments, a recombinant particle comprising a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOs: 461, 471, 483, 537, and 553; and a second non-viral membrane bound tropism polypeptide comprising, consisting essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581. In particular embodiments, a recombinant particle comprising a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 461; and a second non-viral membrane bound tropism polypeptide comprising, consisting essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581. In particular embodiments, a recombinant particle comprising a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 471; and a second non-viral membrane bound tropism polypeptide comprising, consisting essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581. In particular embodiments, a recombinant particle comprising a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 483; and a second non-viral membrane bound tropism polypeptide comprising, consisting essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581. In particular embodiments, a recombinant particle comprising a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 537; and a second non-viral membrane bound tropism polypeptide comprising, consisting essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581. In particular embodiments, a recombinant particle comprising a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 553; and a second non-viral membrane bound tropism polypeptide comprising, consisting essentially of, or consisting of the amino acid sequence set forth in any one of SEQ ID NOs: 577, 578, 579, 580, and 581.

Table 11

SEQ ID NO:	AMINO ACID SEQUENCE
577	VIHVTKEVKEVATLSCGHNVSVEELAQTRIYWQKEKKMVLTMMSGDMNIWPEYKNRTIFDITNN LSIVILALRPSDEGTYECVVLKYEKDAFKREHLAEVTLSVKADFPTPSISDFEIPTSNIRRIIC STSGGFPEPHLSWLENGEELNAINTTVSQDPETELYAVSSKLDFNMTTNHSFMCLIKYGHLRVN

	QTFNWNTTKQEHFPDNLLPSWAITLISVNGIFVICCLTYCFAPRCRE
578	APLKIQAYFNETADLPCQFANSQNQSLSELVVFWQDQENLVLNEVYLGKEKFDSVHSKYMGRTS FDSDSWTLRLHNLQIKDKGLYQCIIHHKKPTGMIRIHQMNSELSVLANFSQPEIVPISNITENV YINLTCSSIHGYPEPKKMSVLLRTKNSTIEYDGVMQKSQDNVTELYDVSISLSVSFPDVTSNMT IFCILETDKTRLLSSPFSIELEDPQPPPDHIPWITAVLPTVIICVMVFCLILWKWKKKKR
579	RVLPWALVAGLLLLLLLAAACAVFLACPWAVSGARASPGSAASPRLREGPELSPDDPAGLLDLR QGMFAQLVAQNVLLIDGPLSWYSDPGLAGVSLTGGLSYKEDTKELVVAKAGVYYVFFQLELRRV VAGEGSGSVSLALHLQPLRSAAGAAALALTVDLPPASSEARNSAFGFQGRLLHLSAGQRLGVHL HTEARARHAWQLTQGATVLGLFRVTPEIPAGLPSPRSE
580	ERNKLLLVASVIQGLGLLLCFTYICLHFSALQVSHRYPRIQSIKVQFTEYKKEKGFILTSQKED EIMKVQNNSVIINCDGFYLISLKGYFSQEVNISLHYQKDEEPLFQLKKVRSVNSLMVASLTYKD KVYLNVTTDNTSLDDFHVNGGELILIHQNPGEFCVL
581	DTQEKEVRAMVGSDVELSCACPEGSRFDLNDVYVYWQTSESKTVVTYHIPQNSSLENVDSRYRN RALMSPAGMLRGDFSLRLFNVTPQDEQKFHCLVLSQSLGFQEVLSVEVTLHVAANFSVPVVSAP HSPSQDELTFTCTSINGYPRPNVYWINKTDNSLLDQALQNDTVFLNMRGLYDVVSVLRIARTPS VNIGCCIENVLLQQNLTVGSQTGNDIGERDKITENPVSTGEKNAATWSILAVLCLLVVVAVAIG WVCRDRCL

E. PAYLOAD

Recombinant particles contemplated herein are engineered to efficiently deliver a payload comprising one or more polynucleotides, polypeptides, and/or small molecules to a specific cell type recognized by one or more tropism molecules expressed or displayed on the surface of the particle. A payload may comprise one or more polynucleotides, polypeptides, and/or small molecules sufficient to enable gene therapy, gene editing, or cell therapy. In particular embodiments, the payload is a therapeutic payload. Without wishing to be bound to any particular theory it is further contemplated in particular embodiments that once the particle binds to and fuses with a specific cell, the payload is introduced into the cell and either genetically modifies the cell or is maintained episomally in the cell. In particular embodiments, a recombinant particle delivers a payload comprising one or more gene therapy vectors, therapeutic proteins, and/or genome editing compositions to a specified cell-type in a subject *in vivo*.

Recombinant particles contemplated in particular embodiments comprise a surface and a payload: the surface comprising one or more mutated viral envelope glycoproteins that retain fusogenic activity and substantially lack or lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides engineered to bind a desired cell type, *e.g.*, an immune effector cell; and the payload comprising one or more polynucleotide and/or polypeptides. Suitable recombinant particles include but are not limited to a fusosome; an extracellular vesicle, including a microvesicle, an apoptotic body, and an exosome; a lipid nanoparticle; a virus-like particle (VLPs); or a recombinant viral particle.

In particular embodiments, a recombinant particle comprises (i) a surface comprising one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides that bind an antigen expressed on a cell and (ii) a payload comprising one or more vectors.

In particular embodiments, a recombinant particle comprises (i) a surface comprising one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides that bind an antigen expressed on a cell and (ii) a payload comprising a genome editing composition.

1. VECTOR PAYLOADS

Recombinant particles contemplated in particular embodiments comprise (i) a surface comprising one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides that bind an antigen expressed on a cell and (ii) a payload comprising one or more polynucleotides.

In particular embodiments, a payload comprises one or more polynucleotides. Illustrative examples of polynucleotide payloads include but are not limited to: RNAs including but not limited to circRNAs, miRNAs, siRNAs, sgRNAs, shRNAs, or ribozymes; RNAs include therapeutic polypeptides; RNAs including genome editing enzymes and/or donor templates; non-viral vectors and viral vectors.

Illustrative examples non-viral vectors include but are not limited to: plasmids, phagemids, cosmids, artificial chromosomes such as yeast artificial chromosomes (YAC), bacterial artificial chromosomes (BAC), or P1-derived artificial chromosomes (PAC), and bacteriophages such as lambda phage or M13 phage.

Illustrative examples viral vectors include but are not limited to: Adenoviral (Ad) vectors, adeno-associated virus (AAV) vectors, rhabdovirus (*e.g.*, lyssavirus, vesiculovirus) vectors, paramyxovirus (*e.g.*, henipavirus, morbillivirus, respirovirus, rubelavirus) vectors, herpes simplex virus (*e.g.*, HSV-1, HSV-2) vectors, vaccinia virus vectors, and retroviral vectors, preferably lentiviral vectors (LVV). A "viral vector" is a nucleic acid molecule derived from a viral genome that is used to transfer or deliver another nucleic acid to a cell. A viral vector is based on, and derived from, a virus genome that has been engineered to

remove viral accessory proteins but leave elements intact for packaging, reverse transcription and integration. In preferred embodiments, viral vectors contemplated herein comprise a polynucleotide encoding a promoter operably linked to a polynucleotide encoding an engineered receptor, *e.g.,* a chimeric antigen receptor (CAR), a chimeric costimulatory receptor (CCR), an alpha-beta T cell receptor (αβ TCR), a gamma delta T cell receptor (γδ TCR), a dimerizing agent regulated immunoreceptor complex (DARIC), a chimeric TGF-β receptor (CTBR), or a zetakine receptor.

In particular embodiments, a recombinant particle comprises (i) a surface comprising one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides that bind an antigen expressed on a cell and (ii) a payload comprising an adenoviral vector. High-capacity adenoviral vectors (HC-Ads) (third generation) only retain short non-coding regions from the Ad genome (ITRs and ψ signal), which enables the vector tp carry large polynucleotide payloads (~37kb).

In particular embodiments, a recombinant particle comprises (i) a surface comprising one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides that bind an antigen expressed on a cell and (ii) a payload comprising an AAV vector. Recombinant AAV (rAAV) vectors are primarily episomally maintained and have a polynucleotide payload capacity of about 4.7kb. rAAV vectors are typically composed of, at a minimum, a transgene and its regulatory sequences, and 5' and 3' AAV inverted terminal repeats (ITRs). rAAV vectors may comprise ITRs from any one of AAV1, AAV2, AAV3, AAV4, AAV5, AAV6, AAV7, AAV8, AAV9, or AAV10. Construction of rAAV vectors, and production, and purificationof AAV have been disclosed, *e.g.*, in U.S. Patent Nos. 9,169,494; 9,169,492; 9,012,224; 8,889,641; 8,809,058; and 8,784,799, each of which is incorporated by reference herein, in its entirety.

In particular embodiments, a recombinant particle comprises (i) a surface comprising one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides that bind an antigen expressed on a cell and (ii) a payload comprising an HSV vector. HSV vectors are relatively large, *e.g.,* up to 152 kb. Typically, HSV vectors are rendered replication deficient; moreover, one or more essential or non-essential HSV genes are removed from the vector backbone to make room for polynucleotide payloads. Most

replication deficient HSV vectors contain a deletion to remove one or more intermediate-early, early, or late HSV genes to prevent replication. Advantages of the HSV vector are its ability to enter a latent stage that can result in long-term DNA expression and its large viral DNA genome that can accommodate exogenous DNA inserts of up to 25 kb. HSV-based vectors are described in, for example, U.S. Pat. Nos. 5,837,532, 5,846,782, and 5,804,413, and International Patent Applications WO 91/02788, WO 96/04394, WO 98/15637, and WO 99/06583, each of which are incorporated by reference herein in its entirety.

In particular embodiments, a recombinant particle comprises (i) a surface comprising one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides that bind an antigen expressed on a cell and (ii) a payload comprising a retroviral vector or a lentiviral vector. In particular embodiments, a recombinant particle comprises two copies of a vector, a genomic RNA comprising backbone sequences derived from a retrovirus genome, *e.g.*, a lentivirus genome.

In various embodiments, a retroviral vector is engineered or derived from a retrovirus genome selected from the group consisting of: an alpharetrovirus genome, a betaretrovirus genome, a gammaretrovirus genome, a deltaretrovirus genome, or a spumavirus genome (*e.g.*, an epsilonretrovirus genome, a simiispumavirus genome, a bovispumavirus genome, an equispumavirus genome, a felispumavirus genome, and a prosimiispumavirus genome).

In particular embodiments, a retroviral vector comprises a 5′ LTR and a 3′ LTR each isolated, obtained, or derived from a retrovirus genome selected from the group consisting of: an alpharetrovirus genome, a betaretrovirus genome, a gammaretrovirus genome, a deltaretrovirus genome, an epsilonretrovirus genome, and a spumavirus genome.

Illustrative examples of alpharetroviruses from which a retroviral vector may be isolated, obtained, or derived from include but are not limited to avian leukosis virus, avian carcinoma Mill Hill virus 2, avian myeloblastosis virus, avian myelocytomatosis virus 29, avian sarcoma virus CT10, fujinami sarcoma virus, rous sarcoma virus, UR2 sarcoma virus and Y73 sarcoma virus.

Illustrative examples of betaretroviruses from which a retroviral vector may be isolated, obtained, or derived from include but are not limited to mouse mammary tumor virus, Jaagsiekte sheep retrovirus, langur virus, Mason-Pfizer monkey virus, and squirrel monkey retrovirus (SMRV).

Illustrative examples of deltaretroviruses from which a retroviral vector may be isolated, obtained, or derived from include but are not limited to bovine leukemia virus, primate T-lymphotropic virus 1, primate T-lymphotropic virus 2, primate T-lymphotropic virus 3, and primate T-lymphotropic virus 4.

Illustrative examples of epsilonretroviruses from which a retroviral vector may be isolated, obtained, or derived from include but are not limited to walleye dermal sarcoma virus, walleye epidermal hyperplasia virus 1, and walleye epidermal hyperplasia virus 2.

Illustrative examples of gammaretrovirus from which a retroviral vector may be isolated, obtained, or derived from include but are not limited to baboon endogenous virus (BaEV), chick syncytial virus, feline endogenous virus (*e.g.*, RD114), feline leukemia virus (FeLV), Finkel-Biskis-Jinkins murine sarcoma virus, Gardner-Arnstein feline sarcoma virus, gibbon ape leukemia virus (GALV), guinea pig type-C oncovirus, Hardy-Zuckerman feline sarcoma virus, Harvey murine sarcoma virus, Kirsten murine sarcoma virus, koala retrovirus, murine leukemia virus (MLV), Moloney murine leukemia virus (MoMLV), Moloney murine sarcoma virus, porcine endogenous virus (PERV), Porcine type-C oncovirus, reticuloendotheliosis virus (REV), Snyder-Theilen feline sarcoma virus, Trager duck spleen necrosis virus, viper retrovirus, xenotropic murine leukemia virus- related virus (XMRV), and woolly monkey sarcoma virus.

Illustrative examples of spumaviruses from which a retroviral vector may be isolated, obtained, or derived from include but are not limited to simian foamy virus, bovine foamy virus, equine foamy virus, feline foamy virus, human foamy virus (HFV), and brown greater galago prosimian foamy virus.

In particular embodiments, a recombinant particle comprises a recombinant retroviral vector engineered or derived from a retrovirus genome selected from the group consisting of: SMRV, BaEV, RD114, FeLV, GALV, MLV, MoMLV, PERV, REV, XMRV, and HFV; gag and pol from an alpharetrovirus, a betaretrovirus, a gammaretrovirus, a deltaretrovirus, an epsilonretrovirus, or a spumavirus; and a 5′ LTR and a 3′ LTR each isolated, obtained, or derived from a retrovirus genome selected from the group consisting of: an alpharetrovirus genome, a betaretrovirus genome, a gammaretrovirus genome, a deltaretrovirus genome, an epsilonretrovirus genome, and a spumavirus genome.

In particular embodiments, a recombinant particle comprises a recombinant lentiviral vector engineered or derived from a lentivirus genome. Illustrative lentiviruses include, but are not limited to, HIV (human immunodeficiency virus; including HIV type 1, and HIV type

2); visna-maedi virus (VMV); caprine arthritis-encephalitis virus (CAEV); equine infectious anemia virus (EIAV); feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV). In particular embodiments, lentiviral vectors are derived from HIV-1 viral genomes, preferably HIV-1 or HIV-2 viral genomes and more preferably, HIV-1 viral genomes (*i.e.*, HIV-1 cis-acting sequence elements are preferred).

In various embodiments, a lentiviral vector payload contemplated herein comprises two copies of a lentiviral vector-based RNA genome comprising a 5′ long terminal repeat (LTR) comprising R and U5 regions, a Psi (Ψ) packaging signal, a cPPT/FLAP, an export element, a polynucleotide comprising a promoter operably linked to a therapeutic polynucleotide or a polynucleotide encoding a therapeutic polypeptide, a 3′ LTR comprising U3 and R regions, a polyadenylation signal, a poly(A) tail; and optionally one or more of a WPRE or HPRE, one or more microRNA (miRNA) target sequences, an insulator element, a selectable marker, and a cell suicide gene.

The term "long terminal repeat (LTR)," as used herein, refers to elements located at the ends of retroviral polynucleotides which, in their natural sequence context, are direct repeats and contain U3, R and U5 regions. LTRs generally provide functions fundamental to the expression of retroviral genes (*e.g.*, promotion, initiation and polyadenylation of gene transcripts) and to viral replication. The LTR contains numerous regulatory signals including transcriptional control elements, polyadenylation signals and sequences needed for replication and integration of the viral genome. The viral LTR is divided into three regions called U3, R and U5. The U3 region contains the enhancer and promoter elements. The U5 region is the sequence between the primer binding site and the R region and contains the polyadenylation signal. The R (repeat) region is flanked by the U3 and U5 regions. A transfer plasmid, which is used as the vector genome template comprises a 5′ LTR comprising U3, R and/or U5 regions and a 3′ LTR comprising U3, R and/or U5 regions. Adjacent to the 5′ LTR are sequences necessary for reverse transcription of the genome (the tRNA primer binding site) and for efficient packaging of viral RNA into particles (the Psi "Ψ" site). A retroviral vector-based genome packaged in a particle comprises a 5′ LTR comprising R and U5 regions and a 3′ LTR comprising U3 and R regions. The retroviral vector-based genome is reverse transcribed and integrated into the host cell genome as a provector. Through reverse transcription and second strand synthesis of the retroviral vector

genome, provectors comprise two copies of the 3′ LTR, one copy that replaces the 5′ LTR and the 3′ LTR.

A "TAR" element as used herein, refers to the "trans-activation response" genetic element located in the R region of lentiviral vector LTRs. This element interacts with the lentiviral trans-activator (tat) genetic element to enhance lentiviral vector genome replication. In third generation lentiviral vectors, this element is not usually present because lentiviral vector transfer vectors comprise a 5′ LTR U3 region replaced by a heterologous promoter.

An "R region," as used herein, refers to the region within LTRs beginning at the start of the capping group (*i.e.*, the start of transcription) and ending immediately prior to the start of the polyA tract. The R region is also defined as being flanked by the U3 and U5 regions. The R region plays a role during reverse transcription in permitting the transfer of nascent DNA from one end of the genome to the other.

As used herein, a "packaging signal" or "packaging sequence" refers to sequences located within the retroviral genome which are required for insertion of the viral RNA into the viral capsid or particle, see *e.g.*, Clever *et al.*, 1995. J. of Virology, Vol. 69, No. 4; pp. 2101-2109. Several retroviral vectors use the minimal packaging signal (also referred to as the psi [Ψ] or [Ψ+] sequence) needed for encapsidation of the viral genome. Thus, as used herein, the terms "packaging sequence," "packaging signal," "psi" and the symbol "Ψ," are used in reference to the non-coding sequence required for encapsidation of retroviral RNA strands during viral particle formation.

A "FLAP element" or "cPPT/FLAP," as used herein refers to a nucleic acid whose sequence includes the central polypurine tract and central termination sequences (cPPT and CTS) of a lentivirus, *e.g.*, HIV-1 or HIV-2. "FLAP element" and "cPPT/FLAP" may used interchangeably to refer to the foregoing FLAP element. Suitable FLAP elements are described in U.S. Pat. No. 6,682,907 and in Zennou, *et al.*, 2000, Cell, 101:173. During HIV-1 reverse transcription, central initiation of the plus-strand DNA at the central polypurine tract (cPPT) and central termination at the central termination sequence (CTS) lead to the formation of a three-stranded DNA structure: the HIV-1 central DNA flap. While not wishing to be bound by any particular theory, the DNA flap may act as a cis-active determinant of lentiviral genome nuclear import and/or may increase virus titer.

As used herein, an "export element" refers to a cis-acting post-transcriptional regulatory element which regulates the transport of an RNA transcript from the nucleus to the cytoplasm of a cell. Examples of RNA export elements include, but are not limited to,

the human immunodeficiency virus (HIV) rev response element (RRE) (see *e.g.*, Cullen *et al.*, 1991. J. Virol. 65: 1053; and Cullen *et al.*, 1991. Cell 58: 423), the woodchuck hepatitis virus posttranscriptional regulatory element (WPRE), and the hepatitis B virus post-transcriptional regulatory element (HPRE).

Expression of heterologous sequences in viral vectors may be increased by incorporating posttranscriptional regulatory elements, efficient polyadenylation signals, and optionally, transcription termination signals into the vectors. A variety of posttranscriptional regulatory elements can increase expression of a heterologous nucleic acid at the protein, *e.g.*, WPRE, HPRE.

Lentiviral vectors may contain one or more safety enhancements to reduce the risk of replication, insertional mutagenesis, and off-target transduction and/or expression. In particular embodiments, a lentiviral vector comprises one or more or the following safety enhancements: one or more modifications of the 5′ and 3′ LTRs, and cell or tissue specific expression control sequences, *e.g.*, promoters, enhancers, miRNA target sequences. A "modified LTR," as used herein, refers to one or more nucleotide additions, deletions or substitutions in the native HIV-1 5′ LTR and/or 3′ LTR. The skilled artisan would be able to determine whether an LTR is modified by comparison to a reference LTR.

"Self-inactivating" (SIN) vectors, as used herein, refer to replication-defective vectors, *e.g.*, retroviral or lentiviral vectors, in which the right (3′) LTR enhancer-promoter region, known as the U3 region, has been modified (*e.g.*, by deletion or substitution) to prevent viral transcription beyond the first round of viral replication. Self-inactivation is achieved through a deletion in the U3 region of the 3′ LTR of the lentiviral vector transfer plasmid that removes the LTR TATA box (*e.g.*, deletions from -418 to -18), without significant reductions in titers.

An additional safety enhancement is provided by replacing the U3 region of the 5′ LTR with a heterologous promoter to drive transcription of the viral genome during production of recombinant viral particles. Examples of heterologous promoters which can be used include, for example, viral simian virus 40 (SV40) (*e.g.*, early or late), cytomegalovirus (CMV) (*e.g.*, immediate early), Moloney murine leukemia virus (MoMLV), Rous sarcoma virus (RSV), and herpes simplex virus (HSV) (thymidine kinase) promoters.

In particular embodiments, a lentiviral vector integrates into the host cell genome.

In certain embodiments, a lentiviral vector is integration defective, episomal, and does not integrate in the cell genome. As used herein, the term "integration defective lentivirus" or "IDLV" refers to a lentivirus having an integrase that lacks the capacity to integrate the viral vector into the host cell genome. Integration-incompetent viral vectors have been described in patent application WO 2006/010834, which is herein incorporated by reference in its entirety. Illustrative mutations in HIV-1 integrase suitable to reduce integrase activity include, but are not limited to: H12N, H12C, H16C, H16V, S81R, D41A, K42A, H51A, Q53C, D55V, D64E, D64V, E69A, K71A, E85A, E87A, D116N, D116I, D116A, N120G, N120I, N120E, E152G, E152A, K156E, K156A, E157A, K159E, K159A, K160A, R166A, D167A, E170A, H171A, K173A, K186Q, K186T, K188T, E198A, R199C, R199T, R199A, D202A, K211A, Q214L, Q216L, Q221L, W235F, W235E, K236S, K236A, K246A, G247W, D253A, R262A, R263A and K264H. In particular embodiments, an HIV-1 integration deficient integrase comprises a D64V, D161I, D116A, E152G, or E152A mutation; D64V, D116A, and E152G mutations; D64V, D116A, and E152A mutations; or a D64V mutation.

In preferred embodiments, a recombinant particle, *e.g.,* a lentiviral particle, comprises a lentiviral vector comprising a polynucleotide encoding a promoter operably linked to a polynucleotide encoding an engineered receptor, *e.g.*, a chimeric antigen receptor (CAR), a chimeric costimulatory receptor (CCR), an alpha-beta T cell receptor (αβ TCR), a gamma delta T cell receptor (γδ TCR), a dimerizing agent regulated immunoreceptor complex (DARIC), a chimeric TGF-β receptor (CTBR), or a zetakine receptor.

In particular embodiments, a recombinant particle, *e.g.,* a lentiviral particle, comprises a lentiviral vector comprising a polynucleotide encoding a promoter operably linked to a polynucleotide encoding an engineered receptor that binds an antigen selected from the group consisting of alpha folate receptor (FRα), αvβ6 integrin, BAFFR, B cell maturation antigen (BCMA), B7-H3 (CD276), B7-H6, carbonic anhydrase IX (CAIX), CD16, CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD44, CD44v6, CD44v7/8, CD70, CD79a, CD79b, CD123, CD133, CD138, CD171, carcinoembryonic antigen (CEA), claudin 6, (CLDN6), claudin 18 isoform 2 (CLDN18.2), C-type lectin-like molecule-1 (CLL-1), CD2 subset 1 (CS-1), chondroitin sulfate proteoglycan 4 (CSPG4), cutaneous T cell lymphoma-associated antigen 1 (CTAGE1), delta like canonical Notch ligand 3 (DLL3), epidermal growth factor receptor (EGFR), epidermal growth factor receptor variant III (EGFRvIII), epithelial glycoprotein 2 (EGP2), epithelial glycoprotein 40 (EGP40), epithelial cell adhesion

molecule (EPCAM), ephrin type-A receptor 2 (EPHA2), erb-b2 receptor tyrosine kinase 4 (ERBB4), fibroblast activation protein (FAP), Fc Receptor Like 5 (FCRL5), fetal acetylcholinesterase receptor (AchR), ganglioside G2 (GD2), ganglioside G3 (GD3), Glypican-3 (GPC3), G Protein-Coupled Receptor Class C Group 5 Member D (GPCR5D), EGFR family including ErbB2 (HER2), HER2 p95, IL-10Rα, IL-13Rα2, Kappa, cancer/testis antigen 2 (LAGE-1A), Lambda, Lewis-Y (LeY), L1 cell adhesion molecule (L1-CAM), melanoma antigen gene (MAGE)-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGEA10, melanoma antigen recognized by T cells 1 (MelanA or MART1), Mesothelin (MSLN), MUC1, MUC16, MHC class I chain related proteins A (MICA), MHC class I chain related proteins B (MICB), neural cell adhesion molecule (NCAM), cancer/testis antigen 1 (NY-ESO-1); placenta-specific 1 (PLAC1), preferentially expressed antigen in melanoma (PRAME), prostate stem cell antigen (PSCA), prostate-specific membrane antigen (PSMA), receptor tyrosine kinase-like orphan receptor 1 (ROR1), SLAMF7, synovial sarcoma, X breakpoint 2 (SSX2), Survivin, TACI, tumor associated glycoprotein 72 (TAG72), tumor endothelial marker 1 (TEM1/CD248), tumor endothelial marker 7-related (TEM7R), trophoblast glycoprotein (TPBG), UL16-binding protein (ULBP) 1, ULBP2, ULBP3, ULBP4, ULBP5, ULBP6, vascular endothelial growth factor receptor 2 (VEGFR2), and Wilms tumor 1 (WT-1)

a. Chimeric antigen receptor (CAR)

A CAR is a molecule that combines antibody-based specificity for a target antigen with one or more intracellular T cell signaling domains to generate a chimeric protein that exhibits a specific anti-tumor cellular immune activity. In particular embodiments, a recombinant particle, *e.g.,* a retroviral or lentiviral particles, comprises (a) a phospholipid bilayer, a cellular membrane, or a viral envelope comprising (i) one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof that binds an antigen expressed on an immune effector cell, a spacer polypeptide, a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a recombinant retroviral or lentiviral vector comprising a polynucleotide encoding a promoter operably linked to a polynucleotide encoding a CAR.

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to a polynucleotide encoding a CAR comprising a signal peptide, an extracellular antigen binding domain that specifically binds to a target polypeptide expressed on the surface of a cell, a hinge domain, a transmembrane domain, and one or more intracellular signaling domains, and optionally a polynucleotide encoding a posttranscriptional regulatory element, *e.g.,* a WPRE or HPRE.

In particular embodiments, a CAR comprises an extracellular antigen binding domain that comprises an antibody or antigen binding fragment thereof.

In particular embodiments, a CAR comprises an extracellular antigen binding domain that comprises an antibody or antigen binding fragment thereof selected from the group consisting of: a Camel Ig, a Llama Ig, an Alpaca Ig, Ig NAR, a Fab' fragment, a F(ab')2 fragment, a bispecific Fab dimer (Fab2), a trispecific Fab trimer (Fab3), an Fv, a single chain Fv protein ("scFv"), a bis-scFv, $(scFv)_2$, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a Fibronectin type III (FN3) domain antibody, a single-domain antibody (sdAb or nanobody, *e.g.*, a camelid VHH or shark VNAR) and a centyrin that binds an antigen selected from the group consisting of FRα, αvβ6 integrin, BAFFR, BCMA, CD276, B7-H6, CAIX, CD16, CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD44, CD44v6, CD44v7/8, CD70, CD79a, CD79b, CD123, CD133, CD138, CD171, CEA, CLDN6, CLDN18.2, CLL-1, CS-1, CSPG4, CTAGE1, DLL3, EGFR, EGFRvIII, EGP2, EGP40, EPCAM, EPHA2, ERBB4, FAP, FCRL5, AchR, GD2, GD3, GPC3, GPCR5D, HER2, HER2 p95, IL-10Rα, IL-13Rα2, Kappa, LAGE-1A, Lambda, LeY, L1-CAM, MAGE-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGEA10, MART1, MSLN, MUC1, MUC16, MICA, MICB, NCAM, NY-ESO-1, PLAC1, PRAME, PSCA, PSMA, ROR1, SLAMF7, SSX2, Survivin, TACI, TAG72, TEM1/CD248, TEM7R, TPBG, ULBP1, ULBP2, ULBP3, ULBP4, ULBP5, ULBP6, VEGFR2, and WT-1; a hinge domain selected from the group consisting of a CD4 hinge, a CD8β hinge, a CD8α hinge, a CD28 hinge, a CD134 hinge, a CD137 hinge, a CD152 hinge, a CD278 hinge, an IgG1 hinge, an IgG2 hinge, an IgG3 hinge, an IgG4 hinge; a transmembrane domain isolated or derived from a polypeptide selected from the group consisting of an alpha, beta, gamma, or delta chain of the T-cell receptor, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD5, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD152, CD154, CD278, amnionless (AMN), and programmed cell death 1 (PDCD1); a primary signaling domain isolated or derived from a polypeptide selected from the group consisting of FcRγ,

FcRβ, CD3γ, CD3δ, CD3ε, CD3ζ, CD22, CD79a, CD79b, and CD66d; and optionally, one or more costimulatory signaling domains isolated or derived from a polypeptide selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, CARD11, CD2, CD7, CD27, CD28, CD30, CD40, ICAM, CD83, CD94, CD134 (OX40), CD137 (4-1BB), CD278 (ICOS), DAP10, LAT, SLP76, TRAT1, TNFR2, TNFRS14, TNFRS18, TNFRS25, and ZAP70.

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to a polynucleotide encoding a CAR having an amino acid sequence set forth in any one of SEQ ID NOs: 662-666.

Table 12

SEQ ID NO:	AMINO ACID SEQUENCE
662	DIVLTQSPPSLAMSLGKRATISCRASESVTILGSHLIHWYQQKPGQPPTLLIQLASNVQTGVPA RFSGSGSRTDFTLTIDPVEEDDVAVYYCLQSRTIPRTFGGGTKLEIKGSTSGSGKPGSGEGSTK GQIQLVQSGPELKKPGETVKISCKASGYTFTDYSINWVKRAPGKGLKWMGWINTETREPAYAYD FRGRFAFSLETSASTAYLQINNLKYEDTATYFCALDYSYAMDYWGQGTSVTVSSAAATTTPAPR PPTPAPTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKR GRKKLLYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNEL NLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDG LYQGLSTATKDTYDALHMQALPPR
663	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRLHSGVPSRFSG SGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEITGSTSGSGKPGSGEGSTKGEVK LQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRL TIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSSESKYGPPCPPC PMFWVLVVVGGVLACYSLLVTVAFIIFWVKRGRKKLLYIFKQPFMRPVQTTQEEDGCSCRFEEE EGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRRKNPQEGL YNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATKDTYDALHMQALPPR
664	QVKLEESGGGLVQAGRSLRLSCAASEHTFSSHVMGWFRQAPGKERESVAVIGWRDISTSYADSV KGRFTISRDNAKKTLYLQMNSLKPEDTAVYYCAARRIDAADFDSWGQGTQVTVSSGGGGSEVQL VESGGGLVQAGGSLRLSCAASGRTFTMGWFRQAPGKEREFVAAISLSPTLAYYAESVKGRFTIS RDNAKNTVVLQMNSLKPEDTALYYCAADRKSVMSIRPDYWGQGTQVTVSSTSTTTPAPRPPTPA PTIASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKL LYIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYQQGQNQLYNELNLGRR EEYDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGL STATKDTYDALHMQALPPR
665	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRLHSGVPSRFSG SGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQE SGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTII KDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSSTTTPAPRPPTPAPT IASQPLSLRPEACRPAAGGAVHTRGLDFACDIYIWAPLAGTCGVLLLSLVITLYCKRGRKKLLY IFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCELRVKFSRSADAPAYKQGQNQLYNELNLGRREE YDVLDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLST ATKDTYDALHMQALPPR
666	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSRLHSGVPSRFSG SGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEITGGGGSGGGGSGGGGSEVKLQE SGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIWGSETTYYNSALKSRLTII KDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGSYAMDYWGQGTSVTVSSKIEVMYPPPYLDNE KSNGTIIHVKGKHLCPSPLFPGPSKPFWVLVVVGGVLACYSLLVTVAFIIFWVRSKRSRLLHSD YMNMTPRRPGPTRKHYQPYAPPRDFAAYRSRVKFSRSADAPAYQQGQNQLYNELNLGRREEYDV LDKRRGRDPEMGGKPRRKNPQEGLYNELQKDKMAEAYSEIGMKGERRRGKGHDGLYQGLSTATK

	DTYDALHMQALPPR

b. Chimeric costimulatory receptor (CCR)

A chimeric costimulatory receptor (CCR) is a molecule that combines antibody-based specificity to a desired antigen with a costimulatory domain but that lacks a primary signaling domain. CCRs redirect immune effector cell specificity in an MHC independent manner and enhance the immune effector cell response in the presence of a CAR. In particular embodiments, a CAR comprises a first costimulatory domain and a primary signaling domain and a CCR comprises a second costimulatory domain, wherein the first and second costimulatory domains are different from each other and synergize to immune effector cell proliferation, persistence, cytokine production, and/or phagocytosis or production of molecules that can mediate cell death of the target antigen expressing cell.

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to a polynucleotide encoding a CAR comprising a signal peptide, an extracellular antigen binding domain that specifically binds to a target polypeptide expressed on the surface of a cell, a hinge domain, a transmembrane domain, and one or more intracellular signaling domains; a polypeptide cleavage signal; a CCR that comprises a signal peptide, an extracellular antigen binding domain, a hinge domain, a transmembrane domain, and a costimulatory signaling domain; and optionally a polynucleotide encoding a posttranscriptional regulatory element, *e.g.,* a WPRE or HPRE.

In particular embodiments, the signal peptide of the CAR is the same as, or different from, the signal peptide of the CCR; the extracellular antigen binding domain of the CAR is different than the extracellular antigen binding domain of the CCR; the hinge domain of the CAR is the same as, or different from, the hinge domain of the CCR; the transmembrane domain of the CAR is the same as, or different from, the transmembrane domain of the CCR; the costimulatory domain of the CAR is the same as, or different from, the costimulatory domain of the CCR; and the CAR comprises a primary signaling domain.

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to (a) a polynucleotide encoding a CAR comprising an extracellular antigen binding domain that comprises an antibody or antigen binding fragment thereof selected from the group consisting of: a Camel Ig, a Llama Ig, an Alpaca Ig, Ig NAR, a Fab' fragment, a F(ab')2 fragment, a bispecific Fab dimer (Fab2), a trispecific Fab trimer (Fab3), an Fv, a single chain Fv protein ("scFv"), a bis-scFv, (scFv)2,

a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a Fibronectin type III (FN3) domain antibody, a single-domain antibody (sdAb or nanobody, *e.g.*, a camelid VHH or shark VNAR) and a centyrin that binds an antigen selected from the group consisting of FRα, αvβ6 integrin, BAFFR, BCMA, CD276, B7-H6, CAIX, CD16, CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD44, CD44v6, CD44v7/8, CD70, CD79a, CD79b, CD123, CD133, CD138, CD171, CEA, CLDN6, CLDN18.2, CLL-1, CS-1, CSPG4, CTAGE1, DLL3, EGFR, EGFRvIII, EGP2, EGP40, EPCAM, EPHA2, ERBB4, FAP, FCRL5, AchR, GD2, GD3, GPC3, GPCR5D, HER2, HER2 p95, IL-10Rα, IL-13Rα2, Kappa, LAGE-1A, Lambda, LeY, L1-CAM, MAGE-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGEA10, MART1, MSLN, MUC1, MUC16, MICA, MICB, NCAM, NY-ESO-1, PLAC1, PRAME, PSCA, PSMA, ROR1, SLAMF7, SSX2, Survivin, TACI, TAG72, TEM1/CD248, TEM7R, TPBG, ULBP1, ULBP2, ULBP3, ULBP4, ULBP5, ULBP6, VEGFR2, and WT-1; a hinge domain selected from the group consisting of a CD4 hinge, a CD8β hinge, a CD8α hinge, a CD28 hinge, a CD134 hinge, a CD137 hinge, a CD152 hinge, a CD278 hinge, an IgG1 hinge, an IgG2 hinge, an IgG3 hinge, an IgG4 hinge; a transmembrane domain isolated or derived from a polypeptide selected from the group consisting of an alpha, beta, gamma, or delta chain of the T-cell receptor, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD5, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD152, CD154, CD278, amnionless (AMN), and programmed cell death 1 (PDCD1); a primary signaling domain isolated or derived from a polypeptide selected from the group consisting of FcRγ, FcRβ, CD3γ, CD3δ, CD3ε, CD3ζ, CD22, CD79a, CD79b, and CD66d; and optionally, one or more costimulatory signaling domains isolated or derived from a polypeptide selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, CARD11, CD2, CD7, CD27, CD28, CD30, CD40, ICAM, CD83, CD94, CD134 (OX40), CD137 (4-1BB), CD278 (ICOS), DAP10, LAT, SLP76, TRAT1, TNFR2, TNFRS14, TNFRS18, TNFRS25, and ZAP70; (b) a self-cleaving viral polypeptide or ribosomal skipping polypeptide; (c) a polynucleotide encoding a CCR that comprises an antibody or antigen binding fragment thereof selected from the group consisting of: a Camel Ig, a Llama Ig, an Alpaca Ig, Ig NAR, a Fab' fragment, a F(ab')2 fragment, a bispecific Fab dimer (Fab2), a trispecific Fab trimer (Fab3), an Fv, a single chain Fv protein ("scFv"), a bis-scFv, (scFv)2, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a Fibronectin type III (FN3) domain antibody, a single-domain antibody (sdAb or nanobody, *e.g.*, a camelid VHH or

shark VNAR) and a centyrin that binds an antigen selected from the group consisting of FRα, αvβ6 integrin, BAFFR, BCMA, CD276, B7-H6, CAIX, CD16, CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD44, CD44v6, CD44v7/8, CD70, CD79a, CD79b, CD123, CD133, CD138, CD171, CEA, CLDN6, CLDN18.2, CLL-1, CS-1, CSPG4, CTAGE1, DLL3, EGFR, EGFRvIII, EGP2, EGP40, EPCAM, EPHA2, ERBB4, FAP, FCRL5, AchR, GD2, GD3, GPC3, GPCR5D, HER2, HER2 p95, IL-10Rα, IL-13Rα2, Kappa, LAGE-1A, Lambda, LeY, L1-CAM, MAGE-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGEA10, MART1, MSLN, MUC1, MUC16, MICA, MICB, NCAM, NY-ESO-1, PLAC1, PRAME, PSCA, PSMA, ROR1, SLAMF7, SSX2, Survivin, TACI, TAG72, TEM1/CD248, TEM7R, TPBG, ULBP1, ULBP2, ULBP3, ULBP4, ULBP5, ULBP6, VEGFR2, and WT-1 that is different than the antigen bound by the CAR; a hinge domain selected from the group consisting of a CD4 hinge, a CD8β hinge, a CD8α hinge, a CD28 hinge, a CD134 hinge, a CD137 hinge, a CD152 hinge, a CD278 hinge, an IgG1 hinge, an IgG2 hinge, an IgG3 hinge, an IgG4 hinge, optionally that comprises one or more amino acid substitutions that reduces antigen independent signaling of the CCR compared to the unmodified hinge domain; a transmembrane domain isolated or derived from a polypeptide selected from the group consisting of an alpha, beta, gamma, or delta chain of the T-cell receptor, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD5, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD152, CD154, CD278, amnionless (AMN), and programmed cell death 1 (PDCD1); and one or more costimulatory signaling domains isolated or derived from a polypeptide selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, CARD11, CD2, CD7, CD27, CD28, CD30, CD40, ICAM, CD83, CD94, CD134 (OX40), CD137 (4-1BB), CD278 (ICOS), DAP10, LAT, SLP76, TRAT1, TNFR2, TNFRS14, TNFRS18, TNFRS25, and ZAP70 that are different than the costimulatory domain of the CAR.

c. Engineered T Cell Receptors (TCR)

Naturally occurring T cell receptors have two chains: an αβTCR comprises an alpha chain and a beta chain and a γδTCR comprises a gamma chain and a delta chain. Each TCR is a unique protein produced by a recombination event in each T cell's genome. Libraries of TCRs may be screened for their selectivity to particular target antigens and natural TCRs

with high-avidity and reactivity toward target antigens may be selected, cloned, and incorporated into a payload to deliver to an immune effector cell.

In particular embodiments, a recombinant particle, *e.g.,* a retroviral or lentiviral particles, comprises (a) a phospholipid bilayer, a cellular membrane, or a viral envelope comprising (i) one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof that binds an antigen expressed on an immune effector cell, a spacer polypeptide, a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a recombinant retroviral or lentiviral vector comprising a polynucleotide encoding a promoter operably linked to a polynucleotide encoding an alpha chain and/or a beta chain of an αβTCR or a gamma chain and/or a delta chain of a γδTCR.

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to a polynucleotide encoding an alpha chain and/or a beta chain of an αβTCR or a gamma chain and/or a delta chain of a γδTCR, and optionally a polynucleotide encoding a posttranscriptional regulatory element, *e.g.,* a WPRE or HPRE. In particular embodiments, the vector comprises a polynucleotide encoding a self-cleaving viral polypeptide or ribosomal skipping polypeptide disposed between the chains of the αβTCR or γδTCR.

In particular embodiments, an engineered TCR comprises an extracellular antigen binding domain that binds an antigen selected from the group consisting of FRα, αvβ6 integrin, BAFFR, BCMA, CD276, B7-H6, CAIX, CD16, CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD44, CD44v6, CD44v7/8, CD70, CD79a, CD79b, CD123, CD133, CD138, CD171, CEA, CLDN6, CLDN18.2, CLL-1, CS-1, CSPG4, CTAGE1, DLL3, EGFR, EGFRvIII, EGP2, EGP40, EPCAM, EPHA2, ERBB4, FAP, FCRL5, AchR, GD2, GD3, GPC3, GPCR5D, HER2, HER2 p95, IL-10Rα, IL-13Rα2, Kappa, LAGE-1A, Lambda, LeY, L1-CAM, MAGE-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGEA10, MART1, MSLN, MUC1, MUC16, MICA, MICB, NCAM, NY-ESO-1, PLAC1, PRAME, PSCA, PSMA, ROR1, SLAMF7, SSX2, Survivin, TACI, TAG72, TEM1/CD248, TEM7R, TPBG, ULBP1, ULBP2, ULBP3, ULBP4, ULBP5, ULBP6, VEGFR2, and WT-1.

d. Dimerizing agent regulated immunoreceptor complex (DARIC)

A DARIC is a multi-component signaling receptor comprising one or more non-naturally occurring polypeptides that transduces an immunostimulatory signal in an immune effector cell upon exposure to a multimerizing agent or bridging factor, *e.g.*, stimulating immune effector cell activity and function, increasing production and/or secretion of proinflammatory cytokines.

In particular embodiments, a recombinant particle, *e.g.,* a retroviral or lentiviral particles, comprises (a) a phospholipid bilayer, a cellular membrane, or a viral envelope comprising (i) one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof that binds an antigen expressed on an immune effector cell, a spacer polypeptide, a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a recombinant retroviral or lentiviral vector comprising a polynucleotide encoding a promoter operably linked to a polynucleotide encoding a DARIC signaling component and a DARIC binding component.

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to a polynucleotide encoding a DARIC signaling component comprising a signal peptide, a multimerization domain, a transmembrane domain, a costimulatory domain and/or a primary signaling domain; a self-cleaving viral polypeptide or ribosomal skipping polypeptide; and a DARIC binding component comprising a signal peptide, an extracellular antigen binding domain, a multimerization domain, a transmembrane domain, and optionally, a costimulatory domain, and optionally a polynucleotide encoding a posttranscriptional regulatory element, *e.g.,* a WPRE or HPRE; wherein a bridging factor regulates association of the DARIC binding component and DARIC signaling component by interacting with the multimerization domains.

In particular embodiments, a DARIC signaling component comprises a multimerization domain selected from the group consisting of an FK506 binding protein (FKBP) polypeptide or variants thereof (*e.g.*, FKBP12), or an FKBP-rapamycin binding (FRB) polypeptide or variants thereof (*e.g.*, T2098L); a transmembrane domain isolated or

derived from a polypeptide selected from the group consisting of an alpha, beta, gamma, or delta chain of the T-cell receptor, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD5, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD152, CD154, CD278, amnionless (AMN), and programmed cell death 1 (PDCD1); one or more costimulatory signaling domains isolated or derived from a polypeptide selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, CARD11, CD2, CD7, CD27, CD28, CD30, CD40, ICAM, CD83, CD94, CD134 (OX40), CD137 (4-1BB), CD278 (ICOS), DAP10, LAT, SLP76, TRAT1, TNFR2, TNFRS14, TNFRS18, TNFRS25, and ZAP70; and a primary signaling domain isolated or derived from a polypeptide selected from the group consisting of FcRγ, FcRβ, CD3γ, CD3δ, CD3ε, CD3ζ, CD22, CD79a, CD79b, and CD66d.

In particular embodiments, a DARIC binding component comprises an extracellular antigen binding domain comprising an antibody or antigen binding fragment thereof selected from the group consisting of a Camel Ig, a Llama Ig, an Alpaca Ig, Ig NAR, a Fab' fragment, a F(ab')2 fragment, a bispecific Fab dimer (Fab2), a trispecific Fab trimer (Fab3), an Fv, a single chain Fv protein ("scFv"), a bis-scFv, $(scFv)_2$, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a Fibronectin type III (FN3) domain antibody, and a single-domain antibody (sdAb or nanobody, *e.g.*, a camelid VHH or shark VNAR) that binds an antigen selected from the group consisting of FRα, αvβ6 integrin, BAFFR, BCMA, CD276, B7-H6, CAIX, CD16, CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD44, CD44v6, CD44v7/8, CD70, CD79a, CD79b, CD123, CD133, CD138, CD171, CEA, CLDN6, CLDN18.2, CLL-1, CS-1, CSPG4, CTAGE1, DLL3, EGFR, EGFRvIII, EGP2, EGP40, EPCAM, EPHA2, ERBB4, FAP, FCRL5, AchR, GD2, GD3, GPC3, GPCR5D, HER2, HER2 p95, IL-10Rα, IL-13Rα2, Kappa, LAGE-1A, Lambda, LeY, L1-CAM, MAGE-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGEA10, MART1, MSLN, MUC1, MUC16, MICA, MICB, NCAM, NY-ESO-1, PLAC1, PRAME, PSCA, PSMA, ROR1, SLAMF7, SSX2, Survivin, TACI, TAG72, TEM1/CD248, TEM7R, TPBG, ULBP1, ULBP2, ULBP3, ULBP4, ULBP5, ULBP6, VEGFR2, and WT-1; a multimerization domain selected from the group consisting of an FK506 binding protein (FKBP) polypeptide or variants thereof (*e.g.*, FKBP12), or an FKBP-rapamycin binding (FRB) polypeptide or variants thereof (*e.g.*, T2098L); a transmembrane domain isolated or derived from a polypeptide selected from the group consisting of an alpha, beta, gamma, or delta chain of the T-cell receptor, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD5, CD8α, CD9, CD16, CD22,

CD27, CD28, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD152, CD154, CD278, amnionless (AMN), and programmed cell death 1 (PDCD1); and optionally one or more costimulatory signaling domains isolated or derived from a polypeptide selected from the group consisting of TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, CARD11, CD2, CD7, CD27, CD28, CD30, CD40, ICAM, CD83, CD94, CD134 (OX40), CD137 (4-1BB), CD278 (ICOS), DAP10, LAT, SLP76, TRAT1, TNFR2, TNFRS14, TNFRS18, TNFRS25, and ZAP70.

Illustrative examples of bridging factors suitable for use in particular embodiments comprising a DARIC receptor contemplated herein include, but are not limited to, AP1903, AP20187, AP21967 (also known as C-16-(S)-7-methylindolerapamycin), everolimus, novolimus, pimecrolimus, ridaforolimus, tacrolimus, temsirolimus, umirolimus, and zotarolimus.

e. Chimeric TGF-β receptor (CTBR)

A chimeric TGF-β receptor (CTBR) is a fusion polypeptide that when expressed on an immune effector cell, transduces an immunostimulatory signal to the immune effector cell in the presence of immunosuppressive cytokines (*e.g.,* TGFβ) produced by tumor cells and tumor-infiltrating lymphocytes in the tumor microenvironment (TME).

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to a polynucleotide encoding a CAR, αβ TCR, γδ TCR, DARIC, or zetakine; a self-cleaving viral polypeptide or ribosomal skipping polypeptide; a CTBR; and optionally a polynucleotide encoding a posttranscriptional regulatory element, *e.g.*, a WPRE or HPRE.

In particular embodiments, a CTBR comprises (a) a first polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR2, a transmembrane domain, and a first interleukin receptor intracellular signaling domain; (b) a polypeptide cleavage signal; and (c) a second polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR1, a transmembrane domain, and a second interleukin receptor intracellular signaling domain.

Illustrative examples of first and second interleukin receptor intracellular signaling domains suitable for use in a CTBR include but are not limited to IL-12Rβ1 and IL-12Rβ2 (IL-12 receptor); IL-7Rα and IL-2Rγ (IL-7 receptor); IL-2Rγ and IL-2Rγ (IL-2 receptor); IL-

21R and IL-2Rγ (IL-21 receptor); IL-18R1 and IL-18RAP (IL-18 receptor); and IL-1R1 and IL-1RAP (IL-1 receptor).

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to (a) a CAR, αβ TCR, γδ TCR, DARIC, or zetakine; (b) a self-cleaving viral polypeptide or ribosomal skipping polypeptide; and (c) a polynucleotide encoding a CTBR comprising (i) a first polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR2, a TGFβR2 or an IL-12Rβ2 transmembrane domain and an IL-12Rβ2 intracellular signaling domain; (ii) a self-cleaving viral peptide or ribosomal skipping polypeptide and (iii) a second polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR1; a TGFβR1 or an IL-12Rβ1 transmembrane domain, and an IL-12Rβ1 intracellular signaling domain.

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to (a) a CAR, αβ TCR, γδ TCR, DARIC, or zetakine; (b) a self-cleaving viral polypeptide or ribosomal skipping polypeptide; and (c) a polynucleotide encoding a CTBR comprising (i) a first polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR2, a TGFβR2 or an IL-7Rα transmembrane domain and an IL-7Rα intracellular signaling domain; (ii) a self-cleaving viral peptide or ribosomal skipping polypeptide; and (iii) a second polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR1; a TGFβR1 or an IL-2Rγ transmembrane domain, and an IL-2Rγ intracellular signaling domain.

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to (a) a CAR, αβ TCR, γδ TCR, DARIC, or zetakine; (b) a self-cleaving viral polypeptide or ribosomal skipping polypeptide; and (c) a polynucleotide encoding a CTBR comprising (i) a first polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR2, a TGFβR2 or an IL-2Rβ transmembrane domain and an IL-2Rβ intracellular signaling domain; (ii) a self-cleaving viral peptide or ribosomal skipping polypeptide; and (iii) a second polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR1; a TGFβR1 or an IL-2Rγ transmembrane domain, and an IL-2Rγ intracellular signaling domain.

In particular embodiments, a retroviral or lentiviral vector comprises a polynucleotide comprising or encoding a promoter operably linked to (a) a CAR, αβ TCR, γδ TCR, DARIC, or zetakine; (b) a self-cleaving viral polypeptide or ribosomal skipping polypeptide; and (c) a polynucleotide encoding a CTBR comprising (i) a first polypeptide comprising an

extracellular TGFβ1-binding domain of TGFβR2, a TGFβR2 or an IL-21R transmembrane domain and an IL-21R intracellular signaling domain; (ii) a self-cleaving viral peptide or ribosomal skipping polypeptide; and (iii) a second polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR1; a TGFβR1 or an IL-2Rγ transmembrane domain, and an IL-2Rγ intracellular signaling domain.

2. GENE EDITING PAYLOADS

Recombinant particles contemplated in particular embodiments comprise (i) a surface comprising one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides that bind an antigen expressed on a cell and (ii) a payload comprising a genome editing composition comprising one or more polynucleotides and/or polypeptides. Without wishing to be bound to any particular theory it is believed that genome editing compositions can be delivered using the recombinant particles contemplated herein to modify the target cell genome and introduce one or more exogenous genes or modulate expression of one or more endogenous genes in the cell.

In a particular embodiment, a genome editing payload comprises a template and a nuclease both formatted as circRNAs, mRNAs or DNAs.

In a particular embodiment, a genome editing payload comprises a template formatted as RNA or DNA and a nuclease formatted as a polypeptide.

In a particular embodiment, a genome editing payload comprises a nucleic acid-polypeptide complex comprising a template formatted as RNA or DNA and a nuclease formatted as a polypeptide.

In a particular embodiment, a genome editing payload comprises a nuclease formatted as circRNA, mRNA, DNA, or polypeptide.

In particular embodiments, a genome editing payload comprises a fusion protein comprising a viral accessory protein and a nuclease and optionally, a DNA repair template.

In particular embodiments, a genome editing payload comprises a fusion protein comprising a lentiviral accessory protein, a lentivirus protease cleavage site (*e.g.,* SQNYPIVQ (SEQ ID NO: 714)) and a nuclease and optionally, a DNA repair template.

In particular embodiments, the viral accessory protein is a gag or vpr polypeptide, and in preferred embodiments, a lentiviral (*e.g.,* HIV-1) gag or vpr polypeptide. In particular embodiments, the lentivirus protease cleavage site is an HIV-1 protease cleavage site.

Illustrative examples of genome editing compositions suitable for use in particular embodiments contemplated herein include, but are not limited to base editors (*e.g.,* cytosine base editors (Cas9-cytosine deaminase fusion proteins; CBEs), adenosine base editors (Cas9-deoxyadenosine deaminase fusion proteins; ABEs), sgRNA), prime editors (Cas9-reverse trancriptase fusion proteins; pegRNAs), clustered regularly-interspaced short palindromic repeats (CRISPR)/Cas nuclease systems (Cas9, sgRNA), retrotransposons, homing endonucleases (meganucleases), megaTALs, transcription activator-like effector nucleases (TALENs), zinc finger nucleases (ZFNs), and ARCUS nucleases.

F. POLYNUCLEOTIDES

Polynucleotides comprising vectors, vector-based genomes, transfer vectors, packaging plasmids, expression control sequences, therapeutic polynucleotides, nucleases, DNA repair templates and polynucleotides encoding polypeptides, fusion polypeptides, viral envelope glycoproteins, non-viral membrane-bound tropism polypeptides, CARs, CCRs, TCRs, DARICs, CTBRs, nucleases, and therapeutic polypeptides and variants thereof are contemplated herein.

As used herein, the terms "polynucleotide" or "nucleic acid" refer to deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and DNA/RNA hybrids. Polynucleotides may be single-stranded or double-stranded and either recombinant, synthetic, or isolated. Polynucleotides include but are not limited to: pre-messenger RNA (pre-mRNA), messenger RNA (mRNA), RNA, circular RNA (circRNA), synthetic RNA, short interfering RNA (siRNA), short hairpin RNA (shRNA), microRNA (miRNA), ribozymes, genomic RNA (gRNA), viral genomic RNA, plus strand RNA (RNA(+)), minus strand RNA (RNA(−)), tracrRNA, crRNA, single guide RNA (sgRNA), PCR amplified DNA, complementary DNA (cDNA), synthetic DNA, or recombinant DNA. Polynucleotides refer to a polymeric form of nucleotides of at least 5, at least 10, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, at least 100, at least 200, at least 300, at least 400, at least 500, at least 1000, at least 5000, at least 10000, or at least 15000 or more nucleotides in length, either ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide, as well as all intermediate lengths. It will be readily understood that "intermediate lengths," in this context, means any length between the quoted values, such as 6, 7, 8, 9, *etc.*, 101, 102, 103, *etc.*, 151, 152, 153, *etc.*, 201, 202, 203, *etc.*

In particular embodiments, polynucleotides contemplated herein are polynucleotide variants. As used herein, the terms "polynucleotide variant" and "variant" and the like refer to polynucleotides displaying substantial sequence identity with a reference polynucleotide sequence or polynucleotides that hybridize with a reference sequence under stringent conditions that are defined hereinafter. These terms also encompass polynucleotides that are distinguished from a reference polynucleotide by the addition, deletion, substitution, or modification of one or more nucleotides. Accordingly, the terms "polynucleotide variant" and "variant" include polynucleotides in which one or more nucleotides have been added or deleted, or modified, or replaced with different nucleotides. In this regard, it is well understood in the art that certain alterations inclusive of mutations, additions, deletions and substitutions can be made to a reference polynucleotide whereby the altered polynucleotide retains the biological function or activity of the reference polynucleotide or wherein the function or activity of the altered polynucleotide is modulated.

In particular embodiments, polynucleotides or polynucleotide variants have at least or about 50%, 55%, 60%, 65%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to a reference sequence.

As used herein, "isolated polynucleotide" refers to a polynucleotide that has been isolated from or purified from the sequences which flank it in a naturally-occurring state. In particular embodiments, an isolated polynucleotide is a synthetic polynucleotide, a semi-synthetic polynucleotide, or a polynucleotide obtained or derived from a recombinant source, or other polynucleotide that does not exist in nature and that has been made by the hand of man.

In various embodiments, a polynucleotide comprises a vector, optionally a retroviral vector, optionally a lentiviral vector.

In various embodiments, a polynucleotide comprises a retroviral vector-based RNA genome, optionally a lentiviral vector-based RNA genome.

Illustrative examples of polynucleotides include, but are not limited to, polynucleotide sequences set forth in any one of SEQ ID NOs: 667-672 and polynucleotides encoding polypeptides set forth in SEQ ID NOs: 1-666 and 673-714.

In particular embodiments, polynucleotides may be codon-optimized. As used herein, the term "codon-optimized" refers to substituting codons in a polynucleotide encoding a polypeptide in order to modulate polypeptide expression, stability and/or activity.

Factors that influence codon optimization include, but are not limited to one or more of: (i) variation of codon biases between two or more organisms or genes or synthetically constructed bias tables, (ii) variation in the degree of codon bias within an organism, gene, or set of genes, (iii) systematic variation of codons including context, (iv) variation of codons according to their decoding tRNAs, (v) variation of codons according to GC %, either overall or in one position of the triplet, (vi) variation in degree of similarity to a reference sequence for example a naturally occurring sequence, (vii) variation in the codon frequency cutoff, (viii) structural properties of mRNAs transcribed from the DNA sequence, (ix) prior knowledge about the function of the DNA sequences upon which design of the codon substitution set is to be based, (x) systematic variation of codon sets for each amino acid, and/or (xi) isolated removal of spurious translation initiation sites.

Polynucleotides contemplated in particular embodiments, regardless of the length of the coding sequence itself, may be combined with other polynucleotide sequences, such as expression control sequences, promoters and/or enhancers, untranslated regions (UTRs), polynucleotides encoding signal peptides, Kozak sequences, polyadenylation signals, restriction enzyme sites, multiple cloning sites, internal ribosomal entry sites (IRES), recombinase recognition sites (*e.g.*, LoxP, FRT, and Att sites), termination codons, transcriptional termination signals, and polynucleotides encoding self-cleaving polypeptides or epitope tags, as disclosed elsewhere herein or as known in the art.

In particular embodiments, a polynucleotide encodes a fusion polypeptide, viral envelope glycoprotein, non-viral membrane-bound tropism polypeptide, CAR, CCR, αβ TCR, γδ TCR, DARIC, CTBR, nuclease, or therapeutic polypeptide comprising signal peptide, *e.g.*, a polynucleotide encoding any one of SEQ ID NOs: 449-454.

Signal peptides are short 16 to 30 amino acid N-terminal sequences of nascently synthesized polypeptide chains that mediate protein targeting to the membrane of the endoplasmic reticulum (ER). Typically, signal peptides are cleaved cotranslationally by signal peptidase, a heterooligomeric polypeptide complex. In particular embodiments, a polypeptide comprises a signal peptide. In preferred embodiments, a polynucleotide encoding a polypeptide comprises a polynucleotide encoding a signal polypeptide; and the translated polypeptide does not comprise a signal peptide.

In particular embodiments, a vector comprises a polynucleotide comprising or encoding one or more exogenous, endogenous, or heterologous expression control sequences

operably linked to a polynucleotide encoding one or more polynucleotides and/or polypeptides contemplated herein.

"Expression control sequences," "control elements," or "regulatory sequences" contemplated in particular embodiments include but not limited to promoters, enhancers, translation initiation signals (Shine Dalgarno sequence or Kozak sequence), introns, polyadenylation signals, 5′ and 3′ untranslated regions, all of which may interact with host cell proteins to carry out transcription and translation.

The term "promoter" as used herein refers to a recognition site of a polynucleotide (DNA or RNA) to which an RNA polymerase binds. An RNA polymerase initiates and transcribes polynucleotides operably linked to the promoter. In particular embodiments, promoters operative in mammalian cells comprise an AT-rich region located approximately 25 to 30 bases upstream from the site where transcription is initiated and/or another sequence found 70 to 80 bases upstream from the start of transcription, a CNCAAT region where N may be any nucleotide. The term "enhancer" refers to a segment of DNA which contains sequences capable of providing enhanced transcription and in some instances can function independent of their orientation relative to another control sequence. An enhancer can function cooperatively or additively with promoters and/or other enhancer elements. The term "promoter/enhancer" refers to a segment of DNA which contains sequences capable of providing both promoter and enhancer functions.

The term "operably linked", refers to a juxtaposition wherein the components described are in a relationship permitting them to function in their intended manner. In one embodiment, the term refers to a functional linkage between an expression control sequence (such as a promoter, and/or enhancer) and a second polynucleotide sequence encoding a polypeptide, wherein the expression control sequence directs transcription of the nucleic acid corresponding to the second sequence.

Illustrative expression control sequences suitable for use in particular embodiments include, but are not limited to, a β-actin promoter, a cytomegalovirus (CMV) immediate early promoter, a simian virus 40 (SV40) (*e.g.*, early or late) promoter, a Moloney murine leukemia virus (MoMLV) promoter, a Rous sarcoma virus (RSV) promoter, a herpes simplex virus (HSV) (thymidine kinase) promoter, an SV40/CD43 promoter, a spleen focus forming virus (SFFV) promoter, an elongation factor 1-alpha (EFlα) short promoter (intronless), an EFlα long promoter containing an intron, a Ubiquitin C (UBC) promoter, a phosphoglycerate kinase-1 (PGK) promoter, a cytomegalovirus enhancer/chicken β-actin (CAG) promoter, and

a myeloproliferative sarcoma virus enhancer, negative control region deleted, dl587rev primer-binding site substituted (MND) U3 promoter (Haas *et al.*, Journal of Virology. 2003;77(17): 9439-9450).

In particular embodiments, a polynucleotide comprises one or more cell type- or tissue-specific expression control sequences. In particular embodiments a cell type-specific expression control sequence is specific for immune effector cells. In particular embodiments a cell type-specific expression control sequence is a T cell specific promoter, an NK cell specific promoter, an NKT cell specific promoter, or a mucosal-associated invariant T (MAIT) cell promoter.

In particular embodiments, a cell type-specific expression control sequence is selected from the group consisting of a distal lymphocyte protein tyrosine kinase (LCK) promoter (Brenner *et al.,* Proc. Natl. Acad. Sci. USA 99:2936-2941 (2002)), a CD3δ promoter (Ji *et al.*, J Biol Chem. 277(49):47898-906 (2002)), a CD4 gene promoter (Salmon *et al.*, Proc. Natl. Acad. Sci. USA 90:7739 (1993), a CD2 promoter (Greaves *et al.*, Cell 56:979-86 (1989)), and a TCF7 promoter (van de Wetering *et al.* J. of Bio. Chem. 267: 8530-8536 (1992)).

Efficient expression of polynucleotides can be increased in some embodiments, by using sequences that increase translational efficiency, *e.g.*, through an increase in mRNA ribosomal binding or an increase in mRNA stability. In certain embodiments, polynucleotides encoding a polypeptide of the invention comprise a short recognition sequence, *i.e.*, a Kozak sequence, that greatly facilitates the initial binding of mRNA to the small subunit of the ribosome and increases translation. The consensus Kozak sequence is (GCC)RCCATGG, where R is a purine (A or G) (Kozak, Cell. 44:283-92 (1986), and Kozak, Nucleic Acids Res. 15:8125-48 (1987)).

Elements directing the efficient termination and polyadenylation of heterologous nucleic acid transcripts increases heterologous gene expression. Transcription termination signals are generally found downstream of the polyadenylation signal. In particular embodiments, vectors comprise a polyadenylation sequence 3′ to a sequence to be transcribed and/or expressed. The term "polyadenylation (or poly(A)) signal" refers to a DNA sequence which directs both the termination and polyadenylation of the nascent RNA transcript by RNA polymerase II. Polyadenylation signals can promote mRNA stability by addition of a poly(A) tail to the 3' end of the coding sequence and thus, contribute to increased translational efficiency. Cleavage and polyadenylation are directed by a poly(A) signal in

the RNA. The core poly(A) signal for mammalian pre-mRNAs has two recognition elements flanking a cleavage-polyadenylation site. Typically, an almost invariant AAUAAA hexamer lies 20-50 nucleotides upstream of a more variable element rich in U or GU residues. Cleavage of the nascent transcript occurs between these two elements and is coupled to the addition of up to 250 adenosines to the 5' cleavage product. In particular embodiments, the core poly(A) signal is an ideal poly(A) signal (*e.g.*, AATAAA, ATTAAA, AGTAAA). In particular embodiments, the poly(A) signal is an SV40 poly(A) signal, a bovine growth hormone poly(A) signal (BGHpA), a rabbit β-globin poly(A) signal (rβgpA), variants thereof, or another suitable heterologous or endogenous poly(A) signal known in the art. In particular embodiments, the poly(A) signal is synthetic.

In particular embodiments, a polynucleotide, *e.g.,* a vector, a viral vector, a retroviral vector, or lentiviral vector, comprises one or more off-target (*e.g.*, brain, heart, liver, lung) miR target sequences inserted into a 5′ UTR, intron, and/or 3′ UTR.

In some embodiments, a polynucleotide comprises an inducible suicide gene to reduce the risk of direct toxicity and/or uncontrolled proliferation. In some embodiment, the suicide gene is caspase-8 or caspase-9. Caspase-9 can be activated using a specific chemical inducer of dimerization (CID).

In some embodiments, a polynucleotide comprises a gene or gene segment that when introduced into a cell, renders the cell susceptible to negative selection. Negative selection suitable for use in particular embodiments include but are not limited to the HSV-TK gene which confers ganciclovir sensitivity; the cellular hypoxanthine phosphribosyltransferase (HPRT) gene, the cellular adenine phosphoribosyltransferase (APRT) gene, and bacterial cytosine deaminase.

In some embodiments, a polynucleotide comprises a gene or gene segment that when introduced into a cell, renders the cell susceptible to positive selection. Positive selection genes suitable for use in particular embodiments contemplated herein include but are not limited to hygromycin-B phosphotransferase gene (hph) which confers resistance to hygromycin B, the amino glycoside phosphotransferase gene (neo or aph) from Tn5 which codes for resistance to the antibiotic G418, the dihydrofolate reductase (DHFR) gene, the adenosine deaminase gene (ADA), and the multi-drug resistance (MDR) gene.

In particular embodiments, a polynucleotide is a vector comprising or encoding a promoter operably linked to a polynucleotide encoding one or more engineered receptors, *e.g.,* CAR, CCR, αβ TCR, γδ TCR, DARIC, and/or CTBR, or components thereof.

In particular embodiments, a polynucleotide is a retroviral or lentiviral vector comprising or encoding a promoter active in immune effector cells operably linked to a polynucleotide encoding one or more engineered receptors, *e.g.,* CAR, CCR, αβ TCR, γδ TCR, DARIC, and/or CTBR, or components thereof.

In particular embodiments, a polynucleotide is a retroviral or lentiviral vector comprising or encoding a promoter active in immune effector cells operably linked to a polynucleotide encoding an engineered receptor comprising an extracellular antigen binding domain that binds BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, GPCR5D, MAGE-A4, MSLN, MUC16, NY-ESO-1, PSCA, PSMA and ROR1.

In particular embodiments, a polynucleotide is a retroviral or lentiviral vector comprising or encoding a promoter selected from the group consisting of a CMV promoter, an SFFV promoter, an EFlα short promoter, a UBC promoter, a PGK promoter, a CAG promoter, and an MNDU3 promoter operably linked to a polynucleotide encoding an engineered receptor comprising an extracellular antigen binding domain that binds BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, GPCR5D, MAGE-A4, MSLN, MUC16, NY-ESO-1, PSCA, PSMA and ROR1.

In particular embodiments, a polynucleotide is a retroviral or lentiviral vector comprising or encoding an SFFV promoter, operably linked to a polynucleotide encoding an engineered receptor comprising an extracellular antigen binding domain that binds BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, GPCR5D, MAGE-A4, MSLN, MUC16, NY-ESO-1, PSCA, PSMA and ROR1.

In particular embodiments, a polynucleotide is a retroviral or lentiviral vector comprising or encoding an EFlα short promoter operably linked to a polynucleotide encoding an engineered receptor comprising an extracellular antigen binding domain that binds BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, GPCR5D, MAGE-A4, MSLN, MUC16, NY-ESO-1, PSCA, PSMA and ROR1.

In particular embodiments, a polynucleotide is a retroviral or lentiviral vector comprising or encoding a UBC promoter operably linked to a polynucleotide encoding an engineered receptor comprising an extracellular antigen binding domain that binds BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, GPCR5D, MAGE-A4, MSLN, MUC16, NY-ESO-1, PSCA, PSMA and ROR1.

In particular embodiments, a polynucleotide is a retroviral or lentiviral vector comprising or encoding a CAG promoter operably linked to a polynucleotide encoding an

engineered receptor comprising an extracellular antigen binding domain that binds BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, GPCR5D, MAGE-A4, MSLN, MUC16, NY-ESO-1, PSCA, PSMA and ROR1.

In particular embodiments, a polynucleotide is a retroviral or lentiviral vector comprising or encoding an MND promoter operably linked to a polynucleotide encoding an engineered receptor comprising an extracellular antigen binding domain that binds BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, GPCR5D, MAGE-A4, MSLN, MUC16, NY-ESO-1, PSCA, PSMA and ROR1.

In particular embodiments, a polynucleotide is a retroviral or lentiviral vector comprising or encoding a promoter comprising a polynucleotide sequence set forth in any one of SEQ ID NOs: 667-672 operably linked to a polynucleotide encoding an engineered receptor comprising an amino acid sequence set forth in any one of SEQ ID NOs: 662-666.

Table 13: Exemplary Promoters

SEQ ID NO:	NUCLEIC ACID SEQUENCE
667	GCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAACGACCCCCGCCCATTGAC GTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTCCATTGACGTCAATGGGTG GAGTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATCATATGCCAAGTACGCCCC CTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCAGTACATGACCTTATGGGA CTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACCATGGTCGAGGTGAGCCCC ACGTTCTGCTTCACTCTCCCCATCTCCCCCCCCTCCCCACCCCCAATTTTGTATTTATTTATTT TTTAATTATTTTGTGCAGCGATGGGGGCGGGGGGGGGGGGGGGCGCGCGCCAGGCGGGGCGGG GCGGGGCGAGGGGCGGGGCGGGGCGAGGCGGAGAGGTGCGGCGGCAGCCAATCAGAGCGGCGCG CTCCGAAAGTTTCCTTTTATGGCGAGGCGGCGGCGGCGGCGGCCCTATAAAAAGCGAAGCGCGC GGCGGGCG
668	CGTGAGGCTCCGGTGCCCGTCAGTGGGCAGAGCGCACATCGCCCACAGTCCCCGAGAAGTTGGG GGGAGGGGTCGGCAATTGAACCGGTGCCTAGAGAAGGTGGCGCGGGGTAAACTGGGAAAGTGAT GTCGTGTACTGGCTCCGCCTTTTTCCCGAGGGTGGGGGAGAACCGTATATAAGTGCAGTAGTCG CCGTGAACGTTCTTTTTCGCAACGGGTTTGCCGCCAGAACACAGGTAAGTGCCGTGTGTGGTTC CCGCGGGCCTGGCCTCTTTACGGGTTATGGCCCTTGCGTGCCTTGAATTACTTCCACCTGGCTG CAGTACGTGATTCTTGATCCCGAGCTTCGGGTTGGAAGTGGGTGGGAGAGTTCGAGGCCTTGCG CTTAAGGAGCCCCTTCGCCTCGTGCTTGAGTTGAGGCCTGGCCTGGGCGCTGGGGCCGCCGCGT GCGAATCTGGTGGCACCTTCGCGCCTGTCTCGCTGCTTTCGATAAGTCTCTAGCCATTTAAAAT TTTTGATGACCTGCTGCGACGCTTTTTTTCTGGCAAGATAGTCTTGTAAATGCGGGCCAAGATC TGCACACTGGTATTTCGGTTTTTGGGGCCGCGGGCGGCGACGGGGCCCGTGCGTCCCAGCGCAC ATGTTCGGCGAGGCGGGGCCTGCGAGCGCGGCCACCGAGAATCGGACGGGGGTAGTCTCAAGCT GGCCGGCCTGCTCTGGTGCCTGGCCTCGCGCCGCCGTGTATCGCCCCGCCCTGGGCGGCAAGGC TGGCCCGGTCGGCACCAGTTGCGTGAGCGGAAAGATGGCCGCTTCCCGGCCCTGCTGCAGGGAG CTCAAAATGGAGGACGCGGCGCTCGGGAGAGCGGGCGGGTGAGTCACCCACACAAAGGAAAAGG GCCTTTCCGTCCTCAGCCGTCGCTTCATGTGACTCCACGGAGTACCGGGCGCCGTCCAGGCACC TCGATTAGTTCTCGAGCTTTTGGAGTACGTCGTCTTTAGGTTGGGGGGAGGGGTTTTATGCGAT GGAGTTTCCCCACACTGAGTGGGTGGAGACTGAAGTTAGGCCAGCTTGGCACTTGATGTAATTC TCCTTGGAATTTGCCCTTTTTGAGTTTGGATCTTGGTTCATTCTCAAGCCTCAGACAGTGGTTC AAAGTTTTTTTCTTCCATTTCAGGTGTCGTGA
669	AATGAAAGACCCCACCTGTAGGTTTGGCAAGCTAGGATCAAGGTTAGGAACAGAGAGACAGCAG AATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGGCCAAGAACAGT TGGAACAGCAGAATATGGGCCAAACAGGATATCTGTGGTAAGCAGTTCCTGCCCCGGCTCAGGG CCAAGAACAGATGGTCCCCAGATGCGGTCCCGCCCTCAGCAGTTTCTAGAGAACCATCAGATGT

	TTCCAGGGTGCCCCAAGGACCTGAAATGACCCTGTGCCTTATTTGAACTAACCAATCAGTTCGC TTCTCGCTTCTGTTCGCGCGCTTCTGCTCCCCGAGCTCAATAAAAGAGCCCACAACCCCTCACT CGGC
670	GGGTAGGGGAGGCGCTTTTCCCAAGGCAGTCTGGAGCATGCGCTTTAGCAGCCCCGCTGGGCAC TTGGCGCTACACAAGTGGCCTCTGGCCTCGCACACATTCCACATCCACCGGTAGGCGCCAACCG GCTCCGTTCTTTGGTGGCCCCTTCGCGCCACCTTCTACTCCTCCCCTAGTCAGGAAGTTCCCCC CCGCCCCGCAGCTCGCGTCGTGCAGGACGTGACAAATGGAAGTAGCACGTCTCACTAGTCTCGT GCAGATGGACAGCACCGCTGAGCAATGGAAGCGGGTAGGCCTTTGGGGCAGCGGCCAATAGCAG CTTTGCTCCTTCGCTTTCTGGGCTCAGAGGCTGGGAAGGGGTGGGTCCGGGGGCGGGCTCAGGG GCGGGCTCAGGGGCGGGGCGGGCGCCCGAAGGTCCTCCGGAGGCCCGGCATTCTGCACGCTTCA AAAGCGCACGTCTGCCGCGCTGTTCTCCTCTTCCTCATCTCCGGGCCTTTCG
671	TGAAAGACCCCACCTGTAGGTTTGGCAAGATAGCTGCAGTAACGCCATTTTGCAAGGCATGGAA AAATACCAAACCAAGAATAGAGAAGTTCAGATCAAGGGCGGGTACATGAAAATAGCTAACGTTG GGCCAAACAGGATATCTGCGGTGAGCAGTTTCGGCCCCGGCCCGGGGCCAAGAACAGATGGTCA CCGCAGTTTCGGCCCCGGCCCGAGGCCAAGAACAGATGGTCCCCAGATATGGCCCAACCCTCAG CAGTTTCTTAAGACCCATCAGATGTTTCCAGGCTCCCCCAAGGACCTGAAATGACCCTGCGCCT TATTTGAATTAACCAATCAGCCTGCTTCTCGCTTCTGTTCGCGCGCTTCTGCTTCCCGAGCTCT ATAAAAGAGCTCACAACCCCTCACTCGGCGCGCCAGTCCTCCGATTGACTGAGTCGCCC
672	GGCCTCCGCGCCGGGTTTTGGCGCCTCCCGCGGGCGCCCCCCTCCTCACGGCGAGCGCTGCCAC GTCAGACGAAGGGCGCAGCGAGCGTCCTGATCCTTCCGCCCGGACGCTCAGGACAGCGGCCCGC TGCTCATAAGACTCGGCCTTAGAACCCCAGTATCAGCAGAAGGACATTTTAGGACGGGACTTGG GTGACTCTAGGGCACTGGTTTTCTTTCCAGAGAGCGGAACAGGCGAGGAAAAGTAGTCCCTTCT CGGCGATTCTGCGGAGGGATCTCCGTGGGGCGGTGAACGCCGATGATTATATAAGGACGCGCCG GGTGTGGCACAGCTAGTTCCGTCGCAGCCGGGATTTGGGTCGCGGTTCTTGTTTGTGGATCGCT GTGATCGTCACTTGGTGAGTAGCGGGCTGCTGGGCTGGCCGGGGCTTTCGTGGCCGCCGGGCCG CTCGGTGGGACGGAAGCGTGTGGAGAGACCGCCAAGGGCTGTAGTCTGGGTCCGCGAGCAAGGT TGCCCTGAACTGGGGGTTGGGGGGAGCGCAGCAAAATGGCGGCTGTTCCCGAGTCTTGAATGGA AGACGCTTGTGAGGCGGGCTGTGAGGTCGTTGAAACAAGGTGGGGGGCATGGTGGGCGGCAAGA ACCCAAGGTCTTGAGGCCTTCGCTAATGCGGGAAAGCTCTTATTCGGGTGAGATGGGCTGGGGC ACCATCTGGGGACCCTGACGTGAAGTTTGTCACTGACTGGAGAACTCGGTTTGTCGTCTGTTGC GGGGGCGGCAGTTATGGCGGTGCCGTTGGGCAGTGCACCCGTACCTTTGGGAGCGCGCGCCCTC GTCGTGTCGTGACGTCACCCGTTCTGTTGGCTTATAATGCAGGGTGGGGCCACCTGCCGGTAGG TGTGCGGTAGGCTTTTCTCCGTCGCAGGACGCAGGGTTCGGGCCTAGGGTAGGCTCTCCTGAAT CGACAGGCGCCGGACCTCTGGTGAGGGGAGGGATAAGTGAGGCGTCAGTTTCTTTGGTCGGTTT TATGTACCTATCTTCTTAAGTAGCTGAAGCTCCGGTTTTGAACTATGCGCTCGGGGTTGGCGAG TGTGTTTTGTGAAGTTTTTTAGGCACCTTTTGAAATGTAATCATTTGGGTCAATATGTAATTTT CAGTGTTAGACTAGTAAATTGTCCGCTAAATTCTGGCCGTTTTTGGCTTTTTTGTTAGAC

G. POLYPEPTIDES

Polypeptides, fusion polypeptides, and polypeptide variants are contemplated herein. Exemplary polypeptides contemplated herein include but not limited to, fusion polypeptides, viral envelope glycoproteins, non-viral membrane-bound tropism polypeptides, CARs, CCRs, TCRs, DARICs, CTBRs, nucleases, and therapeutic polypeptides, and variants and/or fragments thereof, *e.g.,* SEQ ID NOs: 1-666 and 673-714.

Polypeptide," "polypeptide," "peptide," and "protein" are used interchangeably, unless specified to the contrary, and according to conventional meaning, *i.e.*, as a sequence of amino acids. In particular embodiments, a "polypeptide" is a fusion polypeptide or polypeptide variant. Polypeptides can be prepared using any of a variety of well-known recombinant and/or synthetic techniques. Polypeptides are not limited to a specific length,

e.g., they may comprise a full-length protein sequence, a fragment of a full-length protein, or a fusion protein, and may include post-translational modifications, *e.g.*, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring.

An "isolated peptide," "isolated protein" or an "isolated polypeptide" as used herein, refers to isolation, separation, and/or purification of a polypeptide molecule from a cellular environment, and from association with other components of the cell, *i.e.*, it is not significantly associated with *in vivo* substances.

Polypeptides include "polypeptide variants." In particular embodiments, a polypeptide variant is referred to as a "modified polypeptide." Polypeptide variants may differ from a naturally occurring polypeptide in one or more amino acid substitutions, deletions, additions and/or insertions. For example, in particular embodiments, it may be desirable to modulate one or more biological activities of a viral envelope glycoprotein, non-viral membrane-bound tropism polypeptide, or engineered receptor by introducing one or more amino acid substitutions, deletions, additions and/or insertions into the polypeptide. Such variants may be naturally occurring or may be synthetically generated. In particular embodiments, polypeptides include polypeptide variants having at least about 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 86%, 97%, 98%, or 99% amino acid identity to any reference sequence contemplated herein, typically where the variant maintains at least one biological activity of the reference sequence.

In particular embodiments, a polypeptide variant is a viral envelope glycoprotein that has been modified to preserve its fusogenic activity and remove, disable, decrease, eliminate, or abate its binding activity to its cognate receptor on a cell. In particular embodiments, a polypeptide variant is a viral envelope glycoprotein that has at least about 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 86%, 97%, 98%, or 99% amino acid identity to any one of SEQ ID NOs: 582-645 or 646-661, wherein the variant comprises fusogenic activity and but is unable to bind or substantially bind to its cognate receptor on a cell.

Polypeptides variants include biologically active "polypeptide fragments."

Illustrative examples of biologically active polypeptide fragments include but are not limited to binding domains, hinges, transmembrane domains, intracellular domains, and the

like. As used herein, the term "biologically active fragment" or "minimal biologically active fragment" refers to a polypeptide fragment that retains at least 100%, at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, or at least 50% of the naturally occurring polypeptide activity. In particular embodiments, a biologically active fragment is a polypeptide comprising an N-terminal and/or C-terminal truncation of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more amino acids. In particular embodiments, a mutated viral envelope glycoprotein or non-viral membrane-bound tropism polypeptide comprises a truncation of the cytoplasmic domain that results in a cytoplasmic tail or stub comprising, consisting essentially of, or consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acids.

In particular embodiments, polypeptides contemplated herein may comprise one or more amino acids denoted as "X" or "X_n" wherein n is an integer that denotes the particular X amino acid. "X" if present in an amino acid SEQ ID NO, refers to any one or more amino acids or particular amino acids if disclosed.

As noted above, polypeptides may be altered in various ways including amino acid substitutions, deletions, truncations, and insertions. Methods for such manipulations are generally known in the art. For example, amino acid sequence variants of a reference polypeptide can be prepared by mutations in the DNA. Methods for mutagenesis and nucleotide sequence alterations are well known in the art. See, for example, Kunkel (Proc. Natl. Acad. Sci. USA. 82: 488-492. (1985)), Kunkel *et al*., (Methods in Enzymol, 154: 367-382. (1987)), U.S. Pat. No. 4,873,192, Watson, J. D. *et al*., (Molecular Biology of the Gene , Fourth Edition, Benjamin/Cummings, Menlo Park, Calif. (1987)) and the references cited therein. Guidance as to appropriate amino acid substitutions that do not affect biological activity of the protein of interest may be found in the model of Dayhoff *et al.*, Atlas of Protein Sequence and Structure (Natl. Biomed. Res. Found., Washington, D.C. (1978)).

In certain embodiments, a polypeptide variant comprises one or more conservative substitutions or disruptive substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties. In particular embodiments, polypeptide variants contemplated herein comprise one or more conservative amino acid changes compared to a reference polypeptide. In particular embodiments, a conservative amino acid substitution involves substituting an amino acid with an amino acid having a related side chain. A "disruptive substitution" is one in which an amino acid is substituted for another amino acid that has different properties, *e.g.*, polar vs. non-polar,

bulky vs. non-bulky, charged vs. uncharged, acidic vs. basic. In particular embodiments, polypeptide variants contemplated herein comprise one or more disruptive amino acid changes compared to a reference polypeptide. In particular embodiments, a disruptive amino acid substitution involves substituting an amino acid with an amino acid having an unrelated side chain or side change with a different chemical property. Guidance in determining which amino acid residues can be substituted, inserted, or deleted can be found using computer programs well known in the art, such as DNASTAR, DNA Strider, Geneious, Mac Vector, or Vector NTI software.

Naturally occurring amino acids are generally divided into four groups or families: acidic (aspartate, glutamate), basic (lysine, arginine, histidine), non-polar (alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), and uncharged polar (glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine) amino acids. Phenylalanine, tryptophan, and tyrosine are sometimes classified jointly as aromatic amino acids. In particular embodiments, a conservative amino acid substitution refers to substituting amino acids within the same group or family.

Those of skill in this art recognize that, in general, conservative single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, *e.g.*, Watson *et al.* Molecular Biology of the Gene, 4th Edition, 1987, The Benjamin/Cummings Pub. Co., p.224), whereas disruptive single amino acid substitutions may.

In particular embodiments, a conservative amino acid substitution refers to substituting amino acids having a similar hydropathic index or score. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cysteine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5). In particular embodiments, a conservative amino acid substitution refers to substituting amino acids having a similar hydropathic index or score. In particular embodiments, substitution of amino acids whose hydropathic indices are within ±2 is preferred, those within ±1 are particularly preferred, and

those within ±0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity.

In particular embodiments, a conservative amino acid substitution refers to substituting amino acids having a similar hydrophilic index or score. As detailed in U.S. Patent No. 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 ± 1); alanine (-0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5); tryptophan (-3.4). In particular embodiments, a conservative amino acid substitution refers to substituting amino acids having a similar hydrophilic index or score. In particular embodiments, substitution of amino acids whose hydrophilic indices are substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred.

In particular embodiments, a conservative amino acid substitution may be based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. In particular embodiments, a disruptive amino acid substitution may be based on the relative dissimilarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like.

In particular embodiments, a vector comprises one or more polynucleotides encoding two or more polypeptides. In particular embodiments, a polynucleotide encoding a polypeptide cleavage signal is disposed between the polynucleotide sequences encoding the two or more polypeptides to enable efficient translation and subsequent cleavage of a fusion polypeptide.

Polypeptides contemplated in particular embodiments include fusion polypeptides. In particular embodiments, fusion polypeptides and polynucleotides encoding fusion polypeptides are provided. Fusion polypeptides can include one or more polypeptide domains or segments including signal peptides, cell permeable peptide domains (CPP), binding domains, signaling domains, *etc.*, epitope tags (*e.g.*, maltose binding protein ("MBP"), glutathione S transferase (GST), HIS6, MYC, FLAG, V5, VSV-G, and HA), polypeptide linkers, and polypeptide cleavage signals. Fusion proteins and polypeptides are typically linked C-terminus to N-terminus, although they can also be linked C-terminus to C-

terminus, N-terminus to N-terminus, or N-terminus to C-terminus. Fusion polypeptides and fusion proteins refer to a polypeptide having at least two, three, four, five, six, seven, eight, nine, or ten polypeptide segments.

In particular embodiments, a fusion polypeptide, viral envelope glycoprotein, non-viral membrane-bound tropism polypeptide, CAR, CCR, αβ TCR, γδ TCR, DARIC, CTBR, nuclease, or therapeutic polypeptide comprises signal peptide set forth in any one of SEQ ID NOs: 449-454 that is subsequently cleaved from the fusion polypeptide, viral envelope glycoprotein, non-viral membrane-bound tropism polypeptide, CAR, CCR, αβ TCR, γδ TCR, DARIC, CTBR, nuclease, or therapeutic polypeptide.

Table 14: Exemplary Signal Peptides

SEQ ID NO	AMINO ACID SEQUENCE
449	MALPVTALLLPLALLLHAARP
450	METDTLLLWVLLLWVPGSTG
451	MGVKVLFALICIAVAEA
452	MLLLVTSLLLCELPHPAFLLIP
453	MSRSVALAVLALLSLSGLEA
454	MGHTRRQGTSPSKCPYLNFFQLLVLAGLSHFCSG

Fusion polypeptides may optionally comprise a polypeptide linker contemplated elsewhere herein that can be used to link one or more polypeptides or domains within a polypeptide. "Linker," "peptide linker," and "polypeptide linker" are used interchangeably and refer to a plurality of amino acid residues between various polypeptide domains added for appropriate spacing, conformation, and function. A polypeptide linker sequence may be employed to separate any two or more polypeptide components by a distance sufficient to ensure that each polypeptide folds into its appropriate secondary and tertiary structures so as to allow the polypeptide domains to exert their desired functions. Linkers include a "variable domain linking sequence," an amino acid sequence that connects two or more domains of an antibody or antigen binding fragments thereof and provides a spacer function compatible with interaction of the two sub-binding domains so that the resulting polypeptide retains a specific binding affinity to the same target molecule as an antibody that comprises the same light and/or heavy chain variable domains. A linker may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50 or more amino acids long.

Illustrative examples of linkers include, but are not limited to the following amino acid sequences: AS, ASP, GGG; DGGGS (SEQ ID NO: 673); TGEKP (SEQ ID NO: 674); GGRR (SEQ ID NO: 675); $(GGGGS)_n$ wherein n = 1, 2, 3, 4 or 5 (SEQ ID NO: 676-680); $S(GGGGS)_n$ wherein n = 1, 2, 3, 4 or 5 (SEQ ID NO: 681-685); EGKSSGSGSESKVD (SEQ ID NO: 686); KESGSVSSEQLAQFRSLD (SEQ ID NO: 687); GGRRGGGS (SEQ ID NO: 688); LRQRDGERP (SEQ ID NO: 689); LRQKDGGGSERP (SEQ ID NO: 690); LRQKDGGGSGGGSERP (SEQ ID NO: 691), GEGTSTGSGGSGGSGGAD (SEQ ID NO: 692), and GSTSGSGKPGSGEGSTKG (SEQ ID NO: 693).

In particular embodiments, two or more polypeptides can be expressed as a fusion polypeptides that comprises one or more polypeptide cleavage signals disposed between the two or more polypeptides.

In particular embodiments, a fusion polypeptide comprises a CAR, a polypeptide cleavage signal and a CCR. In particular embodiments, a fusion polypeptide comprises a DARIC binding component, a polypeptide cleavage signal and a DARIC signaling component. In particular embodiments, a fusion polypeptide comprises a CAR, αβ TCR, γδ TCR, or DARIC, a polypeptide cleavage signal, and a CTBR.

Exemplary polypeptide cleavage signals include, but are not limited to, protease cleavage sites, nuclease cleavage sites and ribosomal skipping polypeptide or self-cleaving viral polypeptides (see, *e.g.*, in Ryan *et al.*, 1997. J. Gener. Virol. 78, 699-722; deFelipe and Ryan, 2004. Traffic, 5(8); 616-26; and Scymczak *et al.* (2004) Nature Biotech. 5, 589-594).

Exemplary protease cleavage sites include, but are not limited to the cleavage sites of potyvirus NIa proteases (e.g, tobacco etch virus protease), poty virus HC proteases, potyvirus PI (P35) proteases, byovirus NIa proteases, byovirus RNA-2-encoded proteases, aphthovirus L proteases, enterovirus 2A proteases, rhinovirus 2 A proteases, picoma 3C proteases, comovirus 24K proteases, nepovirus 24K proteases, RTSV (rice tungro spherical virus) 3C-like protease, PYVF (parsnip yellow fleck virus) 3C-like protease, heparin, thrombin, factor Xa and enterokinase.

Illustrative examples of ribosomal skipping polypeptides include but are not limited to: a viral 2A peptide or sequence (Donnelly *et al*., 2001. J. Gen. Virol. 82: 1027-1041). In a particular embodiment, the viral 2A peptide is an aphthovirus 2A peptide, a potyvirus 2A peptide, or a cardiovirus 2A peptide.

In one embodiment, the viral 2A peptide is selected from the group consisting of: a foot-and-mouth disease virus (FMDV) 2A peptide, an equine rhinitis A virus (ERAV) 2A

peptide, a Thosea asigna virus (TaV) 2A peptide, a porcine teschovirus-1 (PTV-1) 2A peptide, a Theilovirus 2A peptide, and an encephalomyocarditis virus 2A peptide.

Illustrative examples of viral 2A sequences include, but are not limited to: GSGATNFSLLKQAGDVEENPGP (SEQ ID NO: 694); ATNFSLLKQAGDVEENPGP (SEQ ID NO: 695); LLKQAGDVEENPGP (SEQ ID NO: 696); GSGEGRGSLLTCGDVEENPGP (SEQ ID NO: 697); EGRGSLLTCGDVEENPGP (SEQ ID NO: 698); LLTCGDVEENPGP (SEQ ID NO: 699); GSGQCTNYALLKLAGDVESNPGP (SEQ ID NO: 700); QCTNYALLKLAGDVESNPGP (SEQ ID NO: 701); LLKLAGDVESNPGP (SEQ ID NO: 702); GSGVKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 703); VKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 704); LLNFDLLKLAGDVESNPGP (SEQ ID NO: 705); TLNFDLLKLAGDVESNPGP (SEQ ID NO: 706); NFDLLKLAGDVESNPGP (SEQ ID NO: 707); QLLNFDLLKLAGDVESNPGP (SEQ ID NO: 708); APVKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 709); VTELLYRMKRAETYCPRPLLAIHPTEARHKQKIVAPVKQT (SEQ ID NO: 710); LNFDLLKLAGDVESNPGP (SEQ ID NO: 711); LLAIHPTEARHKQKIVAPVKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 712); and EARHKQKIVAPVKQTLNFDLLKLAGDVESNPGP (SEQ ID NO: 713).

H. CELLS

Recombinant particles contemplated herein are engineered to bind and transduce a cell. In particular embodiments, a recombinant particle contemplated herein is engineered to bind and transduce an immune effector cell. In particular embodiments, a cell transduced with a recombinant particle comprising a payload is modified to modulate the expression of one or more endogenous genes, and/or express one or more therapeutic polynucleotides and/or therapeutic polypeptides (*e.g.,* an engineered receptor) contemplated herein.

In particular embodiments, a recombinant particle, *e.g.,* a recombinant retroviral or lentiviral particle comprises a viral envelope comprising one or more mutated viral envelope glycoproteins that mediate virus-target cell fusion and one or more non-viral membrane-bound tropism polypeptides that bind an antigen expressed on a cell, *e.g.,* an immune effector cell.

An "immune effector cell" is any cell of the immune system that has one or more effector functions (*e.g.*, cytotoxic cell killing activity, secretion of cytokines, induction of

ADCC and/or CDC). Illustrative types of immune effector cells contemplated in particular embodiments include, without limitation, T lymphocytes, dendritic cells (DC), Treg cells, natural killer (NK) cells, natural killer T (NKT) cells, and macrophages. The terms "T cell" or "T lymphocyte" are art-recognized and are intended, in particular embodiments, to include thymocytes, immature T lymphocytes, mature T lymphocytes, resting T lymphocytes, and/or activated T lymphocytes. Illustrative examples of T lymphocytes suitable for use in particular embodiments, include but not limited to cytotoxic T cells (CTLs; $CD8^+$ T cells), TILs, helper T cells (HTLs; $CD4^+$ T cells), $CD4^+CD8^+$ T cells, $CD4^-$ $CD8^-$ T cells, or any other subset of T cells that has an effector function. In a particular embodiment, the cells comprise αβ T cells. In a particular embodiment, the cells comprise γδ T cells.

In particular embodiments, a recombinant particle, *e.g.,* a recombinant retroviral or lentiviral particle comprises a viral envelope comprising one or more mutated viral envelope glycoproteins that mediate virus-target cell fusion and one or more non-viral membrane-bound tropism polypeptides that bind an antigen on an immune effector cell, wherein the antigen is selected from the group consisting of: alpha, beta, gamma, or delta chain of the T cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD8α, CD8β, CD28, CD134 (OX40), CD137 (4-1BB), and CD278 (ICOS).

In particular embodiments, immune effector cells include natural killer (NK) cells. NK cells do not express T cell antigen receptors (TCR), CD3 or surface immunoglobulins (Ig) B cell receptor, but usually express the surface markers CD16 (FcyRIII) and CD56 in humans. In particular embodiments, a recombinant particle, *e.g.,* a recombinant retroviral or lentiviral particle comprises a viral envelope comprising one or more mutated viral envelope glycoproteins that mediate virus-target cell fusion and one or more non-viral membrane-bound tropism polypeptides that bind an antigen on an immune effector cell, wherein the antigen is CD 16 (FcyRIII) and/or CD56.

In particular embodiments, immune effector cells include natural killer T (NKT) cells.

In particular embodiments, a progenitor of an immune effector cell is transduced with a recombinant particle contemplated herein and is subsequently induced to differentiate, or differentiates, into one or more immune effector cells. In particular embodiments, progenitors of immune effectors cells include hematopoietic stem cells (HSCs) contained within the $CD34^+$ population of cells derived from cord blood, bone marrow or mobilized peripheral blood which naturally differentiate into mature immune effector cells, or which

can be induced to differentiate into mature immune effector cells. In particular embodiments, a recombinant particle, *e.g.,* a recombinant retroviral or lentiviral particle comprises a viral envelope comprising one or more mutated viral envelope glycoproteins that mediate virus-target cell fusion and one or more non-viral membrane-bound tropism polypeptides that bind an antigen on a hematopoietic stem cell, wherein the antigen is selected from the group consisting of: CD7, CD33, CD34, CD45, CD49f, CD90, CD98, CD110, CD117, CD123, CD133, CD184, CD201, FMS-like tyrosine kinase 3 (FLT3), and thrombopoietin receptor.

I. COMPOSITIONS AND FORMULATIONS

Formulations and compositions contemplated herein comprise one or more polypeptides, polynucleotides, vectors, genome editing components, recombinant particles and/or immune effector cells modified *ex vivo* formulated in pharmaceutically acceptable or physiologically-acceptable compositions for administration to a cell, tissue, organ, or an animal, either alone, or in combination with one or more other modalities of therapy.

In particular embodiments, a composition comprises a recombinant particle, *e.g.,* a recombinant retroviral or lentiviral particle comprises a viral envelope comprising one or more mutated viral envelope glycoproteins that mediate virus-target cell fusion and one or more non-viral membrane-bound tropism polypeptides, and a payload comprising one or more polynucleotides and/or polypeptides.

In particular embodiments, a composition comprises a recombinant particle, *e.g.,* a recombinant retroviral or lentiviral particle comprises a viral envelope comprising one or more mutated viral envelope glycoproteins that mediate virus-target cell fusion and one or more non-viral membrane-bound tropism polypeptides, and a payload comprising a vector comprising a polynucleotide comprising or encoding a promoter operably linked to one or more polynucleotide encoding one or more engineered receptors.

In particular embodiments, a composition comprises a recombinant particle, *e.g.,* a recombinant retroviral or lentiviral particle comprises a viral envelope comprising one or more mutated viral envelope glycoproteins that mediate virus-target cell fusion and one or more non-viral membrane-bound tropism polypeptides, and a payload comprising a genome editing composition comprising one or more polynucleotides encoding a nuclease, a nuclease, or one or more polynucleotides encoding a DNA repair template and a nuclease.

In particular embodiments, the composition is a pharmaceutical composition. A "pharmaceutical composition" refers to a composition formulated in a pharmaceutically-acceptable or physiologically-acceptable solution for administration to a cell or a subject, either alone, or in combination with one or more other modalities of therapy.

"Pharmaceutically acceptable" refers to molecular entities and compositions that do not produce excessive toxicity, irritation, allergic response, or other problems or complications, commensurate with a reasonable benefit/risk ratio when administered to a human.

In particular embodiments, a composition comprises a pharmaceutically acceptable carrier and a recombinant particle contemplated herein. The term "pharmaceutically acceptable carrier" refers to a diluent, adjuvant, excipient, vehicle and the like with which a recombinant particle, *e.g.,* a recombinant retroviral or lentiviral particle, is physiologically compatible with administration to a human, including but not limited to pharmaceutically acceptable cell culture media, Dulbecco's phosphate buffered saline (PBS), Ringer's solution, 5% dextrose in water (D5W), and normal/physiologic saline (0.9% NaCl).

In particular embodiments, a composition comprises a recombinant particle and a pharmaceutically acceptable carrier suitable for enteral or parenteral, *e.g.*, intravascular (intravenous or intraarterial), intraosseous, intraperitoneal, intraventricular, intracerebral, intracranial, intraspinal, intrathecal, intramuscular, and intramedullary, administration and formulation.

In particular embodiments, a composition is substantially free of mycoplasma, endotoxin, and microbial contamination. By "substantially free" with respect to endotoxin is meant that there is less endotoxin per dose of cells than is allowed by the FDA for a biologic, which is a total endotoxin of 5 EU/kg body weight per day, which for an average 70 kg person is 350 EU per total dose of cells. In particular embodiments, compositions contemplated herein contain about 0.5 EU/mL to about 5.0 EU/mL, or about 0.5 EU/mL, 1.0 EU/mL, 1.5 EU/mL, 2.0 EU/mL, 2.5 EU/mL, 3.0 EU/mL, 3.5 EU/mL, 4.0 EU/mL, 4.5 EU/mL, or 5.0 EU/mL.

In particular embodiments, compositions contemplated herein are used in the treatment of a cancer, GVHD, an infectious disease, an autoimmune disease, an inflammatory disease, or an immunodeficiency. In particular embodiments, a composition comprises a recombinant particle contemplated herein and one or more cytokines, growth factors, steroids, NSAIDs, DMARDs, anti-inflammatories, chemotherapeutics,

radiotherapeutics, therapeutic antibodies, or other active and ancillary agents, either alone or in combination.

It would be understood by the skilled artisan that particular embodiments contemplated herein may comprise other formulations, such as those that are well known in the pharmaceutical art, and are described, for example, in *Remington: The Science and Practice of Pharmacy*, Volume I and Volume II. 23rd Edition. Edited by Adeboye Adejare. Academic Press, 2020, which is incorporated by reference herein, in its entirety.

J. METHODS OF MAKING

The manufacturing processes contemplated herein comprise an upstream process that produces a recombinant particle and a downstream process that purifies the recombinant particle. In preferred embodiments, a method of manufacturing a recombinant retroviral particle or recombinant lentiviral particle comprises an upstream process that produces the recombinant viral particle and a downstream process that purifies the recombinant viral particle. Methods of manufacturing lentiviral particles are described in WO2023/003844, which is hereby incorporated by reference in its entirety. See, also Kutner *et al.*, BMC Biotechnol. 2009;9:10. doi: 10.1186/1472-6750-9-10 and Kutner *et al.* Nat. Protoc. 2009;4(4):495-505. doi: 10.1038/nprot.2009.22.

In particular embodiments, a method of manufacturing recombinant retroviral particles or recombinant lentiviral particles comprises transfecting a host cell culture with packaging plasmids and a transfer plasmid, culturing transfected host cells to produce viral particles; and collecting and processing the culture supernatant that contains the crude viral particles to remove impurities and concentrate and formulate the particles for clinical use.

In particular embodiments, retroviral particles are manufactured by transfecting host cells with a multi-plasmid system comprising (i) an envelope plasmid encoding one or more mutated viral envelope glycoproteins that retain fusogenic activity and substantially lack or lack cognate receptor binding activity and one or more non-viral membrane-bound tropism polypeptides, (ii) a packaging plasmid encoding gag-pol and (iii) a transfer plasmid or vector.

In particular embodiments, lentiviral particles are manufactured by transfecting host cells with a third-generation lentiviral vector plasmid system comprising (i) an envelope plasmid encoding one or more mutated viral envelope glycoproteins that retain fusogenic activity and substantially lack or lack cognate receptor binding activity and one or more non-

viral membrane-bound tropism polypeptides, (ii) a packaging plasmid encoding gag-pol, (iii) a packaging plasmid encoding rev, and (iv) a transfer plasmid or vector.

A "transfer plasmid" or "transfer vector" encodes a viral genomic RNA modified to package a viral vector that comprises a polynucleotide sequence delivered by recombinant viral particle to a cell. In particular embodiments, a transfer plasmid comprises one or more polynucleotide sequences of interest flanked by long terminal repeat (LTR) sequences, which facilitate packaging, reverse transcription and integration of the viral vector and associated polynucleotide sequences into the host genome. Viral vectors contemplated herein are replication incompetent, *i.e.*, lack the genetic elements necessary for generation of infective particles in the host cell. For example, the viral vector may be designed with a deletion of the 3′ LTR, rendering the virus "self-inactivating" (SIN).

Illustrative examples of host cells suitable for transfection with the aforementioned plasmid systems include but are not limited to HEK293 cells, HEK293S cells, HEK293T cells, HEK293T cells adapted for suspension culture (HEK293Ts), HEK293F cells, HEK293FT cells, HEK293FTM cells, and HEK293E cells.

Once host cells are transfected and produce viral particles, the cell culture is subjected to a downstream process that yields particles sufficient for clinical use, In particular embodiments, a downstream process comprises treating the contents of the bioreactor with a DNA endonuclease, *.e.g.,* benzonase; harvesting and clarifying the suspension culture supernatant by filtration; capturing and concentrating the viral particles in the resultant filtrate using affinity chromatography or cation exchange chromatography; filtering the eluate comprising the viral particles; ultrafiltering and diafiltering the viral particles using tangential flow filtration (TFF); and formulating the viral particles in a culture medium to produce a formulated bulk viral particles. In one embodiment, the formulated bulk lentiviral particles are sterile filtered, filled, and frozen; and subsequently thawed, sterile filtered, subjected to a final fill finish, and frozen. In another embodiment, the bulk lentiviral particles are sterile filtered, subjected to a final fill finish, and frozen.

K. METHODS OF USE

Recombinant particles contemplated herein are engineered to modify a cell *in vivo* to express one or more engineered receptors that bind one or more target antigens and redirect the cell to a target cell expressing the target antigen, thereby preventing, treating, or

ameliorating at least one symptom associated with, a cancer, GVHD, an infectious disease, an autoimmune disease, an inflammatory disease, or an immunodeficiency in a subject.

In particular embodiments, a method of preventing, treating, or ameliorating at least one symptom of a cancer, GVHD, an infectious disease, an autoimmune disease, an inflammatory disease, or an immunodeficiency comprises administering the subject an amount of recombinant particle contemplated herein. The term "amount" as used herein, refers to "an amount effective" or "an effective amount" of a recombinant particle contemplated herein comprising a payload contemplated herein, *etc.*, to achieve a beneficial or desired prophylactic or therapeutic result, including clinical results. A "prophylactically effective amount" refers to an amount of recombinant particle contemplated herein comprising payload contemplated herein, effective to achieve the desired prophylactic result. A "therapeutically effective amount" refers to an amount of recombinant particle contemplated herein comprising a paylaod contemplated herein, that is effective to "treat" a subject (*e.g.*, a patient). When a therapeutic amount is indicated, the precise amount of the compositions to be administered can be determined by a physician with consideration of individual differences in age, weight, tumor size, extent of infection or metastasis, and condition of the patient (subject).

In particular embodiments, a recombinant retroviral or lentiviral particle is engineered to modify an immune effector cell *in vivo* to express one or more engineered receptors that bind one or more target antigens to redirect the immune effector cell to a target cell expressing the target antigens, thereby preventing, treating, or ameliorating at least one symptom associated with, a cancer, GVHD, an infectious disease, an autoimmune disease, an inflammatory disease, or an immunodeficiency in a subject.

In particular embodiments, a recombinant particle contemplated herein is administered to a subject to treat, prevent, or ameliorate at least one symptom of a solid tumor in the subject.

In particular embodiments, a recombinant particle contemplated herein is administered to a subject to treat, prevent, or ameliorate at least one symptom of a solid tumor selected from the group consisting of prostate cancer, lung cancer, non-small cell lung cancer (NSCLC), liver cancer, cervical cancer, colon cancer, breast cancer, ovarian cancer, endometrial cancer, pancreatic cancer, melanoma, esophageal cancer, gastric cancer, stomach cancer, renal carcinoma, bladder cancer, hepatocellular carcinoma, renal cell

carcinoma, urothelial carcinoma, head and neck cancer, glioma, glioblastoma, colorectal cancer, thyroid cancer, epithelial cancers, or adenocarcinomas.

In particular embodiments, a recombinant particle contemplated herein is administered to a subject to treat, prevent, or ameliorate at least one symptom of a liquid or hematological cancer in the subject.

In particular embodiments, a recombinant particle contemplated herein is administered to a subject to treat, prevent, or ameliorate at least one symptom of a liquid or hematological cancer selected from the group consisting of leukemias, lymphomas, and multiple myeloma. In particular embodiments, a recombinant particle contemplated herein is administered to a subject to treat, prevent, or ameliorate at least one symptom of a relapsed and/or refractory leukemia, a relapsed and/or refractory lymphoma, or a relapsed and/or refractory multiple myeloma.

In particular embodiments, a recombinant particle contemplated herein is administered to a subject to treat, prevent, or ameliorate at least one symptom of a leukemia or precursor thereof selected from the group consisting of: an acute lymphocytic leukemia (ALL), an acute myeloid leukemia (AML), a myelodysplastic syndrome (MDS), a plasma cell leukemia (PCL), erythroleukemia, a hairy cell leukemia (HCL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML) and polycythemia vera.

In particular embodiments, a recombinant particle contemplated herein is administered to a subject to treat, prevent, or ameliorate at least one symptom of a lymphoma or precursor thereof selected from the group consisting of: a Hodgkin's lymphoma or a non-Hodgkin's lymphoma, *e.g.*, diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle-cell lymphoma (MCL), small lymphocytic lymphoma (SLL), primary mediastinal large B-cell lymphoma, a marginal zone B cell lymphoma (MZL), mucosa-associated lymphatic tissue lymphoma (MALT), Waldenstrom's macroglobulinema, Burkitt's lymphoma (BL), immunoblastic large cell lymphoma, centroblastic large cell lymphoma, anaplastic B-cell lymphoma, mycosis fungoides, Sezary syndrome, T-lymphoblastic lymphoma, and anaplastic large-cell lymphoma (ALCL).

In particular embodiments, a recombinant particle contemplated herein is administered to a subject to treat, prevent, or ameliorate at least one symptom of a multiple myeloma or precursor thereof selected from the group consisting of: monoclonal gammopathy of undetermined significance (MGUS), active multiple myeloma, smoldering

multiple myeloma, light chain myeloma, non-secretory myeloma, IgD myeloma, IgE myeloma, osteosclerotic myeloma, solitary plasmacytoma of bone, and extramedullary plasmacytoma.

In particular embodiments, a recombinant particle is administered to a subject in combination with one or more anti-cancer therapies including, but not limited to, an autologous stem cell transplant (ASCT), radiation, surgery, a chemotherapeutic agent, an immunomodulatory agent and a targeted cancer therapy.

In particular embodiments, the one or more anti-cancer therapies is selected from the group consisting of 6-mercaptopurine, abiraterone, alemtuzumab, all-trans retinoic acid, anastrozole, aprepitant, arsenic trioxide, atezolizumab, avelumab, azacytidine, bafetinib, bavituximab, bevacizumab, bivatuzumab, bleomycin, blinatumomab, bortezomib, bosutinib, cabazitaxel, capecitabine, carboplatin, carfilzomib, cetuximab, cisplatin, cladribine, conatumumab, corticosteroid, crizotinib, cyclophosphamide, cytarabine, dacetuzumab, dalotuzumab, daratumumab, dasatinib, daunorubicin, danusertib, decitabine, denosumab, dexamethasone, docetaxel, doxorubicin, duligotumab, durvalumab, elotozumab, eribulin, erlotinib, etoposide, everolimus, exemestane, filgrastim, fludarabine, fluorouracil, fulvestrant, gemcitabine, gemtuzumab, hydroxyurea, ibritumomab, idarubicin, imatinib, imiquimod, indatuximab, inotuzumab, ipilimumab, ixabepilone, ixazomib, lapatinib, lenalidomide, letrozole, leuprolide, lorvotuzumab, lucatumumab, melphalan, methotrexate, milatuzumab, mitoxantrone, moxetumomab, nilotinib, nivolumab, ocaratuzumab, ofatumumab, oxaliplatin, paclitaxel, palonosetron, pembrolizumab, pemetrexed, pomalidomide, ponatinib, prednisone, radium-223, rituximab, saracatinib, siltuximab, sipuleucel-T, sorafenib, sunitinib, tamoxifen, temozolomide, temsirolimus, teprotumumab, thalidomide, tinorelbine, topotecan, tozasertib, trastuzumab, ublituximab, vincristine, and zoledronic acid.

In particular embodiments, a recombinant particle comprising one or more mutated viral envelope glycoproteins that mediate virus-target cell fusion, one or more non-viral membrane-bound tropism polypeptides, and a vector encoding a CAR, CCR, αβ TCR, γδ TCR, and/or a DARIC that binds BCMA, GPCR5D and/or CD38, and optionally a CTBR is administered to a subject to treat, prevent, or ameliorate at least one symptom of a multiple myeloma in the subject. In preferred embodiments, the recombinant particle is a recombinant retroviral particle or more preferably, a recombinant lentiviral particle.

In particular embodiments, a recombinant lentiviral particle comprising a viral envelope comprising a mutated VSIV-G envelope protein (*e.g.*, SEQ ID NOs: 582-645, or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto) that mediates fusion of the viral particle and a cell but that substantially ablates or ablates the protein's ability to bind its cognate receptor expressed on a cell; one or more non-viral membrane-bound tropism polypeptides comprising an amino acid sequence set forth in any one of SEQ ID NOs: 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, and 486; and a lentiviral vector comprising or encoding a promoter operably linked to a polynucleotide encoding a CAR, CCR, αβ TCR, γδ TCR, and/or a DARIC that binds BCMA (*e.g.*, SEQ ID NOs: 662, 664), GPCR5D and/or CD38, and optionally a CTBR is administered to a subject to treat, prevent, or ameliorate at least one symptom of a multiple myeloma in the subject.

In particular embodiments, a recombinant lentiviral particle comprising a viral envelope comprising a mutated VSIV-G envelope protein (*e.g.*, SEQ ID NOs: 582-645, or an amino acid sequence at least 95%, 96%, 97%, 98%, or 99% identical thereto) that mediates fusion of the viral particle and a cell but that substantially ablates or ablates the protein's ability to bind its cognate receptor expressed on a cell; one or more non-viral membrane-bound tropism polypeptides comprising an amino acid sequence set forth in any one of SEQ ID NOs: 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, and 486; and a lentiviral vector comprising or encoding a promoter operably linked to a polynucleotide encoding a CAR, CCR, αβ TCR, γδ TCR, and/or a DARIC that binds CD19 (*e.g.*, SEQ ID NOs: 663, 665, 666), CD79A, or CD79B and a CCR that binds CD20 or CD22 is administered to a subject to treat, prevent, or ameliorate at least one symptom of a non-Hodgkin's lymphoma in the subject.

L. ENUMERATED EMBODIMENTS

Embodiment 1: A recombinant particle comprising: (a) a surface comprising (i) one or more mutated viral envelope glycoproteins that retain fusogenic activity and that lack cognate receptor binding activity and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof that binds an antigen expressed on an immune effector cell, a spacer polypeptide, a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a therapeutic payload.

Embodiment 2: The particle of embodiment 1, wherein the particle is a fusosome; an extracellular vesicle, including a microvesicle, an apoptotic body, and an exosome; a lipid nanoparticle; a virus-like particle (VLPs); or a recombinant viral particle.

Embodiment 3: The particle of embodiment 1 or embodiment 2, wherein the surface comprises a single layer of phospholipid, a phospholipid bilayer, a cell membrane, a capsid, or a viral envelope.

Embodiment 4: The particle of any one of embodiments 1 to 3, wherein the payload comprises one or more polynucleotides and/or polypeptides.

Embodiment 5: The particle of any one of embodiments 1 to 4, wherein the payload comprises a vector that encodes a therapeutic polynucleotide or polypeptide.

Embodiment 6: The particle of any one of embodiments 1 to 5, wherein the payload comprises a vector that encodes one or more engineered receptors.

Embodiment 7: The particle of any one of embodiments 1 to 6, wherein the payload comprises a vector that encodes a promoter operably linked to a polynucleotide encoding one or more engineered receptors.

Embodiment 8: A recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) one or more mutated viral envelope glycoproteins that retain fusogenic activity and that lack cognate receptor binding activity and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof that binds an antigen expressed on an immune effector cell, a spacer polypeptide, a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a recombinant lentiviral vector comprising a polynucleotide encoding a promoter operably linked to a polynucleotide encoding one or more engineered receptors.

Embodiment 9: The particle of any one of embodiments 1 to 8, wherein the one or more mutated viral envelope glycoproteins comprise a rhabdovirus envelope glycoprotein, or one or more paramyxovirus envelope glycoproteins.

Embodiment 10: The particle of any one of embodiments 1 to 8, wherein the one or more mutated viral envelope glycoproteins comprise a vesiculovirus envelope glycoprotein, one or more morbillivirus envelope glycoproteins or one or more henipavirus envelope glycoproteins.

Embodiment 11: The particle of embodiment 10, wherein the vesiculovirus is selected from the group consisting of: vesicular stomatitis Alagoas virus (VSAV; Alagoas vesiculovirus), Carajás virus (CJSV; Carajas vesiculovirus), Chandipura virus (CHPV;

Chandipura vesiculovirus), Cocal virus (COCV; Cocal vesiculovirus), vesicular stomatitis Indiana virus (VSIV; Indiana vesiculovirus), Isfahan virus (ISFV; Isfahan vesiculovirus), Maraba virus (MARAV; Maraba vesiculovirus), Morreton virus (MORV; Morreton vesiculovirus), vesicular stomatitis New Jersey virus (VSNJV; New Jersey vesiculovirus), and Piry virus (PIRYV; Piry vesiculovirus).

Embodiment 12: The particle of embodiment 10 or embodiment 11, wherein vesiculovirus envelope glycoprotein is a vesiculovirus G protein.

Embodiment 13: The particle of any one of embodiments 10 to 12, wherein the vesiculovirus G protein is a COCV G glycoprotein (COCV-G) or a VSIV G glycoprotein (VSIV-G).

Embodiment 14: The particle of any one of embodiments 10 to 13, wherein the VSIV-G envelope protein comprises one or more of: (a) one or more amino acid substitutions at H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, and R354; (b) an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, and an insertion of GGS between N208 and Y209; or (c) amino acid substitutions at K47 and/or R354; or (d) a deletion of residues 1-8.

Embodiment 15: The particle of any one of embodiments 10 to 14, wherein the VSIV-G envelope protein comprises one or more amino acid substitutions at H8, K47, Y209, and R354.

Embodiment 16: The particle of any one of embodiments 10 to 15, wherein the VSIV-G envelope protein comprises amino acid substitutions selected from the group consisting of: K47A and R354A; K47A and R354G; K47A and R354F; K47A and R354Q; K47G and R354A; K47G and R354G; K47G and R354F; K47G and R354Q;K47F and R354A; K47F and R354G; K47F and R354F; K47F and R354Q; K47Q and R354A; K47Q and R354G; K47Q and R354F; and K47Q and R354Q.

Embodiment 17: The particle of any one of embodiments 10 to 16, wherein the VSIV-G envelope protein comprises the amino acid sequence set forth in SEQ ID NO: 2 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto, wherein X1= I, X2 = A, X3 = Q, and X4 = A; X1= I, X2 = A, X3 = Q, and X4 = G; X1= I, X2 = A, X3 = Q, and X4 = F; X1= I, X2 = A, X3 = Q, and X4 = Q; X1= L, X2 = A, X3 = Q, and X4 = A; X1= L, X2 = A, X3 = Q, and X4 = G; X1= L, X2 = A, X3 =

Q, and X4 = F; X1= L, X2 = A, X3 = Q, and X4 = Q; X1= I, X2 = A, X3 = H, and X4 = A; X1= I, X2 = A, X3 = H, and X4 = G; X1= I, X2 = A, X3 = H, and X4 = F; X1= I, X2 = A, X3 = H, and X4 = Q; X1= L, X2 = A, X3 = H, and X4 = A; X1= L, X2 = A, X3 = H, and X4 = G; X1= L, X2 = A, X3 = H, and X4 = F; X1= L, X2 = A, X3 = H, and X4 = Q; X1= I, X2 = G, X3 = Q, and X4 = A; X1= I, X2 = G, X3 = Q, and X4 = G; X1= I, X2 = G, X3 = Q, and X4 = F; X1= I, X2 = G, X3 = Q, and X4 = Q; X1= L, X2 = G, X3 = Q, and X4 = A; X1= L, X2 = G, X3 = Q, and X4 = G; X1= L, X2 = G, X3 = Q, and X4 = F; X1= L, X2 = G, X3 = Q, and X4 = Q; X1= I, X2 = G, X3 = H, and X4 = A; X1= I, X2 = G, X3 = H, and X4 = G; X1= I, X2 = G, X3 = H, and X4 = F; X1= I, X2 = G, X3 = H, and X4 = Q; X1= L, X2 = G, X3 = H, and X4 = A; X1= L, X2 = G, X3 = H, and X4 = G; X1= L, X2 = G, X3 = H, and X4 = F; X1= L, X2 = G, X3 = H, and X4 = Q; X1= I, X2 = F, X3 = Q, and X4 = A; X1= I, X2 = F, X3 = Q, and X4 = G; X1= I, X2 = F, X3 = Q, and X4 = F; X1= I, X2 = F, X3 = Q, and X4 = Q; X1= L, X2 = F, X3 = Q, and X4 = A; X1= L, X2 = F, X3 = Q, and X4 = G; X1= L, X2 = F, X3 = Q, and X4 = F; X1= L, X2 = F, X3 = Q, and X4 = Q; X1= I, X2 = F, X3 = H, and X4 = A; X1= I, X2 = F, X3 = H, and X4 = G; X1= I, X2 = F, X3 = H, and X4 = F; X1= I, X2 = F, X3 = H, and X4 = Q; X1= L, X2 = F, X3 = H, and X4 = A; X1= L, X2 = F, X3 = H, and X4 = G; X1= L, X2 = F, X3 = H, and X4 = F; X1= L, X2 = F, X3 = H, and X4 = Q; X1= I, X2 = Q, X3 = Q, and X4 = A; X1= I, X2 = Q, X3 = Q, and X4 = G; X1= I, X2 = Q, X3 = Q, and X4 = F; X1= I, X2 = Q, X3 = Q, and X4 = Q; X1= L, X2 = Q, X3 = Q, and X4 = A; X1= L, X2 = Q, X3 = Q, and X4 = G; X1= L, X2 = Q, X3 = Q, and X4 = F; X1= L, X2 = Q, X3 = Q, and X4 = Q; X1= I, X2 = Q, X3 = H, and X4 = A; X1= I, X2 = Q, X3 = H, and X4 = G; X1= I, X2 = Q, X3 = H, and X4 = F; X1= I, X2 = Q, X3 = H, and X4 = Q; X1= L, X2 = Q, X3 = H, and X4 = A; X1= L, X2 = Q, X3 = H, and X4 = G; X1= L, X2 = Q, X3 = H, and X4 = F; and X1= L, X2 = Q, X3 = H, and X4 = Q.

Embodiment 18: The particle of any one of embodiments 10 to 17, wherein the VSIV-G envelope protein comprises the amino acid sequence set forth in any one of SEQ ID NOs: 582-645 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

Embodiment 19: The particle of any one of embodiments 10 to 18, wherein the VSIV-G envelope protein comprises the amino acid sequence set forth in any one of SEQ ID NOs: 630, 634, 638, and 642 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

Embodiment 20: The particle of any one of embodiments 10 to 13, wherein the vesiculovirus G protein is COCV-G.

Embodiment 21: The recombinant lentivirus of embodiment 11, wherein the COCV-G envelope protein comprises one or more amino acid substitutions at K47 and/or R354.

Embodiment 22: The recombinant lentivirus of embodiment 11 or embodiment 12, wherein the COCV-G envelope protein comprises amino acid substitutions selected from the group consisting of: K47A and R354A; K47A and R354G; K47A and R354F; K47A and R354Q; K47G and R354A; K47G and R354G; K47G and R354F; K47G and R354Q;K47F and R354A; K47F and R354G; K47F and R354F; K47F and R354Q; K47Q and R354A; K47Q and R354G; K47Q and R354F; and K47Q and R354Q.

Embodiment 23: The recombinant lentivirus of any one of embodiments 11 to 13, wherein the COCV-G envelope protein comprises the amino acid sequence set forth in SEQ ID NO: 4 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto, wherein X1 = A and X2 = A; X1 = A and X2 = G; X1 = A and X2 = F; X1 = A and X2 = Q; X1 = G and X2 = A; X1 = G and X2 = G; X1 = G and X2 = F; X1 = G and X2 = Q; X1 = F and X2 = A; X1 = F and X2 = G; X1 = F and X2 = F; X1 = F and X2 = Q; X1 = Q and X2 = A; X1 = Q and X2 = G; X1 = Q and X2 = F; or X1 = Q and X2 = Q.

Embodiment 24: The recombinant lentivirus of any one of embodiments 11 to 14, wherein the COCV-G envelope protein comprises the amino acid sequence set forth in any one of SEQ ID NOs: 646-661 or an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% identical thereto.

Embodiment 25: The particle of embodiment 10, wherein the one or more morbillivirus envelope glycoproteins are measles virus F (MV-F) and measles virus H (MV-H).

Embodiment 26: The particle of embodiment 25, wherein the MV-H protein comprises one or more amino acid substitutions at Y463, R515, S530, and F531.

Embodiment 27: The particle of embodiment 16 or embodiment 17, wherein the MV-H protein comprises one or more amino acid substitutions selected from the group consisting of: Y463A, R515A, S530, and F531.

Embodiment 28: The particle of any one of embodiments 25 to 27, wherein the MV-H protein comprises the amino acid sequence set forth in SEQ ID NO: 7.

Embodiment 29: The particle of embodiment 10, wherein the one or more henipavirus envelope glycoproteins are nipah virus F (NiV-F) and nipah virus G (NiV-G).

Embodiment 30: The particle of embodiment 29, wherein the NiV-G protein comprises one or more amino acid substitutions at E468, W471, Q497, and E500.

Embodiment 31: The particle of embodiment 29 or embodiment 30, wherein the NiV-G protein comprises one or more amino acid substitutions selected from the group consisting of: E468A, W471A, Q497A, and E500A.

Embodiment 32: The particle of any one of embodiments 29 to 31, wherein the NiV-G protein comprises the amino acid sequence set forth in SEQ ID NO: 10.

Embodiment 33: The particle of any one of embodiments 1 to 32, wherein the antibody or antigen binding fragment thereof is selected from the group consisting of: a Camel Ig, a Llama Ig, an Alpaca Ig, Ig NAR, a Fab′ fragment, a F(ab′)2 fragment, a bispecific Fab dimer (Fab2), a trispecific Fab trimer (Fab3), an Fv, a single chain Fv protein (scFv), a bis-scFv, (scFv)2, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a Fibronectin type III (FN3) domain antibody, and a single-domain antibody (sdAb, a camelid VHH, Nanobody).

Embodiment 34: The particle of any one of embodiments 1 to 33, wherein the antibody or antigen binding fragment thereof binds an antigen expressed on an immune effector cell selected from the group consisting of: the alpha, beta, gamma, or delta chain of the T cell receptor, CD2, CD3δ, CD3ε CD3γ, CD4, CD8α, and CD8β.

Embodiment 35: The particle of any one of embodiments 1 to 34, wherein the antibody or antigen binding fragment thereof comprises (a) a heavy chain variable region (VH) comprising a CDRH1, a CDRH2, and a CDRH3 of an antibody or antigen binding fragment thereof set forth in Table 5; (b) a polypeptide linker; and (c) a light chain variable region (VL) comprising a CDRL1, a CDRL2, and a CDRL3 of an antibody or antigen binding fragment thereof set forth in Table 5.

Embodiment 36: The particle of any one of embodiments 1 to 35, wherein the antibody or antigen binding fragment thereof comprises (a) a heavy chain variable region (VH) of an antibody or antigen binding fragment thereof set forth in Table 5; (b) a polypeptide linker; and (c) a light chain variable region (VL) of an antibody or antigen binding fragment thereof set forth in Table 5.

Embodiment 37: The particle of any one of embodiments 1 to 36, wherein the antibody or antigen binding fragment thereof comprises: (a) a heavy chain variable region

(VH) of an antibody or antigen binding fragment thereof set forth in Table 5; (b) a polypeptide linker selected from the group consisting of: (GGGGS)n wherein n = 1, 2, 3, 4 or 5; S(GGGGS)n wherein n = 1, 2, 3, 4 or 5; GEGTSTGSGGSGGSGGAD, GSTSGSGKPGSGEGSTKG and variants thereof comprising an amino acid sequence 95% identical thereto; and (c) the corresponding light chain variable region (VL) of the antibody or antigen binding fragment thereof set forth in Table 5.

Embodiment 38: The particle of any one of embodiments 1 to 37, wherein the antibody or antigen binding fragment thereof comprises the amino acid sequence set forth in any one of SEQ ID NOs: 19, 20, 29, 30, 39, 40, 49, 50, 59, 60, 69, 70, 79, 80, 89, 90, 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, 170, 179, 180, 189, 190, 199, 200, 209, 210, 219, 220, 229, 230, 239, 240, 249, 250, 259, 260, 269, 270, 279, 280, 289, 290, 299, 300, 309, 310, 319, 320, 329, 330, 339, 340, 349, 350, 359, 360, 369, 370, 379, 380, 389, 390, 399, 400, 409, and 410.

Embodiment 39: The particle of any one of embodiments 1 to 38, wherein the antibody or antigen binding fragment thereof comprises the amino acid sequence set forth in any one of SEQ ID NOs: 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, and 170.

Embodiment 40: The particle of any one of embodiments 1 to 39, wherein the antibody or antigen binding fragment thereof comprises the amino acid sequence set forth in any one of SEQ ID NOs: 99 or 100, 109 or 110, 119 or 120, 129 or 130, 139 or 140, 149 or 150, 159 or 160, and 169 or 170.

Embodiment 41: The particle of any one of embodiments 1 to 40, wherein the spacer comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 411-434.

Embodiment 42: The particle of any one of embodiments 1 to 41, wherein the spacer comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 411-413, SEQ ID NOs: 414-423, SEQ ID NOs: 424-427, or SEQ ID NOs: 428-434.

Embodiment 43: The particle of any one of embodiments 1 to 42, wherein the transmembrane domain comprises an amino acid sequence at least 85% identical to, at least

90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 435, 436, 437, 438, 439, 440 and 441.

Embodiment 44: The particle of any one of embodiments 1 to 43, wherein the intracellular domain comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 442, 443, 444, 445, 446, 447 and 448.

Embodiment 45: The particle of any one of embodiments 1 to 44, wherein the tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 455-576.

Embodiment 46: The particle of any one of embodiments 1 to 45, wherein the tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 471-486.

Embodiment 47: The particle of any one of embodiments 1 to 45, wherein the tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 535-554.

Embodiment 48: The particle of any one of embodiments 1 to 45, wherein the tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 555-562.

Embodiment 49: The particle of any one of embodiments 1 to 45, wherein the tropism polypeptide comprises an amino acid sequence at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 563 or 564 or SEQ ID NO: 471 or SEQ ID NO: 553.

Embodiment 50: The particle of any one of embodiments 1 to 49, further comprising one or more secondary non-viral membrane bound tropism polypeptides.

Embodiment 51: The particle of embodiment 50, wherein the one or more secondary non-viral membrane bound tropism polypeptides comprise one or more of CD80, CD86, CD137L, OX40L, and ICOSL or variants thereof.

Embodiment 52: The particle of any one of embodiments 1 to 51, further comprising one or more secondary non-viral membrane-bound tropism polypeptides at least 85% identical to, at least 90% identical to, at least 95% identical to, at least 96% identical to, at least 97% identical to, at least 98% identical to, at least 99% identical to, or identical to the amino acid sequence set forth in any one of SEQ ID NOs: 577-581.

Embodiment 53: The particle of any one of embodiments 8 to 52, wherein the recombinant lentiviral vector is engineered or derived from a lentiviral genome of a lentivirus selected from the group consisting of: human immunodeficiency virus 1 (HIV-1); human immunodeficiency virus 2 (HIV-2); visna-maedi virus (VMV); caprine arthritis-encephalitis virus (CAEV); equine infectious anemia virus (EIAV); feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV).

Embodiment 54: The particle of any one of embodiments 8 to 53, wherein the recombinant lentiviral vector further comprises one or more polynucleotides encoding one or more of the following: a signal peptide, a post-transcriptional regulatory element, an insulator element, a selectable marker, and a cell suicide gene.

Embodiment 55: The particle of embodiment 54, wherein the post-transcriptional regulatory element is a woodchuck hepatitis virus post-transcriptional regulatory element (WPRE) or a hepatitis B virus post-transcriptional regulatory element (HPRE).

Embodiment 56: The particle of any one of embodiments 7 to 55, wherein the promoter is selected from the group consisting of: a β-actin promoter, a cytomegalovirus (CMV) immediate early promoter, a simian virus 40 (SV40) (*e.g.*, early or late) promoter, a Moloney murine leukemia virus (MoMLV) promoter, a Rous sarcoma virus (RSV) promoter, a herpes simplex virus (HSV) (thymidine kinase) promoter, an SV40/CD43 promoter, a spleen focus forming virus (SFFV) promoter, an elongation factor 1-alpha (EFlα) short promoter (intronless), an EFlα long promoter containing an intron, a Ubiquitin C (UBC) promoter, a phosphoglycerate kinase-1 (PGK) promoter, a cytomegalovirus enhancer/chicken β-actin (CAG) promoter, and a myeloproliferative sarcoma virus enhancer,

negative control region deleted, dl587rev primer-binding site substituted (MND) U3 promoter.

Embodiment 57: The particle of any one of embodiments 6 to 56, wherein the one or more engineered receptors are selected from the group consisting of: a chimeric antigen receptor (CAR), a chimeric costimulatory receptor (CCR), an alpha-beta T cell receptor (αβ TCR), a gamma delta T cell receptor (γδ TCR), a dimerizing agent regulated immunoreceptor complex (DARIC), a chimeric TGF-β receptor (CTBR), and a zetakine receptor.

Embodiment 58: The particle of any one of embodiments 6 to 57, wherein the one or more engineered receptors bind an antigen selected from the group consisting of: alpha folate receptor (FRα), αvβ6 integrin, BAFFR, B cell maturation antigen (BCMA), B7-H3 (CD276), B7-H6, carbonic anhydrase IX (CAIX), CD16, CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD44, CD44v6, CD44v7/8, CD70, CD79A, CD79B, CD123, CD133, CD138, CD171, carcinoembryonic antigen (CEA), claudin 6, (CLDN6), claudin 18 isoform 2 (CLDN18.2), C-type lectin-like molecule-1 (CLL-1), CD2 subset 1 (CS-1), chondroitin sulfate proteoglycan 4 (CSPG4), cutaneous T cell lymphoma-associated antigen 1 (CTAGE1), delta like canonical Notch ligand 3 (DLL3), epidermal growth factor receptor (EGFR), epidermal growth factor receptor variant III (EGFRvIII), epithelial glycoprotein 2 (EGP2), epithelial glycoprotein 40 (EGP40), epithelial cell adhesion molecule (EPCAM), ephrin type-A receptor 2 (EPHA2), erb-b2 receptor tyrosine kinase 4 (ERBB4), fibroblast activation protein (FAP), Fc Receptor Like 5 (FCRL5), fetal acetylcholinesterase receptor (AchR), ganglioside G2 (GD2), ganglioside G3 (GD3), Glypican-3 (GPC3), G Protein-Coupled Receptor Class C Group 5 Member D (GPCR5D), EGFR family including ErbB2 (HER2), HER2 p95, IL-10Rα, IL-13Rα2, Kappa, cancer/testis antigen 2 (LAGE-1A), Lambda, Lewis-Y (LeY), L1 cell adhesion molecule (L1-CAM), melanoma antigen gene (MAGE)-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGEA10, melanoma antigen recognized by T cells 1 (MelanA or MART1), Mesothelin (MSLN), MUC1, MUC16, MHC class I chain related proteins A (MICA), MHC class I chain related proteins B (MICB), neural cell adhesion molecule (NCAM), cancer/testis antigen 1 (NY-ESO-1), placenta-specific 1 (PLAC1), preferentially expressed antigen in melanoma (PRAME), prostate stem cell antigen (PSCA), prostate-specific membrane antigen (PSMA), receptor tyrosine kinase-like orphan receptor 1 (ROR1), SLAMF7, synovial sarcoma, X breakpoint 2 (SSX2), Survivin, TACI, tumor associated glycoprotein 72 (TAG72), tumor endothelial marker 1 (TEM1/CD248), tumor endothelial marker 7-related (TEM7R), transforming growth factor

beta 1 (TFGβ1), trophoblast glycoprotein (TPBG), UL16-binding protein (ULBP) 1, ULBP2, ULBP3, ULBP4, ULBP5, ULBP6, vascular endothelial growth factor receptor 2 (VEGFR2), and Wilms tumor 1 (WT-1).

Embodiment 59: The particle of any one of embodiments 6 to 58, wherein the one or more engineered receptors bind an antigen selected from the group consisting of: BCMA, CD19, CD20, CD22, CD33, CD38, CD79A, CD79B, GPCR5D, MAGE-A4, MSLN, MUC16, NY-ESO-1, PSCA, PSMA and ROR1.

Embodiment 60: The particle of any one of embodiments 6 to 58, wherein the one or more engineered receptors bind an antigen selected from the group consisting of: BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, and GPCR5D.

Embodiment 61: The particle of any one of embodiments 6 to 60, wherein the one or more engineered receptors bind an antigen selected from the group consisting of: BCMA, CD38, and GPCR5D.

Embodiment 62: The particle of any one of embodiments 6 to 60, wherein the one or more engineered receptors bind an antigen selected from the group consisting of: CD19, CD20, CD22, CD79A, and CD79B.

Embodiment 63: The particle of any one of embodiments 6 to 62, wherein the one or more engineered receptors comprises an extracellular antigen binding domain, a hinge domain, a transmembrane domain, and one or more intracellular signaling domains.

Embodiment 64: The particle of any one of embodiments 6 to 63, wherein the one or more engineered antigen receptors comprises an extracellular antigen binding domain selected from the group consisting of: a receptor ectodomain, a ligand, or an antibody or antigen binding fragment thereof selected from the group consisting of: a Camel Ig, a Llama Ig, an Alpaca Ig, Ig NAR, a Fab′ fragment, a F(ab′)2 fragment, a bispecific Fab dimer (Fab2), a trispecific Fab trimer (Fab3), an Fv, a single chain Fv protein (scFv), a bis-scFv, (scFv)2, a minibody, a diabody, a triabody, a tetrabody, a disulfide stabilized Fv protein ("dsFv"), a Fibronectin type III (FN3) domain antibody, a single-domain antibody (sdAb, a camelid VHH, Nanobody), and a centyrin.

Embodiment 65: The particle of any one of embodiments 57 to 64, wherein the CAR comprises a hinge domain isolated or derived from a polypeptide selected from the group consisting of: CD4, CD8β, CD8α, CD28, CD134, CD137, CD152, CD278, IgG1, IgG2, IgG3, and IgG4.

Embodiment 66: The particle of any one of embodiments 57 to 65, wherein the CAR comprises a transmembrane domain isolated or derived from a polypeptide selected from the group consisting of: alpha, beta, gamma, or delta chain of the T-cell receptor, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD5, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD152, CD154, CD278, amnionless (AMN), and programmed cell death 1 (PDCD1).

Embodiment 67: The particle of any one of embodiments 57 to 66, wherein CAR comprises a primary signaling domain isolated or derived from a polypeptide selected from the group consisting of: FcRγ, FcRβ, CD3γ, CD3δ, CD3ε, CD3ζ, CD22, CD79A, CD79B, and CD66d.

Embodiment 68: The particle of any one of embodiments 57 to 67, wherein the CAR comprises one or more costimulatory domains isolated or derived from a polypeptide selected from the group consisting of: Toll-like receptor 1 (TLR1), TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, caspase recruitment domain family member 11 (CARD11), CD2, CD7, CD27, CD28, CD30, CD40, CD54 (ICAM), CD83, CD94, CD134 (OX40), CD137 (4-1BB), CD278 (ICOS), DNAX-Activation Protein 10 (DAP10), Linker for activation of T-cells family member 1 (LAT), SH2 Domain-Containing Leukocyte Protein Of 76 kD (SLP76), T cell receptor associated transmembrane adaptor 1 (TRAT1), TNFR2, TNFRS14, TNFRS18, TNFRS25, and zeta chain of T cell receptor associated protein kinase 70 (ZAP70).

Embodiment 69: The particle of any one of embodiments 6 to 68, wherein the one or more engineered receptors further comprises a CCR comprising an extracellular antigen binding domain that binds an antigen different than the antigen bound by the CAR, a hinge domain, a transmembrane domain, and one or more intracellular signaling domains.

Embodiment 70: The particle of any one of embodiments 6 to 57, wherein the one or more engineered receptors comprises a DARIC comprising a DARIC signaling component comprising a multimerization domain, a transmembrane domain and one or more intracellular signaling domains; and a DARIC binding component comprising an extracellular antigen binding domain, an extracellular antigen binding domain, a transmembrane domain, and optionally one or more intracellular signaling domains.

Embodiment 71: The particle of any one of embodiments 6 to 70, wherein the one or more engineered receptors comprises a CTBR comprising (a) a first polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR2, a transmembrane domain,

and a first interleukin receptor intracellular signaling domain; (b) a polypeptide cleavage signal; and (c) a second polypeptide comprising an extracellular TGFβ1-binding domain of TGFβR1, a transmembrane domain, and a second interleukin receptor intracellular signaling domain.

Embodiment 72: A recombinant lentiviral particle comprising: (a) a surface comprising (i) one or more mutated viral envelope glycoproteins that retain fusogenic activity and that lack cognate receptor binding activity, wherein the one or more mutated viral envelope glycoproteins comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to any one of SEQ ID NOs: 630, 634, 638, and 642 and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof comprising an amino acid sequence set forth in any one of SEQ ID NOs: 91 and 95, and 99 or 100, that binds an antigen expressed on an immune effector cell, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a therapeutic payload encoding an engineered antigen receptor.

Embodiment 73: A recombinant lentiviral particle comprising: (a) a surface comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642 and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof comprising an amino acid sequence set forth in SEQ ID NO: 99 or 100, that binds an antigen expressed on an immune effector cell, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a lentiviral vector encoding an engineered antigen receptor.

Embodiment 74: A recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642 and (ii) a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOs: 99 or 100, that binds an antigen expressed on an immune effector cell, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no

more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a therapeutic payload encoding an engineered antigen receptor.

Embodiment 75: A recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOs: 461, 471, 483, 537, and 553; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor.

Embodiment 76: A recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 471; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor comprising an amino acid sequence set forth in any one of SEQ ID NOs: 662-666.

Embodiment 77: A recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 471; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor that binds a polypeptide selected from any one of BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, and GPCR5D.

Embodiment 78: A recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid

sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 471; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor that binds BCMA.

Embodiment 79: A recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 471; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor that binds GPCR5D.

Embodiment 80: A recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 642; (ii) a non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 471; and optionally (iii) a secondary non-viral membrane-bound tropism polypeptide that comprises an amino acid sequence at least 95%, at least 96%, at least 97%, at least 98%, at least 99% identical to or identical to SEQ ID NO: 577; and (b) a lentiviral vector encoding a chimeric antigen receptor that binds CD19.

Embodiment 81: A cell transduced with the particle of any one of embodiments 1 to 80.

Embodiment 82: The cell of embodiment 81, wherein the cell is an immune effector cell.

Embodiment 83: The cell of embodiment 81 or embodiment 82, wherein the cell is a T cell, a natural killer (NK) cell, or a natural killer T (NKT) cell.

Embodiment 84: A composition comprising the particle of any one of embodiments 1 to 80 or the cell of any one of embodiments 81 to 83.

Embodiment 85: A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the particle of any one of embodiments 1 to 80, the cell of any one of embodiments 81 to 83, or the composition of embodiment 84.

Embodiment 86: A method of treating, preventing, or ameliorating at least one symptom of a disease, disorder or condition associated therewith in a subject, comprising administering to the subject an effective amount of the particle of any one of embodiments 1 to 80, the cell of any one of embodiments 81 to 83, the composition of embodiment 84, or the pharmaceutical composition of embodiment 85.

Embodiment 87: The method of embodiment 86, wherein the disease, disorder, or condition is a cancer.

Embodiment 88: The method of embodiment 86 or embodiment 87, wherein the cancer is leukemia selected from the group consisting of: acute lymphocytic leukemia (ALL), an acute myeloid leukemia (AML), a myelodysplastic syndrome (MDS), a plasma cell leukemia (PCL), erythroleukemia, a hairy cell leukemia (HCL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML) and polycythemia vera.

Embodiment 89: The method of embodiment 86 or embodiment 87, wherein the cancer is non-NHL or NHL selected from the group consisting of: diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle-cell lymphoma (MCL), small lymphocytic lymphoma (SLL), primary mediastinal large B-cell lymphoma, a marginal zone B cell lymphoma (MZL), mucosa-associated lymphatic tissue lymphoma (MALT), Burkitt's lymphoma (BL), immunoblastic large cell lymphoma, centroblastic large cell lymphoma, anaplastic B-cell lymphoma, mycosis fungoides, Sezary syndrome, T-lymphoblastic lymphoma, and anaplastic large-cell lymphoma (ALCL).

Embodiment 90: The method of embodiment 86 or embodiment 87, wherein the cancer is MM selected from the group consisting of: active multiple myeloma, smoldering multiple myeloma, light chain myeloma, non-secretory myeloma, IgD myeloma, IgE myeloma, osteosclerotic myeloma, solitary plasmacytoma of bone, and extramedullary plasmacytoma.

Embodiment 91: The method of any one of embodiments 86 to 90, wherein the cancer is relapsed and/or refractory.

Embodiment 92: The method of embodiment 86, wherein the disease, disorder, or condition is an autoimmune disease.

Embodiment 93: The method of embodiment 92, wherein the autoimmune disease is systemic lupus erythematosus, rheumatoid arthritis, idiopathic thrombocytopenic purpura, myasthenia gravis, or autoimmune hemolytic anemia.

Embodiment 94: A method of transducing an immune effector cell *in vivo*, comprising administering to a subject a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of the particle of any one of embodiments 1 to 80.

Embodiment 95: A method of making the particle of any one of embodiments 1 to 80 comprising (a) transfecting a host cell with four polynucleotides: a first polynucleotide that encodes lentiviral gag-pol, a second polynucleotide that encodes lentiviral rev, a third polynucleotide that encodes the one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and the one or more non-viral membrane-bound tropism polypeptides, and a fourth polynucleotide that is a transfer plasmid encoding a recombinant lentiviral vector encoding an engineered antigen receptor; and b) culturing the transduced cell for about 1 to 3 days to produce the particle.

Embodiment 96: A kit comprising the particle of any one of embodiments 1 to 80, a pharmaceutically acceptable carrier, and instructions for use.

All publications, patent applications, and issued patents cited in this specification are herein incorporated by reference as if each individual publication, patent application, or issued patent were specifically and individually indicated to be incorporated by reference.

Although the foregoing embodiments have been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the teachings contemplated herein that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims. The following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of noncritical parameters that could be changed or modified to yield essentially similar results.

M. EXAMPLES

EXAMPLE 1

T CELL SPECIFIC TROPISM MOLECULES TRANSDUCE AND ACTIVATE JURKAT CELLS AND PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCS)

Transduction and activation of Jurkat cells and human PBMCs with recombinant lentivirus generated with an envelope expressing T cell specific tropism molecules, *e.g.*, CD3.2, CD3.3, CD3.4, CD3.5, CD3.6, CD3.8, CD3.9, CD3.11, and CD3.15, was determined. The tropism molecules comprised anti-CD3 scFvs in either or both heavy chain (HC) – light chain (LC) orientations, fused to a CD8α stalk, transmembrane and intracellular domains (*e.g.*, SEQ ID NOs: 457, 459, 460, 461, 462, 463, 464, 465, 469, 471, 475, and 483).

1 x 10^5 Jurkat cells were plated in each well of a 96-well plate. Some wells were used as untransduced controls (UTD), controls harboring a wild-type fusogen (WT), or controls lacking a mutant fusogen (-) and/or tropism molecule (-). The remaining wells were treated with recombinant lentivirus comprising a lentiviral vector (LVV) encoding GFP, a CD3-based tropism molecule (*e.g.*, SEQ ID NOs: 457, 459, 460, 461, 462, 463, 464, 465, 469, 471, 475, and 483), and a mutant fusogen (+; *e.g.*, SEQ ID NO: 642). Three days post-transduction, Jurkat cells were harvested and CD69 expression (activation) and GFP expression (transduction) analyzed by flow cytometry. Recombinant lentivirus expressing different tropism molecules independently led to different amounts of transduction and CD69 expression. For example, lentivirus expressing CD3.4 based tropism molecules transduced relatively fewer cells than CD3.3, CD3.6, CD3.9, CD3.11, or CD3.15 based tropism molecules whereas the level of activation among lentivirus expressing these tropism molecules was comparable. See Figure 1A.

1 x 10^6 human PBMCs were plated in each well of a 24-well plate. Some wells were used as untransduced controls (UTD), controls harboring a wild-type fusogen (VSIV-G WT) or controls lacking a mutant fusogen (CD3.4) and/or tropism molecule (mVSIV-G). The remaining wells were treated with recombinant lentivirus comprising a LVV encoding GFP, a CD3-based tropism molecule (*e.g.*, SEQ ID NOs: 457, 459, 460, 461, 462, 463, 464, 465, 469, 471, 475, and 483), and a mutant fusogen (*e.g.*, SEQ ID NO: 642). Three days post-transduction, PBMCs were harvested and CD69 expression (activation) and GFP expression (transduction) analyzed by flow cytometry. Recombinant lentivirus expressing different

tropism molecules independently led to different amounts of transduction and CD69 expression. For example, lentivirus expressing CD3.4 based tropism molecules transduced relatively fewer cells than CD3.3, CD3.5, and CD3.9 based tropism molecules whereas the level of activation among lentivirus expressing these tropism molecules was comparable. See Figure 1B.

Taken together, the data indicated that binder selection impacts target cell transduction and activation in a cell type specific manner.

EXAMPLE 2

TROPISM MOLECULES WITH MONOMERIC OR DIMERIC CD8A STALKS SHOW COMPARABLE EXPRESSION

Tropism molecule expression (as determined by anti-CD3 surface expression) was examined on HEK293T cells transfected with plasmids encoding tropism molecules encoding anti-CD3 scFvs, *e.g.*, CD3.3, CD3.4, CD3.9, CD3.11, CD3.12, CD3.13, CD3.15, and CD3.16 (*e.g.*, SEQ ID NOs: 459, 461, 471, 475, 477, 479, 483, 485), fused to monomeric or dimeric CD8α stalk architectures (*e.g.*, SEQ ID NOs: 412, 411); mutant VSIV-G fusogen (*e.g.*, SEQ ID NOs: 642); lentiviral GAG/POL; lentiviral REV; and a transfer vector plasmid encoding GFP or an anti-BCMA CAR.

6×10^5 HEK293T cells were plated in each well of a 6-well plate, and the next day transfected with tropism plasmids, lentiviral packaging plasmids, and one of two transfer vector plasmids using standard techniques. After 3 days, producer cells were harvested for flow cytometry analysis of cell-surface anti-CD3 expression. Flow cytometry plots depict anti-CD3 molecule expression on HEK293T producer cells. Many of the anti-CD3 binders were highly expressed on the producer cell surface regardless of the monomeric or dimeric CD8α stalk architecture. See Figure 2. In addition, CAR expression did not significantly alter the relative expression levels among the tropism molecules assayed.

These data indicated that tropism molecules are sufficiently expressed on producer cells and that CD8α stalk architecture had little to no detectable impact on tropism molecule expression in the presence or absence of CAR expression.

EXAMPLE 3

TROPISM MOLECULE ARCHITECTURE AND TROPISM MOLECULE EXPRESSION, FUNCTIONAL LENTIVIRAL TITER, AND SPECIFICITY

Tropism Molecule Architecture

Tropism molecules were built using CD4, CD8α, CD45, CEACAM, and CADHERIN 1 (ECAD) stalks of different predicted lengths and rigidity. See Figure 3A.

Tropism Molecule Expression

Tropism molecule expression (as determined by anti-CD3 surface expression) was examined on HEK293T cells transfected with plasmids encoding tropism molecules identified in the following table; mutant VSIV-G fusogen (*e.g.*, SEQ ID NO: 642); lentiviral GAG/POL; lentiviral REV; and a transfer vector plasmid encoding GFP.

Table 15 lists the lentivirus ID, and the SEQ ID NOs for tropism molecule components as well as a representative SEQ ID NO of the complete tropism molecule. Note that lentivirus (LV) 1 also comprises a human CD80 molecule, *e.g.*, SEQ ID NO: 577.

Table 15

Lentivirus ID	Tropism Molecule Architecture					
	Binder	Stalk	Est. Stalk Length (nm)	TM domain	IC domain	Tropism
1	49	411	13	437	444	461
2	99	411	13	437	444	471
3	99	415	25	439	446	537
4	99	419	30	439	446	545
5	99	416	35	439	446	539
6	99	423	17	439	446	553
7	99	422	21	439	446	551
8	99		16			
9	99		not determined			
10	99		16			
11	99	427	20	440	447	561
12	99	426	15	440	447	559
13	99	425	10	440	447	557
14	99	424	5	440	447	555
15	99	428	24	NA	NA	565
16	99	429	24	439	446	563
17	99	430	16	NA	NA	567
18	99	431	8	NA	NA	569
19	99	432	20	NA	NA	571
20	99	433	12	NA	NA	573

21	99	434	4	NA	NA	575
22	99	412	13	437	444	-
23	99	414	40	439	446	535

6 x 10^5 HEK293T producer cells were plated in each well of a 6-well plate, and the next day transfected with tropism plasmids, lentiviral packaging plasmids, and transfer vector plasmid using standard techniques. After 3 days, producer cells were harvested for flow cytometry analysis of cell-surface anti-CD3 expression. Flow cytometry plots depict anti-CD3 molecule expression on HEK293T producer cells. Anti-CD3 binders were expressed on producer cells, and expression appeared independent of stalk architecture, with a minimum log-fold difference in anti-CD3 geometric mean fluorescence intensity (gMFI) from untransfected controls. See Figure 3B.

These data indicated that tropism molecules comprising stalks and transmembrane domains or GPI anchors are sufficiently expressed and/or presented on producer cells and that stalk length and rigidity did not substantially alter the relative expression levels among most tropism molecules assayed.

Functional Lentiviral Titer

Recombinant lentiviral particles were generated as described in the *Tropism Molecule Expression* section and Table 15 of this Example and the transducing units per nanogram of P24 of each lentivirus was determined.

1 x 10^5 Jurkat cells were plated in each well of a 96-well plate and treated with LV1-LV21. The number of transduced cells was determined three days after transduction using GFP expression analyzed by flow cytometry. The number of recombinant lentiviral particles per transduction was quantified using a P24 ELISA and the transducing units per nanogram P24 was determined. See Figure 3C.

These data indicated that tropism molecule stalk architecture may influence the functional titer of recombinant lentivirus and that some stalk architectures may enable more potent lentivirus than others, *e.g.*, compare LVs 2, 3, 7, 8 with LVs 11-14.

In vitro Specificity

Recombinant lentiviral particles were generated as described in the *Tropism Molecule Expression* section and Table 15 of this Example and specificity of LV comprising tropism molecules with different stalk architectures was determined *in vitro*.

5 x 10^5 human PBMCs ($CD3^+$) from three donors were each plated in a well of a 24-well plate and treated with P24-matched (9083 pg P24) of LV 2, LV 3, LV 22, or LV 23. After three days, the PBMCs in each well were transferred to a well of a 24-well GREX vessel and supplemented with growth media. On day 9, the cells were harvested and the number of transduced cells expressing GFP was determined using flow cytometry. 1 x 10^5 Jurkat cells ($CD3^+$) were plated in each well of a 96-well plate and treated with P24-matched (1816 pg P24) of LV1, LV 2, LV 3, LV6, LV7, LV 15, LV16, or LV19. After 3 days, the cells were harvested and the number of transduced cells expressing GFP was determined using flow cytometry. 1 x 10^5 A549 cells ($CD3^-$) were plated in each well of a 24-well plate and treated with P24-matched (1816 pg P24) of LV1, LV 2, LV 3, LV6, LV7, LV 15, LV16, LV19, LV 22, or LV 23. After 3 days, the cells were harvested and the number of transduced cells expressing GFP was determined using flow cytometry.

On-target PBMC transduction was plotted against off-target A549 transduction. These data indicated that tropism molecules comprising an anti-CD3 scFv with different stalk architectures can affect lentivirus specificity *in vitro*. See Figure 3D, left panel. On-target Jurkat cell transduction was plotted against off-target A549 transduction using LVs expressing different stalk architectures. These data indicated that stalk architectures can be engineered to substantially improve LV specificity *in vitro*. See Figure 3D, right panel.

EXAMPLE 4

TROPISM MOLECULE ARCHITECTURE VERSUS FUNCTIONAL LENTIVIRAL TITER AND SPECIFICITY

The relationship between stalk length, LV titer, and specificity was determined for recombinant lentiviral particles expressing tropism molecules with different stalk architectures. Recombinant lentiviruses were generated as described in the *Tropism Molecule Expression* section and Table 15 of Example 3.

1 x 10^5 Jurkat cells ($CD3^+$) were plated in each well of a 96-well plate and treated with P24-matched (1816 pg P24) of LV 1 - LV 21. After 3 days, the cells were harvested and the number of transduced cells expressing GFP was determined using flow cytometry. 1 x 10^5 A549 cells ($CD3^-$) were plated in each well of a 24-well plate and treated with P24-matched (1816 pg P24) of LV 1 – LV 21.

Tropism molecule stalk length did not positively correlate with LV functional titer when assessed in either Jurkat or A549 cells. See Figure 4, left panel. Tropism molecule stalk length showed a positive correlation with LV specificity, measured as the ratio of Jurkat cell (on-target) transduction to A549 cell (off-target) transduction. See Figure 4, right panel. In addition to being a general trend among the data, the correlation between tropism molecule stalk length and LV specificity also depended on the specific protein from which the stalk was derived. These data indicated that stalk length is a variable that affects LV specificity.

EXAMPLE 5

TROPISM MOLECULE ARCHITECTURE AFFECTS LENTIVIRAL TRANSDUCTION AND ACTIVATION OF PBMCS

Transduction and activation of human PBMCs with recombinant lentivirus generated as described in the *Tropism Molecule Expression* section and Table 15 of Example 3 were determined.

5 x 10^5 human PBMCs were plated in each well of a 24-well plate and treated with untransduced control (UTD) cells activated with anti-CD3 and anti-CD28 coated beads or P24-matched (0.5 ng or 2 ng of P24) of LV 1 – LV 21. After three days, the PBMCs in each well were transferred to a well of a 24-well GREX vessel and supplemented with growth media. On days 9 and 10, cells were harvested and the number of transduced cells expressing GFP was determined using flow cytometry.

Recombinant lentivirus expressing anti-CD3-based tropism molecules with different stalks displayed different levels of PBMC transduction and activation at day 9. For example, LV 2, 3, 6, and 7 transduced relatively more cells than LV 14, 15, 17, and 18 whereas the level of activation among lentivirus expressing these tropism molecules was somewhat comparable. See Figure 5A, compare top and bottom panels.

Dose-dependent differences in PBMC transduction were also apparent in day 10 cells transduced with LV expressing anti-CD3-based tropism molecules with different stalks; PBMCs transduced with increased amounts of LV (2 ng P24) displayed increased GFP expression compared to PBMCs transduced with less LV (0.5 ng P24). See Figure 5B, left panel. P24 matched titers of LV 1 – LV 21 on both PBMCs and Jurkat cells were positively correlated. Moreover, LV comprising anti-CD3-based tropism molecules with particular

stalks, *e.g.*, LV 3, 6, 7 favored on-target transduction in both cell types. See Figure 5B, right panel.

These data indicated that anti-CD3-based tropism molecule stalk length contributes to LV transduction and activation in primary cells and cell lines *in vitro*.

EXAMPLE 6

TROPISM MOLECULE ARCHITECTURE AFFECTS LENTIVIRAL TRANSDUCTION AND ACTIVATION OF CD3 POSITIVE CELLS *IN VIVO*

Transduction and activation of human T cells with recombinant lentivirus expressing different tropism molecules were determined in an *in vivo* NOD scid gamma (NSG) mouse model.

Recombinant lentivirus was produced by transient transfection of HEK293T cells with plasmids encoding tropism molecules identified in the following table; a wild type VSIV-G fusogen or mutant VSIV-G fusogen (*e.g.*, SEQ ID NO: 642); lentiviral GAG/POL; lentiviral REV; and a transfer vector plasmid encoding GFP.

Table 16 lists the lentivirus ID, and the SEQ ID NOs for tropism molecule components as well as a representative SEQ ID NO of the complete tropism molecule and the fusogen that was used. Note that lentivirus (LV) 1 also comprises a human CD80 molecule, *e.g.*, SEQ ID NO: 577.

Table 16

Lentivirus ID	Tropism Molecule Architecture						VSIV-G Fusogen
	Binder	Stalk	Est. Stalk Length (nm)	TM domain	IC domain	Tropism	
1	49	411	13	437	444	461	642
2	99	411	13	437	444	471	642
3	99	415	25	439	446	537	642
24	159	411	13	437	444	483	642
25	159	415	25	439	446	-	642
26	No tropism molecule						wild type

NSG mice were injected intravenously with 1 x 10^6 human PBMCs, one day later mice were intravenously with vehicle (DMEM; (-)) or 2.5 x 10^7 TU of LV 1-3 or 24-26. Mice received three doses of 2 x 10^5 IU recombinant human IL-2 at 6, 24, and 48h post LV administration. Seven days post LV administration, mice were sacrificed. LV transduction

and activation of GFP-expressing human PBMCs in mouse blood and spleens was analyzed using flow cytometry.

LV 2 and LV 24, which share the same stalk architecture, transduced human PBMCs as well as control LV 1, which expresses both an anti-CD3-based tropism molecule (same stalk as LV 2 and LV 24) and a CD80-based tropism molecule. In addition, LV 1, LV 2 and LV 24 demonstrably activated human PBMCs in both the blood and spleen. In contrast, LV 3 and LV 25, which share the same stalk architecture but a different stalk architecture than the anti-CD3-based tropism molecules in LV 1, 2 and 24, did not transduce or activate human PBMCs to the same extent. See Figure 6, top panel (transduction), bottom panel (activation).

These data indicated that anti-CD3-based tropism molecule stalk architecture affects PBMC transduction and activation in mice.

EXAMPLE 7

TROPISM MOLECULE DEMONSTRATES EXQUISITE SPECIFICITY *IN VIVO*

The specificity of recombinant lentivirus comprising an envelope that expresses an anti-CD3-based tropism molecule and a mutant VSIV-G fusogen and a lentiviral vector encoding GFP was investigated in a mouse model.

8-week-old NOD scid gamma (NSG) mice were intravenously administered 1 x 10^6 human PBMCs. The next day, mice were intravenously administered vehicle (DMEM) or LV 2 or LV 26 (Example 6) at 1 x 10^7 TU, 2.5 x 10^7 TU, 1 x 10^8 TU, or 2.5 x 10^8 TU per mouse. 2.5 x 10^7 TU was previously identified as the therapeutic dose in a related model.

Seven days later, mice were euthanized and heart, brain, ovary, stomach, eye, skeletal muscle, skin, large intestine, small intestine, pancreas, kidney, lung, liver, bone marrow, blood, and spleen among others were collected and analyzed. Vector copy number (VCN), immunohistochemistry (IHC), and flow cytometry were used to assess the safety/biodistribution profile of LV 2.

Mice treated with LV 2 displayed dose dependent increases in GFP positive T cells in the blood (Figure 7A) and spleen (Figure 7B, rightmost column). No GFP positive T cells were seen in mice treated with vehicle or LV 26, which lacks a CD3-based tropism molecule.

At the therapeutic dose level (2.5 x 10^7 TU/mouse), flow cytometry detected LV 2 transduced cells in the spleen (13.1% GFP positive T cells). Importantly, GFP expression was only detected in resident immune cells and phagocytic cells in some non-target tissues.

GFP expression was not detected in the majority of tissues examined. At log-fold higher doses (2.5 x 10^8 TU/mouse), flow cytometry detected LV 2 transduced cells in the spleen (29.6% GFP positive T cells). Importantly, GFP expression was only detected in resident immune cells and phagocytic cells in some non-target tissues. GFP expression was not detected in the majority of tissues examined at therapeutic dose levels.

Together these data showed the exquisite sensitivity mediated by the anti-CD3-based tropism molecule expressed on the envelope of LV 2 highlighted by the on-target transduction detected in CD3 expressing cells in the spleen; the lack of GFP expression detected in non-target tissues such as the brain and heart; and GFP expression restricted to resident immune cells and phagocytic cells in some non-target tissues. See Figure 7B.

EXAMPLE 8

IN VIVO ADMINISTERED LENTIVIRUS DEMONSTRATES ANTI-TUMOR EFFICACY IN A MULTIPLE MYELOMA MOUSE MODEL

The anti-tumor efficacy of *in vivo* administered recombinant lentivirus comprising an envelope that expresses an anti-CD3-based tropism molecule and a mutant VSIV-G fusogen and a lentiviral vector encoding an anti-BCMA CAR was investigated in a multiple myeloma mouse model.

Recombinant lentivirus for *in vivo* administration was produced by transient transfection of HEK293T cells with plasmids encoding an anti-CD3-based tropism molecule (SEQ ID NO: 471); a mutant VSIV-G fusogen (*e.g.*, SEQ ID NO: 642); lentiviral GAG/POL; lentiviral REV; and a transfer vector plasmid encoding GFP (LV GFP) or an anti-BCMA CAR (LV anti-BCMA CAR).

Ex vivo anti-BCMA CAR T cells were also prepared. Briefly, HEK293T cells were transiently transfected with plasmids encoding a wild-type VSIV-G fusogen; lentiviral GAG/POL; lentiviral REV; and a transfer vector plasmid encoding the same anti-BCMA CAR used in manufacturing the *in vivo* administered lentivirus. PBMCs were then transduced with the recombinant lentivirus and cultured for 7 days to generate anti-BCMA CAR T cells.

RPMI Model First Study

NOD scid gamma (NSG) mice were subcutaneously injected with 1 x 10^6 RPMI-8226 cells (a BMCA positive tumor cell line). Tumors were allowed to grow to a size of about 50mm^3 (about two weeks).

Three groups of mice were then intravenously administered 1 x 10^6 human PBMCs. The next day: a fourth group of mice was administered 2 x 10^6 unmodified *ex vivo* cultured T cells; a fifth group of mice was administered 2 x 10^6 *ex vivo* anti-BCMA CAR T cells; mice that received the 1 x 10^6 human PBMCs the day before were administered vehicle control (DMEM) or 2.5 x 10^7 TU LV GFP or LV anti-BCMA CAR. All groups of mice then received three doses of 2 x 10^5 IU recombinant human IL-2 at 6, 24, and 48 hours post LV administration. Tumor volume was measured externally using calipers and mice were euthanized at pre-determined humane endpoints based on tumor size and body condition.

Tumor size increased in mice treated with vehicle, unmodified *ex vivo* cultured T cells, and LV GFP. Mice treated with *ex vivo* anti-BCMA CAR T cells or *in vivo* with LV anti-BCMA CAR experienced complete and comparable tumor regression. Figure 8, left panel.

RPMI Model Second Study

NSG mice were subcutaneously injected with 1 x 10^6 RPMI-8226 and tumors were allowed to grow to a size of about 50mm^3 (about two weeks).

Two groups of mice were then intravenously administered 1 x 10^6 human PBMCs. The next day: a third group of mice was administered 2 x 10^6 *ex vivo* anti-BCMA CAR T cells; mice that received the 1 x 10^6 human PBMCs the day before were administered vehicle control (DMEM) or 2.5 x 10^7 TU LV anti-BCMA CAR. All groups of mice then received three doses of 2 x 10^5 IU recombinant human IL-2 at 6, 24, and 48 hours post LV administration. Tumor volume was measured externally using calipers and mice were euthanized at pre-determined humane endpoints based on tumor size and body condition.

Tumor size increased in mice treated with vehicle. Mice treated with *ex vivo* anti-BCMA CAR T cells or *in vivo* with LV anti-BCMA CAR experienced complete and comparable tumor regression. Figure 8, right panel.

EXAMPLE 9

IN VIVO ADMINISTERED LENTIVIRUS DEMONSTRATES ANTI-TUMOR EFFICACY IN A MULTIPLE MYELOMA MOUSE MODEL

The anti-tumor efficacy of *in vivo* administered recombinant lentivirus comprising an envelope that expresses an anti-CD3-based tropism molecule and a mutant VSIV-G fusogen and a lentiviral vector encoding an anti-BCMA CAR was investigated in a multiple myeloma mouse model.

Recombinant lentivirus for *in vivo* administration was produced by transient transfection of HEK293T cells with plasmids encoding an anti-CD3-based tropism molecule (SEQ ID NO: 471 or SEQ ID NO: 553); a mutant VSIV-G fusogen (*e.g.*, SEQ ID NO: 642); lentiviral GAG/POL; lentiviral REV; and a transfer vector plasmid encoding an anti-BCMA CAR (LV anti-BCMA CAR).

Ex vivo anti-BCMA CAR T cells were also prepared. Briefly, HEK293T cells were transiently transfected with plasmids encoding a wild-type VSIV-G fusogen; lentiviral GAG/POL; lentiviral REV; and a transfer vector plasmid encoding the same anti-BCMA CAR used in manufacturing the *in vivo* administered lentivirus. PBMCs were then transduced with the recombinant lentivirus and cultured for 7 days to generate anti-BCMA CAR T cells.

Daudi Model Study

NSG mice were intravenously injected with 2 x 10^6 Daudi cells labeled with firefly luciferase. After four days, five out of six groups of mice were intravenously administered 1 x 10^6 human PBMCs. The next day mice that received the 1 x 10^6 human PBMCs were administered vehicle control (DMEM); 1.25 x 10^7 or IU 1.25 x 10^8 IU of recombinant lentivirus comprising a viral envelope expressing SEQ ID NO: 471 (LV 27) or SEQ ID NO: 553 (LV 28). Mice that were not administered PBMCs were administered 5 x 10^6 *ex vivo* anti-BCMA CAR T cells. All groups of mice then received three doses of 2 x 10^5 IU recombinant human IL-2 at 6, 24, and 48 hours post LV administration. Tumor volume was measured by using a bioluminescence imaging system.

Tumor size increased in mice treated with vehicle. Mice treated with *ex vivo* anti-BCMA CAR T cells demonstrated transient control of tumor growth. Mice treated with

recombinant lentivirus comprising a viral envelope expressing SEQ ID NO: 471 or SEQ ID NO: 553 experienced dose-dependent tumor regression. Figure 9.

In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

What is claimed is:

1. A recombinant lentiviral particle comprising:

(a) a viral envelope comprising:

(i) a mutated vesiculovirus G protein that retains fusogenic activity and that lacks cognate receptor binding activity; and

(ii) a non-viral membrane-bound tropism polypeptide comprising:

(x) an antibody or antigen binding fragment comprising a heavy chain variable region (VH); a polypeptide linker; and a light chain variable region (VL),

wherein the VH comprises: a CDRH1 comprising the amino acid sequence set forth in SEQ ID NO: 92; a CDRH2 comprising the amino acid sequence set forth in SEQ ID NO: 93; and a CDRH3 comprising the amino acid sequence set forth in any one of SEQ ID NOs: 94, 104, 114, 124, 134, 144, 154, and 164; and

wherein the VL comprises: a CDRL1 comprising the amino acid sequence set forth in SEQ ID NO: 96; a CDRL2 comprising the amino acid sequence set forth in SEQ ID NO: 97; and a CDRL3 comprising the amino acid sequence set forth in SEQ ID NO: 98;

(y) a spacer polypeptide; and

(z) a transmembrane domain; and

(b) a recombinant lentiviral vector comprising a polynucleotide encoding a promoter operably linked to a polynucleotide encoding one or more engineered receptors.

2. The recombinant lentiviral particle of claim 1, wherein the vesiculovirus G protein is a COCV G glycoprotein (COCV-G) or a VSIV G glycoprotein (VSIV-G).

3. The recombinant lentiviral particle of claim 2, wherein the VSIV-G envelope protein comprises one or more of:

(a) one or more amino acid substitutions at H8, N9, Q10, K47, K50, A51, S183, S179, N180, I182, M184, Y209, I347, T350, T352, E353, and R354;

(b) an insertion of TT between N9 and Q10, an insertion of GGS between H8 and N9, an insertion of GGS between N9 and Q10, an insertion of TT between N208 and Y209, an insertion of GGS between P46 and K47, and an insertion of GGS between N208 and Y209; or

(c) amino acid substitutions at K47 and/or R354; or

(d) a deletion of residues 1-8.

4. The recombinant lentiviral particle of claim 2 or claim 3, wherein the VSIV-G envelope protein comprises:

(a) amino acid substitutions selected from the group consisting of: K47A and R354A; K47A and R354G; K47A and R354F; K47A and R354Q; K47G and R354A; K47G and R354G; K47G and R354F; K47G and R354Q; K47F and R354A; K47F and R354G; K47F and R354F; K47F and R354Q; K47Q and R354A; K47Q and R354G; K47Q and R354F; and K47Q and R354Q; or

(b) the amino acid sequence set forth in any one of SEQ ID NOs: 630, 634, 638, and 642 or an amino acid sequence at least 99% identical thereto, and comprises the amino acid substitutions K47A or K47Q and R354A or R354Q.

5. The recombinant lentiviral particle of any one of claims 1 to 4, wherein the antibody or antigen binding fragment thereof comprises:

(a) the VH amino acid sequence set forth in any one of SEQ ID NOs: 91, 101, 111, 121, 131, 141, 151, and 161;

(b) the polypeptide linker selected from the group consisting of: $(GGGGS)_n$ wherein n = 1, 2, 3, 4 or 5; $S(GGGGS)_n$ wherein n = 1, 2, 3, 4 or 5; GEGTSTGSGGSGGSGGAD, GSTSGSGKPGSGEGSTKG and variants thereof comprising an amino acid sequence 95% identical thereto; and

(c) the VL amino acid sequence set forth in SEQ ID NO: 95.

6. The recombinant lentiviral particle of any one of claims 1 to 5, wherein the antibody or antigen binding fragment thereof comprises the amino acid sequence set forth in any one of SEQ ID NOs: 99, 100, 109, 110, 119, 120, 129, 130, 139, 140, 149, 150, 159, 160, 169, and 170.

7. The recombinant lentiviral particle of any one of claims 1 to 6, wherein

(a) the spacer comprises an amino acid sequence at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 411; and

(b) the transmembrane domain comprises an amino acid sequence at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 437.

8. The recombinant lentiviral particle of any one of claims 1 to 7, wherein the non-viral membrane-bound tropism polypeptide further comprises an intracellular domain that comprises an amino acid sequence at least 95% identical to the amino acid sequence set forth in SEQ ID NO: 444.

9. The recombinant lentiviral particle of any one of claims 1 to 8, wherein the non-viral membrane-bound tropism polypeptide comprises an amino acid sequence at least 99% identical to the amino acid sequence set forth in SEQ ID NO: 471.

10. The recombinant lentiviral particle of any one of claims 1 to 9, further comprising one or more secondary non-viral membrane bound tropism polypeptides.

11. The recombinant lentiviral particle of claim 10, wherein the one or more secondary non-viral membrane bound tropism polypeptides comprise one or more of CD80, CD86, CD137L, OX40L, and ICOSL or variants thereof.

12. The recombinant lentiviral particle of any one of claims 1 to 11, wherein the promoter is selected from the group consisting of: a β-actin promoter, a cytomegalovirus (CMV) immediate early promoter, a simian virus 40 (SV40) (*e.g.*, early or late) promoter, a Moloney murine leukemia virus (MoMLV) promoter, a Rous sarcoma virus (RSV) promoter, a herpes simplex virus (HSV) (thymidine kinase) promoter, an SV40/CD43 promoter, a spleen focus forming virus (SFFV) promoter, an elongation factor 1-alpha (EFlα) short promoter (intronless), an EFlα long promoter containing an intron, a Ubiquitin C (UBC) promoter, a phosphoglycerate kinase-1 (PGK) promoter, a cytomegalovirus enhancer/chicken β-actin (CAG) promoter, and a myeloproliferative sarcoma virus enhancer, negative control region deleted, dl587rev primer-binding site substituted (MND) U3 promoter.

13. The recombinant lentiviral particle of any one of claims 1 to 12, wherein the one or more engineered receptors are selected from the group consisting of: a chimeric antigen receptor (CAR), a chimeric costimulatory receptor (CCR), an alpha-beta T cell receptor (αβ TCR), a gamma delta T cell receptor (γδ TCR), a dimerizing agent regulated immunoreceptor complex (DARIC), a chimeric TGF-β receptor (CTBR), and a zetakine receptor.

14. The recombinant lentiviral particle of any one of claims 1 to 13, wherein the one or more engineered receptors comprises an extracellular antigen binding domain that binds an antigen selected from the group consisting of: alpha folate receptor (FRα), αvβ6 integrin, BAFFR, B cell maturation antigen (BCMA), B7-H3 (CD276), B7-H6, carbonic anhydrase IX (CAIX), CD16, CD19, CD20, CD22, CD30, CD33, CD37, CD38, CD44, CD44v6, CD44v7/8, CD70, CD79A, CD79B, CD123, CD133, CD138, CD171, carcinoembryonic antigen (CEA), claudin 6, (CLDN6), claudin 18 isoform 2 (CLDN18.2), C-type lectin-like molecule-1 (CLL-1), CD2 subset 1 (CS-1), chondroitin sulfate proteoglycan 4 (CSPG4), cutaneous T cell lymphoma-associated antigen 1 (CTAGE1), delta like canonical Notch ligand 3 (DLL3), epidermal growth factor receptor (EGFR), epidermal growth factor receptor variant III (EGFRvIII), epithelial glycoprotein 2 (EGP2), epithelial glycoprotein 40 (EGP40), epithelial

cell adhesion molecule (EPCAM), ephrin type-A receptor 2 (EPHA2), erb-b2 receptor tyrosine kinase 4 (ERBB4), fibroblast activation protein (FAP), Fc Receptor Like 5 (FCRL5), fetal acetylcholinesterase receptor (AchR), ganglioside G2 (GD2), ganglioside G3 (GD3), Glypican-3 (GPC3), G Protein-Coupled Receptor Class C Group 5 Member D (GPCR5D), EGFR family including ErbB2 (HER2), HER2 p95, IL-10Rα, IL-13Rα2, Kappa, cancer/testis antigen 2 (LAGE-1A), Lambda, Lewis-Y (LeY), L1 cell adhesion molecule (L1-CAM), melanoma antigen gene (MAGE)-A1, MAGE-A3, MAGE-A4, MAGE-A6, MAGEA10, melanoma antigen recognized by T cells 1 (MelanA or MART1), Mesothelin (MSLN), MUC1, MUC16, MHC class I chain related proteins A (MICA), MHC class I chain related proteins B (MICB), neural cell adhesion molecule (NCAM), cancer/testis antigen 1 (NY-ESO-1), placenta-specific 1 (PLAC1), preferentially expressed antigen in melanoma (PRAME), prostate stem cell antigen (PSCA), prostate-specific membrane antigen (PSMA), receptor tyrosine kinase-like orphan receptor 1 (ROR1), SLAMF7, synovial sarcoma, X breakpoint 2 (SSX2), Survivin, TACI, tumor associated glycoprotein 72 (TAG72), tumor endothelial marker 1 (TEM1/CD248), tumor endothelial marker 7-related (TEM7R), transforming growth factor beta 1 (TFGβ1), trophoblast glycoprotein (TPBG), UL16-binding protein (ULBP) 1, ULBP2, ULBP3, ULBP4, ULBP5, ULBP6, vascular endothelial growth factor receptor 2 (VEGFR2), and Wilms tumor 1 (WT-1).

15. The recombinant lentiviral particle of any one of claims 1 to 14, wherein the one or more engineered receptors is a CAR comprising:

(a) an antibody or antigen binding fragment thereof that binds an antigen selected from the group consisting of: BCMA, CD19, CD20, CD22, CD33, CD38, CD79A, CD79B, GPCR5D, MAGE-A4, MSLN, MUC16, NY-ESO-1, PSCA, PSMA and ROR1;

(b) a hinge domain isolated or derived from a polypeptide selected from the group consisting of: CD4, CD8β, CD8α, CD28, CD134, CD137, CD152, CD278, IgG1, IgG2, IgG3, and IgG4;

(c) a transmembrane domain isolated or derived from a polypeptide selected from the group consisting of: alpha, beta, gamma, or delta chain of the T-cell receptor, CD3δ, CD3ε, CD3γ, CD3ζ, CD4, CD5, CD8α, CD9, CD16, CD22, CD27, CD28, CD33, CD37, CD45, CD64, CD80, CD86, CD134, CD137, CD152, CD154, CD278, amnionless (AMN), and programmed cell death 1 (PDCD1);

(d) one or more costimulatory domains isolated or derived from a polypeptide selected from the group consisting of: Toll-like receptor 1 (TLR1), TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8, TLR9, TLR10, caspase recruitment domain family member 11 (CARD11), CD2, CD7, CD27, CD28, CD30, CD40, CD54 (ICAM), CD83, CD94, CD134 (OX40), CD137 (4-1BB), CD278 (ICOS), DNAX-Activation Protein 10 (DAP10), Linker for activation of T-cells family member 1 (LAT), SH2 Domain-Containing Leukocyte Protein Of 76 kD (SLP76), T

cell receptor associated transmembrane adaptor 1 (TRAT1), TNFR2, TNFRS14, TNFRS18, TNFRS25, and zeta chain of T cell receptor associated protein kinase 70 (ZAP70); and

(e) a primary signaling domain isolated or derived from a polypeptide selected from the group consisting of: FcRγ, FcRβ, CD3γ, CD3δ, CD3ε, CD3ζ, CD22, CD79A, CD79B, and CD66d.

16. A recombinant lentiviral particle comprising: (a) a surface comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 99% identical to or identical to any one of SEQ ID NOs: 630, 634, 638, and 642, wherein the mutated VSIV-G envelope glycoprotein comprises the amino acid substitutions K47A or K47Q and R354A or R354Q, and (ii) a non-viral membrane-bound tropism polypeptide comprising an antibody or antigen binding fragment thereof comprising an amino acid sequence set forth in any one of SEQ ID NOs: 99, 109, 119, 129, 139, 149, 159 and 169, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a therapeutic payload encoding a chimeric antigen receptor.

17. A recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95% identical to SEQ ID NO: 642, wherein the mutated VSIV-G envelope glycoprotein comprises the amino acid substitutions K47Q and R354A; and (ii) a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in any one of SEQ ID NOs: 99 or 100, that binds an antigen expressed on an immune effector cell, a spacer polypeptide, and a GPI anchor domain or a transmembrane domain, and optionally, an intracellular domain comprising no more than 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acids; and (b) a lentiviral vector encoding a chimeric antigen receptor.

18. A recombinant lentiviral particle comprising: (a) a viral envelope comprising (i) a mutated VSIV-G envelope glycoprotein that comprises an amino acid sequence at least 95% identical to SEQ ID NO: 642, wherein the mutated VSIV-G envelope glycoprotein comprises the amino acid substitutions K47Q and R354A; (ii) a non-viral membrane-bound tropism polypeptide comprising an amino acid sequence set forth in SEQ ID NO: 471; and (b) a lentiviral vector encoding a chimeric antigen receptor.

19. The recombinant lentiviral particle of any one of claims 16 to 18, wherein the chimeric antigen receptor comprises an amino acid sequence set forth in any one of SEQ ID NOs: 662-666 or the chimeric antigen receptor that comprises an extracellular antigen binding domain that binds a polypeptide selected from any one of BCMA, CD19, CD20, CD22, CD38, CD79A, CD79B, and GPCR5D.

20. An immune effector cell transduced *in vitro* or *ex vivo* with the recombinant lentiviral particle of any one of claims 1 to 19.

21. A pharmaceutical composition comprising the recombinant lentiviral particle of any one of claims 1 to 19 or the immune effector cell of claim 20.

22. Use of the recombinant lentiviral particle of any one of claims 1 to 19, the immune effector cell of claim 20, or the pharmaceutical composition of claim 21 in the manufacture of a medicament for treating, preventing, or ameliorating at least one symptom of a disease, disorder or condition associated therewith in a subject.

23. The use of claim 22, wherein the disease, disorder, or condition is a cancer selected from the group consisting of:

(a) a leukemia selected from the group consisting of: acute lymphocytic leukemia (ALL), an acute myeloid leukemia (AML), a myelodysplastic syndrome (MDS), a plasma cell leukemia (PCL), erythroleukemia, a hairy cell leukemia (HCL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML) and polycythemia vera;

(b) a non-NHL or NHL selected from the group consisting of: diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle-cell lymphoma (MCL), small lymphocytic lymphoma (SLL), primary mediastinal large B-cell lymphoma, a marginal zone B cell lymphoma (MZL), mucosa-associated lymphatic tissue lymphoma (MALT), Burkitt's lymphoma (BL), immunoblastic large cell lymphoma, centroblastic large cell lymphoma, anaplastic B-cell lymphoma, mycosis fungoides, Sezary syndrome, T-lymphoblastic lymphoma, and anaplastic large-cell lymphoma (ALCL);

(c) a multiple myeloma selected from the group consisting of: active multiple myeloma, smoldering multiple myeloma, light chain myeloma, non-secretory myeloma, IgD myeloma, IgE myeloma, osteosclerotic myeloma, solitary plasmacytoma of bone, and extramedullary plasmacytoma; and

(d) a relapsed and/or refractory cancer.

24. The use of claim 22, wherein the disease, disorder, or condition is an autoimmune disease or an autoimmune disease selected from the group consisting of: systemic lupus erythematosus, rheumatoid arthritis, idiopathic thrombocytopenic purpura, myasthenia gravis, and autoimmune hemolytic anemia.

25. Use of the recombinant lentiviral particle of any one of claims 1 to 19 in the manufacture of a medicament for transducing an immune effector cell in vivo.

26. A method of making the recombinant lentiviral particle of any one of claims 1 to 19 comprising (a) transfecting a host cell *in vitro* with four polynucleotides: a first polynucleotide that encodes lentiviral gag-pol, a second polynucleotide that encodes lentiviral rev, a third polynucleotide that encodes the one or more mutated viral envelope glycoproteins that retain fusogenic activity and lack cognate receptor binding activity and the one or more non-viral membrane-bound tropism polypeptides, and a fourth polynucleotide that is a transfer plasmid encoding a recombinant lentiviral vector encoding an engineered antigen receptor; and b) culturing the transduced cell for about 1 to 3 days to produce the particle.

27. A kit comprising the recombinant lentiviral particle of any one of claims 1 to 19, a pharmaceutically acceptable carrier, and instructions for use.