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(54) **ANTIBODIES AND CHIMERIC ANTIGEN RECEPTORS SPECIFIC FOR CD19**

ANTIKÖRPER UND CHIMÄRE CD19-SPEZIFISCHE ANTIGENREZEPTOREN

ANTICORPS ET RÉCEPTEURS ANTIGÉNIQUES CHIMÉRIQUES SPÉCIFIQUES DU CD19

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(56) References cited:
WO-A2-2009/054863 WO-A2-2009/091826
WO-A2-2012/170807 US-B2- 7 109 304

- **KOCHENDERFER JAMES N ET AL: "B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells.", BLOOD 22 MAR 2012, vol. 119, no. 12, 22 March 2012 (2012-03-22), pages 2709-2720, ISSN: 1528-0020**
- **TURTLE CAMERON J ET AL: "CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients.", THE JOURNAL OF CLINICAL INVESTIGATION 01 JUN 2016, vol. 126, no. 6, 1 June 2016 (2016-06-01), pages 2123-2138, ISSN: 1558-8238**

(Cont. next page)

- **DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 22 March 2012 (2012-03-22), KOCHENDERFER JAMES N ET AL: "B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells.", Database accession no. NLM22160384 & BLOOD 22 MAR 2012, vol. 119, no. 12, 22 March 2012 (2012-03-22), pages 2709-2720, ISSN: 1528-0020**
- **DATABASE MEDLINE [Online] US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; 1 June 2016 (2016-06-01), TURTLE CAMERON J ET AL: "CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients.", Database accession no. NLM27111235 & THE JOURNAL OF CLINICAL INVESTIGATION 01 JUN 2016, vol. 126, no. 6, 1 June 2016 (2016-06-01), pages 2123-2138, ISSN: 1558-8238**
- **SOMMERMEYER D ET AL: "Fully human CD19-specific chimeric antigen receptors for T-cell therapy.", LEUKEMIA 10 2017, vol. 31, no. 10, October 2017 (2017-10), pages 2191-2199, ISSN: 1476-5551**

Description

Cross-Reference to Related Applications

[0001] This application claims priority from U.S. provisional application No. 62/043,273 filed August 28, 2014, entitled "Antibodies and Chimeric Antigen Receptors Specific for CD19," and U.S. provisional application No. 62/078,942 filed November 12, 2014, entitled "Antibodies and Chimeric Antigen Receptors Specific for CD19".

Incorporation By Reference of Sequence Listing

[0002] The present application is being filed with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled 735042000740seqlist.txt, created August 28, 2015, with is 215 kilobytes in size.

Field

[0003] The present disclosure relates in some aspects to CD19 binding molecules, in particular, to anti-CD19 antibodies, including antibody fragments. The present disclosure further relates to recombinant receptors containing such antibodies, including chimeric antigen receptors (CARs), which contain such antibodies. The disclosure further relates to genetically engineered cells expressing such receptors and antibodies, and use thereof in adoptive cell therapy.

Background

[0004] CD19 is expressed on normal B cells and by cells and tissues of various diseases and conditions, including most B cell malignancies. Most patients with B cell malignancies are not cured by available therapies, including therapies targeting CD19 and/or other B cell markers. Various CD19-binding molecules, including anti-CD19 antibodies, and chimeric antigen receptors containing anti-CD19 antibody portions, and cells expressing such chimeric receptors, are available. Improved CD19-binding molecules and engineered CD19-targeting cells are needed. For example, there is a need for molecules and cells with reduced immunogenicity and/or human antibodies, including antibody fragments that specifically bind to CD19 and chimeric receptors expressing such human antibodies for use in adoptive cell therapy. Provided are instances that meet such needs.

[0005] WO2012170807 describes anti-Pseudomonas PSL binding molecules and uses thereof.

[0006] WO2009054863 describes human antibodies that bind CD19 and uses thereof.

[0007] WO2009091826 describes compositions and methods related to a human CD19-specific chimeric antigen receptor.

[0008] US2005070693 describes therapy using anti-CD-19 antibodies.

[0009] Kochenderfer et al. (2012) describe B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-tarnsduced T cells (Blood, vol.119(12):2709-2720).

[0010] Turtle et al. (2016) describe CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients (The Journal of Clinical Investigation, vol.126(6):2123-2138).

Summary

[0011] The subject-matter of the invention is defined by the appended claims.

[0012] The invention provides antibody or antigen binding fragment thereof comprising: a VH region comprising the amino acid sequence of SEQ ID NO: 11, and a VL region comprising the amino acid sequence of SEQ ID NO: 13; or a VH region comprising the amino acid sequence of SEQ ID NO: 11, and a VL region comprising the amino acid sequence of SEQ ID NO: 14; or a VH region comprising the amino acid sequence of SEQ ID NO: 11, and a VL region comprising the amino acid sequence of SEQ ID NO: 16; or a VH region comprising the amino acid sequence of SEQ ID NO: 12, and a VL region comprising the amino acid sequence of SEQ ID NO: 15; or a VH region comprising the amino acid sequence of SEQ ID NO: 12, and a VL region comprising the amino acid sequence of SEQ ID NO: 17. Embodiments of the invention are described in some of the instances below. The following disclosure provides CD19-binding molecules, including polypeptides, such as anti-CD19 antibodies, including antigen-binding antibody fragments such as single-chain fragments including scFv fragments, and polypeptides containing such antibodies, including fusion proteins, receptors, e.g., recombinant receptors, including chimeric receptors such as chimeric antigen receptors (CARs) containing the antibody as an antigen-recognition component. In particular instances, the antibodies are human antibodies, such as human single-chain fragments including scFvs.

[0013] Provided are antibodies or antigen-binding fragments thereof, including those that specifically bind to CD19. In some instances, the antibodies contain particular complementarity determining regions (CDRs), including heavy chain

CDRs (CDR-Hs) and light chain CDRs (CDR-Ls). In some instances, the CDRs have or include amino acid sequences of CDRs of a reference antibody or chain or sequence thereof.

[0014] In some instances, the antibody or antigen-binding fragment thereof includes a heavy chain variable (VH) region and a light chain variable (VL) region. In some instances, the antibody, e.g., the VH region thereof, includes a heavy chain complementarity determining region 3 (CDR-H3) comprising the amino acid sequence set forth as SEQ ID NO: 20. In some instances, the VH region comprises at least at or about 90 % sequence identity to the VH region amino acid sequence set forth in SEQ ID NO: 11, 12, 60, 61, 63, or 62, e.g., at least at or about 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity thereto. In some instances, the antibody or fragment includes a CDR-H1 of SEQ ID NO: 18 and a CDR-H3 of SEQ ID NO: 20. In some instances, the antibody or fragment further includes a CDR-H2 sequence comprising SEQ ID NO: 81, 82, 19 or 72.

[0015] In some instances, the antibody has a CDR-H1, a CDR-H2, and/or a CDR-H3 that respectively include the amino acid sequences of CDR 1, 2, and 3 sequences contained within the heavy chain variable (V_H) region of a reference antibody. In some instances, the VH region of the reference antibody has the amino acid sequence set forth in SEQ ID NO: 11 or 12. In some instances, it has the amino acid sequence set forth in SEQ ID NO: 11, 12, 60, 61, 63, or 62.

[0016] In some instances, the antibody has, e.g., further includes, a CDR-L1, a CDR-L2, and/or a CDR-L3, respectively comprising the amino acid sequences of CDR 1, 2, and 3 sequences contained within the light chain variable (V_L) region of a reference antibody. In some instances, the V_L of the reference antibody has the amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16, or 17. In some instances, the VL of the reference antibody has the amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16, 17, 71, 65, 64, 66, 70, 69, 67, 90 or 91.

[0017] In some instances, the CDR within the reference antibody, VH, or VL refers to the CDR as defined by any numbering scheme, e.g., those defined herein. In some instances, the CDR in the reference antibody or VH or VL refers to the CDR as defined by Kabat numbering scheme as described herein, the CDR as defined by the Chothia scheme as described herein, or the Contact scheme as described herein.

[0018] In some instances, the antibody contains a VH chain that includes a CDR-H1, CDR-H2 and/or CDR-H3 in which the CDR-H1 comprises the amino acid sequence of DYAMH (SEQ ID NO: 18) or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity to SEQ ID NO: 18; the CDR-H2 comprises the amino acid sequence of SEQ ID NO: 81 or 82 or 19 or 72 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity to SEQ ID NO: 81 or to SEQ ID NO: 82 or to SEQ ID NO: 19 or to SEQ ID NO: 72; and/or the CDR-H3 comprises the amino acid sequence of SEQ ID NO: 20 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity to SEQ ID NO: 20.

[0019] In some instances, the antibody comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 18, a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 81 or 82, and a CDR-H3 comprising the amino acid sequence set forth as SEQ ID NO: 20.

[0020] In some instances, the antibody has a CDR-1 comprising the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ (SEQ ID NO: 110), wherein X_1 is T, W, S or R; X_2 is G or A; X_3 is I, T, D or S; X_4 is S, R, T or Q; X_5 is null or S; X_6 is null, D, N or G; X_7 is null, V or L; X_8 is X or null; X_9 is X or null; X_{10} is X; X_{11} is X; X_{12} is Y, F, D or W; X_{13} is V, A or L and X_{14} is S, N or A. For example, in some instances, the antibody has a CDR-L1 comprising the amino acid sequence of $X_1X_2X_3X_4X_5$X6$X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$(SEQ ID NO: 111), wherein X_1 is T, Q, S, or R; X_2 is G or A; X_3 is I, T, D, or S; X_4 is S, R, T, or Q; X_5 is null or S; X_6 is G, D, N, or null; X_7 is null, V, or L; X_8 is D, G, I, L, S, or null; X_9 is S, G, A, I, R, or null; X_{10} is H, Y, F, S, or N; X_{11} is R, N, D, H, or Y; X_{12} is Y, F, D, or W; X_{13} is V, A, or L; and X_{14} is S, N, or A; and/or

a CDR-L2 comprising the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7$ (SEQ ID NO: 112), wherein X_1 is D or S; X_2 is F, V, N, K, or A; X_3 is S, T, D, or N; X_4 is K, V, N, Q, or R; X_5 is R, V, or L; X_6 is P, K, A, or E; and X_7 is S, P, A, or T, and/or a CDR-L3 comprising the amino acid sequence of $X_1X_2X_3X_4X_5$X6$X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 115), wherein X_1 is X; X_2 is S, Q, A, or T; X_3 is Y, S, W, R; X_4 is A, D, R, T, or Y; X_5 is X; X_6 is X; X_7 is S, P, L, Y, G; X_8 is X or null; X_9 is X or null; X_{10} is L or null; X_{11} is X; and X_{12} is V, T, or L. For example, in some instances, the antibody has a CDR-L3 comprising the amino acid sequence $X_1X_2X_3X_4X_5$X6$X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 114), wherein X_1 is S, G, T, A, Q, C or N; X_2 is S, Q, A, or T; X_3 is Y, S, W, R; X_4 is A, D, R, T, or Y; X_5 is A, S, P, G, N or D; X_6 is I, S, G, T, A, L, H, R, N; X_7 is S, P, L, Y, G; X_8 is P, T, S, Q, M, R, N or null; X_9 is S, L, N, A, M or null; X_{10} is L or null; X_{11} is Y, W, F, V, A or L; and X_{12} is V, T, or L.

[0021] In some such instances, in said CDR-L1, X_3 is I, T, or S; X_4 is S, T, or Q; X_8 is D, G, I, S, or null; X_9 is S, G, I, or null; X_{10} is H, Y, S, or N; X_{11} is R, N, D, or H; X_{12} is Y or D; and X_{13} is V or L; and/or in said CDR-L2, X_1 is D; X_4 is K, V, N, Q, or R; X_6 is P, K, or A; and X_7 is S, A, or T ; and/or in said CDR-L3, X_1 is S, G, T, A, Q, C, or N; X_5 is A, S, P, G, N, or D; X_6 is I, S, G, T, A, L, H, R, or N; X_8 is P, T, S, Q, M, R, N, or null; X_9 is S, L, N, A, M or null; and X_{11} is Y, W, F, V, A, or L. In some instances, in said CDR-L3, X_1 is S, G, Q, or N; X_2 is S, Q, or T; X_4 is A, D, T, or Y; X_5 is A, S, or G; and X_6 is I, S, N, R, A, H, or T.

[0022] In some instances, the CDR-H2 comprises the amino acid sequence set forth in SEQ ID NO: 19 (GISWNS-

GRIGYADSVKG); or the CDR-H2 comprises the amino acid sequence set forth in SEQ ID NO: 72 (GISWNSGSIGYADSVKG).

[0023] In some instances, the CDR-L1 comprises the amino acid sequence set forth in SEQ ID NO: 80, 77, 74, 73, 75, 79, 78, 76, 21, 25, 28, or 31. In some instances, the CDR-L1 comprises the amino acid sequence set forth in SEQ ID NO: 80, 77, 74, 73, 78, 21, or 28.

[0024] In some instances, the CDR-L2 comprises the amino acid sequence set forth in SEQ ID NO: 100, 97, 94, 93, 95, 99, 98, 96, 22, 26, 29, or 32. In some instances, the CDR-L2 comprises the amino acid sequence set forth in SEQ ID NO: 100, 97, 94, 93, 98, 22, or 29.

[0025] In some instances, the CDR-L3 comprises the amino acid sequence set forth in SEQ ID NO: 109, 106, 103, 101, 104, 108, 107, 105, 102, 23, 24, 27, 30, or 33. In some instances, the CDR-L3 comprises the amino acid sequence set forth in SEQ ID NO: 109, 106, 103, 101, 107, 24 or 30.

[0026] In some instances, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22, and 23, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22, and 24 or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 25, 26, and 27, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 28, 29 and 30, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 31, 32, and 33, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 80, 100, and 109, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs:77, 97, and 106, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 74, 94, and 103, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 73, 93, and 101, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs:75, 95, and 104, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 79, 99, and 108, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 78, 98, and 107, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 76, 96, and 105, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 73, 93, and 102, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; or the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 77, 97, and 106, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto.

[0027] In some instances, the CDR-L3 comprises the amino acid sequence set forth as SEQ ID NO: 116, 117, 118, 119, 120, or 121, or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto.

[0028] In some instances, the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 81, and 20, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 19, and 20, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 82, and 20, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto; or the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 72, and 20, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, respectively, thereto.

[0029] In some instances, the antibody has a CDR-L1 comprising the amino acid sequence $X_1GX_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}S$ (SEQ ID NO: 36), wherein X1 is T, S, or Q, X3 is T, S, or D, X4 is T or S, X5 is null or S, X6 is null, D, or N, X7 is null or V, X8 is null, G, or I, X9 is null, G, or R, X10 is S, Y, or N, X11 is D or N, X12 is D or Y, X13 is V or A; the CDR-L2 comprises the amino acid sequence $X_1X_2X_3X_4RPS$ (SEQ ID NO: 37), wherein X1 is D or S, X2 is V, N, or K, X3 is S, N, or D, and X4 is K, Q, or N; and/or the CDR-L3 comprises the amino acid sequence $X_1X_2X_3X_4X_5X6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 113), wherein X1 is C, S, A, G, or N; X2 is S, A, or T; X3 is Y, W, or R; X4 is A or D; X5 is G, D, or S; X6 is R, S, or N; X7 is Y, L, or G; X8 is N or S; X9 is S, N, or null; X10 is null; X11 is V, A, or W; and X12 is L or V.

[0030] In some instances, the antibody has a CDR-L1 comprising the amino acid sequence $X_1GX_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}S$ (SEQ ID NO: 36), wherein X1 is T, S, or Q, X3 is T, S, or D, X4 is T or S, X5 is null or S, X6 is null, D, or N, X7 is null or V, X8 is null, G, or I, X9 is null, G, or R, X10 is S, Y, or N, X11 is D or N, X12 is D or Y, X13 is V or A; the CDR-L2 comprises the amino acid sequence $X_1X_2X_3X_4RPS$ (SEQ ID NO: 37), wherein X1 is D or S, X2 is V, N, or K, X3 is S, N, or D, and X4 is K, Q, or N; and/or the CDR-L3 comprises the amino acid sequence $X_1X_2X_3X_4X_5X6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 38), wherein X1 is C, S, A, G, or N; X2 is S, A, or T; X3 is Y, W, or R; X4 is A or D; X5 is G, D, or S; X6 is R, S, or N; X7 is Y, L, or G; X8 is N or S; X9 is S or null; X10 is V, A or N; X11 is W or null; and X12 is L or V.

[0031] In some such instances, in the CDR-L1, X1 is T or S, X3 is T or S, X11 is D or N, and X13 is V; and/or in the CDR-L2, X2 is V or N and X4 is K or Q.

[0032] In some instances, the CDR-H2 comprises the amino acid sequence set forth in SEQ ID NO: 19 (GISWNS-GRIGYADSVKG) or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity to SEQ ID NO: 19.

[0033] In some instances, the CDR-L1 comprises the sequence set forth in SEQ ID NO: 21, 25, 28, or 31 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto; and/or the CDR-L2 comprises the sequence set forth in SEQ ID NO: 22, 26, 29, or 32 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto; and/or the CDR-L3 comprises the sequence set forth in SEQ ID NO: 23, 24, 27, 30, or 33 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0034] In some instances, the CDR-L1, CDR-L2, and/or CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22, and/or 23, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively.

[0035] In some instances, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22, and 24, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively.

[0036] In some instances, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 25, 26, and 27, respectively or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively.

[0037] In some instances, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 28, 29, and 30, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively. In some instances, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 31, 32, and 33, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0038] In some instances, the heavy and light chain CDRs are any combination of the aforementioned CDR-L and CDR-H sequences, including sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0039] In particular instances, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 11 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0040] In particular instances, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 12 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0041] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 13 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0042] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 14 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0043] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 15 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0044] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 16 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0045] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 17 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0046] In particular instances, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 63 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0047] In particular instances, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 60 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0048] In particular instances, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 61 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0049] In particular instances, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 63 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0050] In particular instances, the antibody or fragment comprises a VH region comprising the amino acid sequence of SEQ ID NO: 62 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0051] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 71 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0052] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 90 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0053] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 91 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0054] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 68 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0055] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 65 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0056] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 64 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0057] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 66 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0058] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 70 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0059] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 69 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0060] In particular instances, the antibody or fragment comprises a VL region comprising the amino acid sequence of SEQ ID NO: 67 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0061] In particular instances, the VH region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 11, 60, 63, or 62 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto; and/or the VL region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 14, 16, 71, 90, 65, 64, or 69 or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0062] In some instances, the VH and VL regions of the antibody or fragment comprise the amino acid sequences of

SEQ ID NOs: 12 and 17, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 15, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 13, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 14, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 16, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 71, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 62 and 68, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 65, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 60 and 64, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 61 and 66, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 70, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 62 and 69, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 67, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively;
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 91, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively; or
the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 90, respectively, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto, respectively.

[0063] In some instances, the VH region comprises SEQ ID NO: 11 and the VL region comprises SEQ ID NO: 13; in some instances, the VH region comprises SEQ ID NO: 11 and the VL region comprises SEQ ID NO: 14; in some instances, the VH region comprises SEQ ID NO: 11 and the VL region comprises SEQ ID NO: 15; in some instances, the VH region comprises SEQ ID NO: 11 and the VL region comprises SEQ ID NO: 16, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto; in some instances, the VH region comprises SEQ ID NO: 11 and the VL region comprises SEQ ID NO: 17, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0064] In some instances, the VH region comprises SEQ ID NO: 12 and the VL region comprises SEQ ID NO: 13; in some instances, the VH region comprises SEQ ID NO: 12 and the VL region comprises SEQ ID NO: 14; in some instances, the VH region comprises SEQ ID NO: 12 and the VL region comprises SEQ ID NO: 15; in some instances, the VH region comprises SEQ ID NO: 12 and the VL region comprises SEQ ID NO: 16, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto; in some instances, the VH region comprises SEQ ID NO: 12 and the VL region comprises SEQ ID NO: 16, or sequences having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0065] In some instances, the antibody is a single chain fragment, such as one with two or more variable regions joined by one or more flexible immunoglobulin linker. In some instances, the antibody is an scFv. In some instances, the scFv comprises a linker that is rich in serine and/or glycine, such as a linker comprising GGGS (SEQ ID NO: 122) or GGGGS (SEQ ID NO:123) repeats, such as one comprising the sequence set forth SEQ ID NO: 34. In some instances the linker comprises a sequence of SEQ ID NO: 43.

[0066] In some instances, the antibody fragment, e.g., scFv, contains a V_H region or portion thereof, followed by a linker, followed by a V_L or portions thereof. In some instances, the antibody fragment, e.g., scFv, contains a V_L region or portion thereof followed by a linker, followed by a V_H region or portion thereof.

[0067] In some instances, the scFv comprises the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, or 10, or a sequence having at least or at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity thereto.

[0068] In some instances, the scFv comprises the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 47, 49, 51, 53, 55, 57, 59, 87, or 89, or has a sequence at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence.

[0069] In some instances, the antibody or fragment specifically binds to the same, similar, and/or an overlapping epitope of CD19 as the epitope specifically bound by a reference antibody, and/or the antibody competes for binding to CD19 with the reference antibody. In some aspects, the reference antibody is a murine or chimeric or human or humanized anti-CD 19 antibody, FMC63, SJ25C1, an antibody having a variable region sequence of SEQ ID NO: 39 and/or 40, or an antibody having a variable region sequence of SEQ ID NO: 41 and/or 42. In some aspect, the reference antibody is an antibody including a sequence as described herein, including sequence(s) of any of the aforementioned instances. For example, in some instances, the reference antibody can be an scFv that contains the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 47, 49, 51, 53, 55, 57, 59, 87, or 89. In some instances, the provided antibody or fragment contains one or more or all CDRs that are distinct from those in the reference antibody. For example, in some instances, the provided antibody or fragment contains one or more or all CDRs that are distinct from the corresponding CDRs in the antibody designated FMC63 or SJ25C1.

[0070] For example, provided are human antibody and antigen-binding fragments that specifically bind to the same or an overlapping epitope of CD19 as the epitope specifically bound by the reference antibody, such as FMC63, SJ25C1, an antibody having a variable region sequence of SEQ ID NO: 39 and/or 40, or an antibody having a variable region sequence of SEQ ID NO: 41 and/or 42, and comprising heavy and light chain CDRs that are distinct from the CDRs present in the reference antibody.

[0071] In some instances, the antibody competes for binding with the reference antibody to at least the same degree as the reference antibody competes for binding with itself to CD19, or a degree of competition that is no more than 1.5-fold or 2-fold lower, 3-fold lower, 4-fold lower, 5-fold lower, or 10-fold lower than the competition by the reference antibody, and/or a measured IC50 that is no more than 1.5-fold or 2-fold or 3-fold or 4-fold or 5-fold or 10-fold higher than the IC50 of the reference antibody competing for binding with itself, for example, as measured in the same assay.

[0072] In some instances, the antibody has a binding affinity that is at least as high or substantially as high as the binding affinity for CD19 of the reference antibody. In some aspects, the antibody has a binding affinity of an EC50 that is about the same or lower than the EC50 reference antibody or no more than about 1.5-fold or no more than about 2-fold greater, no more than 3-fold greater, and/or no more than 10-fold greater, than the EC50 of the reference antibody. In some instances, binding affinity of the antibody is compared to the corresponding form of the reference antibody. Comparison is generally by the same or a similar assay.

[0073] In some of any such instances, CD19 is a human CD19. In some of any such instances, the antibody or fragment specifically binds, exhibits binding affinity and/or competes for binding to human CD19.

[0074] In some instances, the antibody is human. In some instances, the antibody is recombinant. In some instances, the antibody is monoclonal. In some instances, the antibody is isolated.

[0075] In some instances, the antibody or fragment further includes at least a portion of an immunoglobulin constant region. The constant region may include any one or more of CH1, CH2, CH3, and/or CH4, and/or CL, of a human or other antibody, and be of any class, including IgG, IgM, IgA, IgE, and IgD, for example, including human IgG, e.g., IgG1 or IgG4, constant region domains. In some instances, the constant region comprises or is an Fc region, such as a human IgG Fc region.

[0076] Also provided are molecules such as chimeric and/or fusion molecules, including receptors, such as recombinant receptors, that include the antibody of any of the instances (e.g., contained in or part of an extracellular domain) and additional domains, such as intracellular signaling domains, spacers, linkers, and/or transmembrane domains. In some instances, the receptor is a chimeric antigen receptor, comprising an extracellular portion comprising the antibody or fragment of any of the instances and an intracellular signaling domain.

[0077] In some instances, the antibody or fragment comprises an scFv. In some instances, the intracellular signaling domain comprises an ITAM and/or signaling domain capable of delivering a signal approximating that of natural ligation of an ITAM-containing molecule or receptor complex such as a TCR receptor complex. In some aspects, the intracellular signaling domain comprises a signaling domain of a zeta chain of a CD3-zeta (CD3ζ) chain.

[0078] In some instances, the receptor further includes one or more domains, such as a transmembrane domain, linking the antibody transmembrane domain linking the extracellular domain and the intracellular signaling domain. In some aspects, the transmembrane domain comprises a transmembrane portion of a costimulatory molecule, such as a T cell costimulatory molecule, e.g., CD28 and/or 41BB. In some instances, the T cell costimulatory molecule is selected from the group consisting of CD28 and 41BB, and in some instances, the receptor includes signaling domains from CD28 and 41BB.

[0079] Also provided are nucleic acids encoding the antibody (including fragments) of any of instances or the receptor, e.g., chimeric antigen receptor of any of the instances, vectors including such nucleic acids, and cells containing the vectors and/or nucleic acids, for example, for expression of the antibodies and/or molecules.

[0080] Thus, also provided are cells and vectors for producing and expressing the molecules, including the antibodies and molecules such as receptors, e.g., chimeric antigen receptors (CARs). For example, provided are engineered cells expressing the chimeric antigen receptor of any of the instances. In some aspects, the cell is a T cell. In some aspects, the cell is an NK cell. In some aspects, the cell is a stem cell.

[0081] Also provided are compositions comprising the antibodies, receptors, molecules, and/or cells, including pharmaceutical compositions, e.g., further including pharmaceutically acceptable substances such as carriers.

[0082] Also provided are methods of administration, including methods of treatment, carried out by administering the cell, antibody, receptor, composition, or other molecule, of any of the instances, to a subject, for example, in an effective, e.g., therapeutically effective, amount. In some instances, the subject has or is suspected of having a disease or disorder associated with CD19, such as a B cell malignancy, such as B cell chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), pro-lymphocytic leukemias, hairy cell leukemias, common acute lymphocytic leukemias, Null-acute lymphoblastic leukemias, non-Hodgkin lymphomas, diffuse large B cell lymphomas (DLBCLs), multiple myelomas, follicular lymphoma, splenic, marginal zone lymphoma, mantle cell lymphoma, indolent B cell lymphoma, or Hodgkin lymphoma, or an autoimmune or inflammatory disease in which B cells are implicated.

[0083] In some instances, administration of the antibody or receptor is associated with a lower degree of immunogenicity as compared to administration of a reference antibody (or receptor containing the reference antibody) that competes for binding with the antibody or binds to an overlapping epitope. In some aspects, the reference antibody is a humanized, chimeric, or non-human antibody.

Brief Description of the Drawings

[0084]

Figure 1: Figures 1A and **1B** show results from a binding assay comparing binding of exemplary human scFvs to CD19-expressing HEK293 cells as compared to binding to non-CD 19-expressing HEK293 cells. MFI=mean fluorescence intensity.

Figure 2 shows an SDS gel assessing purification of exemplary anti-CD19 antibodies (scFv fragments).

Figure 3: Figures 3A, 3B, and **3C** show results from studies assessing binding affinities of various exemplary scFv antibodies (scFv fragments), including anti-CD19 antibodies. MFI=mean fluorescence intensity.

Figure 4 show results from studies assessing binding affinities of various exemplary scFv antibodies, including anti-CD19 scFv antibody fragments. MFI=mean fluorescence intensity.

Figure 5: Figures 5A and **5B** show results from competitive binding assays, assessing binding of respective labeled antibody in the presence of varying concentrations of competing antibodies. MFI=mean fluorescence intensity.

Figure 6 shows results from competitive binding assays, assessing binding of a labeled reference scFv antibody in the presence of varying concentrations of competing scFv antibodies. MFI=mean fluorescence intensity.

Figure 7: Figure 7A shows results from size-exclusion chromatography; a column was calibrated, standard proteins injected, and fractions collected to generate references. **Figure 7B** shows results following injection of an anti-CD19 scFv (clone 18B) into the same column and collection of fraction under the same conditions.

Figure 8A show results from a binding assay assessing binding of exemplary human scFv clones to CD19-expressing cells in order from left to right as follows: cells only, mock supernatant (Moc. Supe.) negative control antibody (Neg. Ctrl.), Clone 18, Clones 200 to 287, cells only, Moc. Supe, Neg. Ctrl. and Clone 18. Exemplary hits that show CD19-specific binding (indicated by an asterisk) are (in order from left to right): Clone 213, Clone 227, Clone 241, Clone 255, Clone 272, Clone 278, Clone 283 and Clone 285. MFI=mean fluorescence intensity.

Figure 8B shows results from a binding assay assessing binding of exemplary human scFv clones to CD19-expressing cells in order from left to right as follows: cells only, mock supernatant (Moc. Supe.) negative control antibody (Neg. Ctrl.), Clone 18B, Clones 300-387, cells only, Moc. Supe., Neg. Ctrl. and Clone 18B. Exemplary hits that show CD19-specific binding (indicated by an asterisk) are (in order from left to right): Clone 302, Clone 305, Clone 313, Clone 314, Clone 318, Clone 324, Clone 327, Clone 328, Clone 336, Clone 339, Clone 377, Clone 379 and Clone 382. MFI=mean fluorescence intensity.

Figure 8C shows results from a binding assay assessing binding of exemplary human scFv clones to CD19-expressing cells in order from left to right as follows: cells only, mock supernatant (Moc. Supe.) negative control antibody (Neg. Ctrl.), Clone 18B, Clones 400-487, cells only, Moc. Supe., Neg. Ctrl. and Clone 18B. Exemplary hits that show CD19-specific binding (indicated by an asterisk) are (in order from left to right): Clone 440 and Clone 448.

Figure 8D shows results from a binding assay comparing binding of exemplary human scFvs to CD19-expressing K562 cells as compared to non-CD19-expressing K562 cells. MFI=mean fluorescence intensity.

Figure 9 shows an SDS gel assessing purification of exemplary anti-CD19 antibodies (scFv fragments).

Figure 10: Figures 10A-E show results from separate binding assays assessing binding affinities of various exemplary scFv antibodies, including anti-CD19 scFv antibody fragments. MFI=mean fluorescence intensity.

Figure 11 shows results from competitive binding assays, assessing binding of a labeled reference scFv antibody in the presence of varying concentrations of competing scFv antibodies. MFI=mean fluorescence intensity.

Figure 12A shows cell surface expression of the various CARs, in either VH-VL (HL) orientation HL; dark line) or VL-VH orientation (LH; grey line), in transduced CD8+ T cells as measured by expression of EGFRt for cells before enrichment (pre) and after enrichment following sorting with an anti-EGFR antibody and expansion by stimulation with $CD19^+$ B-LCL (post).

Figure 12B shows an SDS gel assessing expression of exemplary human anti-CD19 CARs in transduced primary human T cells.

Figures 13A and 13B show cytolytic activity of primary human $CD8^+$ T cells expressing various anti-CD19 specific CARs against CD19-expressing cells. C is EGFRt alone (negative control); FM is FMC63 scFv CAR, 18 is Clone 18 scFv CAR, 17 is Clone 17 scFv CAR, 76 is Clone 76 scFv CAR, 5 is Clone 5 scFv CAR and 18B is Clone 18B scFv CAR.

Figures 14A and 14B show cytokine secretion of primary human $CD8^+$ T cells expressing various anti-CD19 specific CARs after co-culture with CD19-expressing cells. C is EGFRt alone (negative control); FM is FMC63 scFv CAR, 18 is Clone 18 scFv CAR, 17 is Clone 17 scFv CAR, 76 is Clone 76 scFv CAR, 5 is Clone 5 scFv CAR and 18B is Clone 18B scFv CAR.

Figure 15 shows cytokine secretion of primary human $CD4^+$ T cells expressing various anti-CD19 specific CARs after co-culture with CD19-expressing cells. C is EGFRt alone (negative control); FM is FMC63 scFv CAR, 18 is Clone 18 scFv CAR, 17 is Clone 17 scFv CAR, 76 is Clone 76 scFv CAR, 5 is Clone 5 scFv CAR and 18B is Clone 18B scFv CAR.

Figure 16A and 16B show proliferation of primary human CD8+ T cells or CD4+ T cells, respectively, expressing various anti-CD19 specific CARs against CD19-expressing cells after co-culture with CD19-expressing cells.

Figure 17: Figure 17A shows the antitumor activity of primary human CD8+ T cells expressing various anti-CD19 specific CARs following administration to NSG mice engrafted with Raji cells that express firefly luciferase. **Figure 17B** shows antitumor activity of primary human CD4+ and CD8+ T cells expressing various anti-CD 19 specific CARs and administered at a 1:1 ratio to NSG mice engrafted with Raji cells.

Figure 18: Figure 18A shows the amino acid sequence of a 74-residue or 75-residue membrane-proximal region for each of the three different chimeric CD19 molecules. Below all three sequences shown in Figure 18A, each aligned position of the depicted region at which the human and rhesus sequences contain an identical amino acid is marked with an asterisk ("*"). Positions at which the rhesus sequence contains a non-identical but conservative amino acid substitution compared to the human sequence are marked with a ":". Positions at which the rhesus sequence contains a non-identical but semi-conservative amino acid substitution compared to the human sequences are marked with a ".". Positions at which the rhesus sequence contains an insertion or a non-identical, non-conservative/semi-conservative substitution compared with the human sequence are not marked with a symbol. **Figure 18B** show cytokine secretion of primary human $CD8^+$ T cells expressing various anti-CD19 specific CARs after co-culture with cells expressing human CD19, rhesus CD19 or chimeric rhesus/human CD19 molecules (V1, V2 or V3). C is EGFRt alone (negative control); FM is FMC63 scFv CAR, 18 is Clone 18 scFv CAR, 17 is Clone 17 scFv CAR, 76 is Clone 76 scFv CAR, 5 is Clone 5 scFv CAR and 18B is Clone 18B scFv CAR.

Detailed Description

[0085] Provided are CD19-binding molecules, including antibodies (including antigen-binding antibody fragments, such as single chain fragments, including scFvs) and recombinant receptors, including chimeric receptors containing such antibodies and fragments, nucleic acids encoding such antibodies and fragments, and cells, such as recombinant cells, expressing and for production of these antibodies and fragments. Also provided are methods of making and using the antibodies and fragments as well as cells expressing or containing the antibodies and fragments.

I. CD19 Binding Molecules

[0086] Provided in some aspects are CD19 binding molecules, such as CD19-binding polypeptides. Such binding molecules include antibodies that specifically bind to CD19, such as a human CD19 molecule, including antigen-binding fragments thereof. Also among the binding molecules are recombinant receptors such as chimeric antigen receptors containing such antibodies.

A. CD19 Antibodies

[0087] Provided are anti-CD19 antibodies, including functional antibody fragments, including those comprising a variable heavy chain and a variable light chain, such as scFvs. Also provided are molecules containing such antibodies, e.g., fusion proteins and/or recombinant receptors such as chimeric receptors, including antigen receptors. Among the provided anti-CD19 antibodies are human antibodies. In some instances, the antibodies, such as the human antibodies, specifically bind to a particular epitope or region of CD19, generally an extracellular epitope or region. In some instances, the antibodies bind to the same or a similar epitope or region of CD19 as bound by another antibody, such as one or more of the mouse antibodies, FMC63 or SJ25C1. In some instances, the antibodies bind to an overlapping epitope of CD19 as bound by one of these known antibodies and/or compete for binding with such an antibody. The antibodies include isolated antibodies. The molecules include isolated molecules.

[0088] The term "antibody" herein is used in the broadest sense and includes polyclonal and monoclonal antibodies, including intact antibodies and functional (antigen-binding) antibody fragments, including fragment antigen binding (Fab) fragments, $F(ab')_2$ fragments, Fab' fragments, Fv fragments, recombinant IgG (rIgG) fragments, single chain antibody fragments, including single chain variable fragments (scFv), and single domain antibodies (e.g., sdAb, sdFv, nanobody) fragments. The term encompasses genetically engineered and/or otherwise modified forms of immunoglobulins, such as intrabodies, peptibodies, chimeric antibodies, fully human antibodies, humanized antibodies, and heteroconjugate antibodies, multispecific, e.g., bispecific, antibodies, diabodies, triabodies, and tetrabodies, tandem di-scFv, tandem tri-scFv. Unless otherwise stated, the term "antibody" should be understood to encompass functional antibody fragments thereof. The term also encompasses intact or full-length antibodies, including antibodies of any class or subclass, including IgG and sub-classes thereof, IgM, IgE, IgA, and IgD.

[0089] The terms "complementarity determining region," and "CDR," synonymous with "hypervariable region" or "HVR," are known in the art to refer to non-contiguous sequences of amino acids within antibody variable regions, which confer antigen specificity and/or binding affinity. In general, there are three CDRs in each heavy chain variable region (CDR-H1, CDR-H2, CDR-H3) and three CDRs in each light chain variable region (CDR-L1, CDR-L2, CDR-L3). "Framework regions" and "FR" are known in the art to refer to the non-CDR portions of the variable regions of the heavy and light chains. In general, there are four FRs in each full-length heavy chain variable region (FR-H1, FR-H2, FR-H3, and FR-H4), and four FRs in each full-length light chain variable region (FR-L1, FR-L2, FR-L3, and FR-L4).

[0090] The precise amino acid sequence boundaries of a given CDR or FR can be readily determined using any of a number of well-known schemes, including those described by Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD ("Kabat" numbering scheme), Al-Lazikani et al., (1997) JMB 273,927-948 ("Chothia" numbering scheme), MacCallum et al., J. Mol. Biol. 262:732-745 (1996), "Antibody-antigen interactions: Contact analysis and binding site topography," J. Mol. Biol. 262, 732-745." ("Contact" numbering scheme), Lefranc MP et al., "IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains," Dev Comp Immunol, 2003 Jan;27(1):55-77 ("IMGT" numbering scheme), and Honegger A and Plückthun A, "Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool," J Mol Biol, 2001 Jun 8;309(3):657-70, ("Aho" numbering scheme).

[0091] The boundaries of a given CDR or FR may vary depending on the scheme used for identification. For example, the Kabat scheme is based structural alignments, while the Chothia scheme is based on structural information. Numbering for both the Kabat and Chothia schemes is based upon the most common antibody region sequence lengths, with insertions accommodated by insertion letters, for example, "30a," and deletions appearing in some antibodies. The two schemes place certain insertions and deletions ("indels") at different positions, resulting in differential numbering. The Contact scheme is based on analysis of complex crystal structures and is similar in many respects to the Chothia numbering scheme.

[0092] Table 1, below, lists exemplary position boundaries of CDR-L1, CDR-L2, CDR-L3 and CDR-H1, CDR-H2, CDR-H3 as identified by Kabat, Chothia, and Contact schemes, respectively. For CDR-H1, residue numbering is listed using both the Kabat and Chothia numbering schemes. FRs are located between CDRs, for example, with FR-L1 located between CDR-L1 and CDR-L2, and so forth. It is noted that because the shown Kabat numbering scheme places insertions at H35A and H35B, the end of the Chothia CDR-H1 loop when numbered using the shown Kabat numbering convention varies between H32 and H34, depending on the length of the loop.

Table 1

CDR	Kabat	Chothia	Contact
CDR-L1	L24--L34	L24--L34	L30--L36
CDR-L2	L50--L56	L50--L56	L46--L55
CDR-L3	L89--L97	L89--L97	L89--L96
CDR-H1 (Kabat Numbering[1])	H31--H35B	H26--H32..34	H30--H35B
CDR-H1 (Chothia Numbering[2])	H31--H35	H26--H32	H30--H35
CDR-H2	H50--H65	H52--H56	H47--H58
CDR-H3	H95--H102	H95--H102	H93-H101
1 - Kabat et al. (1991), "Sequences of Proteins of Immunological Interest," 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD 2 - Al-Lazikani et al., (1997) JMB 273,927-948			

[0093] Thus, unless otherwise specified, a "CDR" or "complementary determining region," or individual specified CDRs (e.g., "CDR-H1, CDR-H2), of a given antibody or region thereof, such as a variable region thereof, should be understood to encompass a (or the specific) complementary determining region as defined by any of the aforementioned schemes. For example, where it is stated that a particular CDR (e.g., a CDR-H3) contains the amino acid sequence of a corresponding CDR in a given V_H or V_L amino acid sequence, it is understood that such a CDR has a sequence of the corresponding CDR (e.g., CDR-H3) within the variable region, as defined by any of the aforementioned schemes. In some instances, specified CDR sequences are specified.

[0094] Likewise, unless otherwise specified, a FR or individual specified FR(s) (e.g., FR-H1, FR-H2), of a given antibody or region thereof, such as a variable region thereof, should be understood to encompass a (or the specific) framework region as defined by any of the known schemes. In some instances, the scheme for identification of a particular CDR, FR, or FRs or CDRs is specified, such as the CDR as defined by the Kabat, Chothia, or Contact method. In other cases, the particular amino acid sequence of a CDR or FR is given.

[0095] The term "variable region" or "variable domain" refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable domains of the heavy chain and light chain (V_H and V_L, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three CDRs. (See, e.g., Kindt et al. Kuby Immunology, 6th ed., W.H. Freeman and Co., page 91 (2007). A single V_H or V_L domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a V_H or V_L domain from an antibody that binds the antigen to screen a library of complementary V_L or V_H domains, respectively. See, e.g., Portolano et al., J. Immunol. 150:880-887 (1993); Clarkson et al., Nature 352:624-628 (1991).

[0096] Among the provided antibodies are antibody fragments. An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, $F(ab')_2$; diabodies; linear antibodies; single-chain antibody molecules (*e.g.* scFv); and multispecific antibodies formed from antibody fragments. In particular instances, the antibodies are single-chain antibody fragments comprising a variable heavy chain region and/or a variable light chain region, such as scFvs.

[0097] Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain instances, a single-domain antibody is a human single-domain antibody.

[0098] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells. In some instances, the antibodies are recombinantly-produced fragments, such as fragments comprising arrangements that do not occur naturally, such as those with two or more antibody regions or chains joined by synthetic linkers, e.g., peptide linkers, and/or that are may not be produced by enzyme digestion of a naturally-occurring intact antibody. In some aspects, the antibody fragments are scFvs.

[0099] A "humanized" antibody is an antibody in which all or substantially all CDR amino acid residues are derived from non-human CDRs and all or substantially all FR amino acid residues are derived from human FRs. A humanized antibody optionally may include at least a portion of an antibody constant region derived from a human antibody. A "humanized form" of a non-human antibody, refers to a variant of the non-human antibody that has undergone humanization, typically to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. In some instances, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (e.g., the antibody from which the CDR residues are derived), e.g., to restore or improve antibody specificity or affinity.

[0100] Among the provided anti-CD19 antibodies are human antibodies. A "human antibody" is an antibody with an amino acid sequence corresponding to that of an antibody produced by a human or a human cell, or non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences, including human antibody libraries. The term excludes humanized forms of non-human antibodies comprising non-human antigen-binding regions, such as those in which all or substantially all CDRs are non-human.

[0101] Human antibodies may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extrachromosomally or integrated randomly into the animal's chromosomes. In such transgenic animals, the endogenous immunoglobulin loci have generally been inactivated. Human antibodies also may be derived from human antibody libraries, including phage display and cell-free libraries, containing antibody-encoding sequences derived from a human repertoire.

[0102] Among the provided antibodies are monoclonal antibodies, including monoclonal antibody fragments. The term "monoclonal antibody" as used herein refers to an antibody obtained from or within a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical, except for possible variants containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different epitopes, each monoclonal antibody of a monoclonal antibody preparation is directed against a single epitope on an antigen. The term is not to be construed as requiring production of the antibody by any particular method. A monoclonal antibody may be made by a variety of techniques, including but not limited to generation from a hybridoma, recombinant DNA methods, phage-display and other antibody display methods.

[0103] The terms "polypeptide" and "protein" are used interchangeably to refer to a polymer of amino acid residues, and are not limited to a minimum length. Polypeptides, including the provided antibodies and antibody chains and other peptides, e.g., linkers and CD19-binding peptides, may include amino acid residues including natural and/or non-natural amino acid residues. The terms also include post-expression modifications of the polypeptide, for example, glycosylation, sialylation, acetylation, phosphorylation, and the like. In some aspects, the polypeptides may contain modifications with respect to a native or natural sequence, as long as the protein maintains the desired activity. These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutations of hosts which produce the proteins or errors due to PCR amplification.

Exemplary Anti-CD19 Antibodies

[0104] In some instances, the anti-CD19 antibody, e.g., antigen-binding antibody fragment, contains particular heavy and/or light chain CDR sequences and/or heavy and/or light chain variable (V_H or V_L) region sequences. Also among the provided antibodies are those having sequences at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence.

[0105] In some instances, the antibody, e.g., antigen-binding fragment thereof, includes a heavy chain complementarity determining region 3 (CDR-H3) comprising an amino acid sequence of a CDR-H3 present in a reference antibody, such as one present in a reference antibody having a VH region with the amino acid sequence set forth in set forth in SEQ ID NO: 11, 12, 60, 61, 63 62, 167 or 185, such as set forth in SEQ ID NO: 11, 12, 60, 61, 63, or 62. In some instances, the CDR-H3 comprises SEQ ID NO: 20. In some instances, the antibody, e.g., antigen-binding fragment thereof, has a VH region having at least 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% sequence identity to (or 100 % identity thereto) the VH region amino acid sequence of the reference antibody, such as to the VH region amino acid sequence set forth in SEQ ID NO: 11, 12, 60, 61, 63 62, 167 or 185, such as set forth in SEQ ID NO: 11, 12, 60, 61, 63, or 62.

[0106] In some instances, the CDR-H1 contains the amino acid sequence DYAMH (SEQ ID NO: 18), the CDR-H2 contains the amino acid sequence GISWNSGRIG (SEQ ID NO: 81), GISWNSGSIG (SEQ ID NO: 82), the amino acid sequence set forth in SEQ ID NO: 19 (GISWNSGRIGYADSVKG), or the amino acid sequence set forth in SEQ ID NO: 72 (GISWNSGSIGYADSVKG), and/or the CDR-H3 contains the amino acid sequence of SEQ ID NO: 20.

[0107] In some instances, the provided antibody contains a CDR-H3 having the amino acid sequence of SEQ ID NO: 20.

[0108] In some instances, the antibody contains a V_H having the amino acid sequence set forth in SEQ ID NO: 11 or 12, or has a sequence at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence. In some instances, the antibody, e.g., antigen-binding fragment thereof, contains a VH region having the amino acid sequence set forth in SEQ ID NO: 11, 12, 60, 61, 63, or 62, or a sequence at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence. In some instances, the antibody, e.g., antigen-binding fragment thereof, contains a VH region having the amino acid sequence set forth in SEQ ID NO: 11, 12, 60, 61, 63, 62, 167 or 185, or a sequence at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence.

[0109] In some instances, the antibody contains the sequence of residues 1-119 of SEQ ID NO: 11,12, 60, 61, 63, 62, 167 or 185 or a sequence comprising the portion of SEQ ID NO: 11, 12, 60, 61, 63, 62, 167 or 185 including the first three framework regions and the three heavy chain CDRs. In some instances, the antibody contains the sequence of residues 1-119 of SEQ ID NO: 11,12, 60, 61, 63 or 62 or a sequence comprising the portion of SEQ ID NO: 11, 12, 60, 61, 63, or 62 including the first three framework regions and the three heavy chain CDRs.

[0110] In some instances, the anti-CD19 antibody includes light chain complementarity determining regions 1, 2, and/or 3 (CDR-L1, CDR-L2, and/or CDR-L3), respectively, having the amino acid sequences of CDR 1, 2, and/or 3 sequences contained within the light chain variable (V_L) region amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16, 17, 71, 65, 64, 66, 70, 69, 67, 90, 91 or 187-205, such as set forth in SEQ ID NO: 13, 14, 15, 16, or 17, or in SEQ ID NO: 13, 14, 15, 16, 17, 71, 90, 91, 68, 65, 64, 66, 70, 69, or 67.

[0111] In some instances, the anti-CD19 antibody includes a CDR-L1, CDR-L2, and/or CDR-L3 in which:

[0112] In some instances, the CDR-L1 contains the amino acid sequence: $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ (SEQ ID NO: 110), wherein X_1 is T, W, S or R; X_2 is G or A; X_3 is I, T, D or S; X_4 is S, R, T or Q; X_5 is null or S; X_6 is null, D, N or G; X_7 is null, V or L; X_8 is X or null; X_9 is X or null; X_{10} is X; X_{11} is X; X_{12} is Y, F, D or W; X_{13} is V, A or L and X_{14} is S, N or A. For example, in some instances, the CDR-L1 contains the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ (SEQ ID NO: 226), wherein X_1 is T, Q, S, or R; X_2 is G, A or E; X_3 is I, T, A, D, or S; X_4 is S, R, T Q, G or I; X_5 is null, S, R or T; X_6 is G, D, N, or null; X_7 is null, V, L or I; X_8 is D, G, I, L, S, or null; X_9 is S, G, A, I, D, R, or null; X_{10} is H, Y, F, S, or N; X_{11} is R, N, D, H, Y or T; X_{12} is Y, F, D, W, H, T or S; X_{13} is V, A, or L; and X_{14} is S, N, or A. In some instances, the CDR-L1 contains the amino acid sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ (SEQ ID NO: 111), wherein X_1 is T, Q, S, or R; X_2 is G or A; X_3 is I, T, D, or S; X_4 is S, R, T, or Q; X_5 is null or S; X_6 is G, D, N, or null; X_7 is null, V, or L; X_8 is D, G, I, L, S, or null; X_9 is S, G, A, I, R, or null; X_{10} is H, Y, F, S, or N; X_{11} is R, N, D, H, or Y; X_{12} is Y, F, D, or W; X_{13} is V, A, or L; and X_{14} is S, N, or A.

[0113] In some instances, the CDR-L2 contains the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7$ (SEQ ID NO: 227), wherein X_1 is D,S or G; X_2 is F, V, N, K, or A; X_3 is S, T, D, or N; X_4 is K, V, N, Q, or R; X_5 is R, V, or L; X_6 is P, K, A, or E; and X_7 is S, P, A, or T. In some instances, the CDR-L2 contains the amino acid sequence of $X_1X_2X_3X_4X_5X_6X_7$ (SEQ ID NO: 112), wherein X_1 is D or S; X_2 is F, V, N, K, or A; X_3 is S, T, D, or N; X_4 is K, V, N, Q, or R; X_5 is R, V, or L; X_6 is P, K, A, or E; and X_7 is S, P, A, or T.

[0114] In some instances, the CDR-L3 contains the amino acid sequence of $X_1X_2X_3X_4X_5X6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 228), wherein X_1 is S, G, T, A, Q, C, or N; X_2 is S, Q, A, or T; X_3 is Y, S, W, R; X_4 is A, D, R, T, or Y; X_5 is A, S, P, G, N, or D; X_6 is I, S, G, T, A, L, H, R, or N; X_7 is S, P, L, Y, G; X_8 is P, T, S, Q, M, R, N or null; X_9 is S, L, N, A, M, R or null; X_{10} is L, D or null; X_{11} is Y, W, F, V, A, or L; and X_{12} is V, T, P or L. In some instances, the CDR-L3 contains the amino acid sequence of $X_1X_2X_3X_4X_5X6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 115), wherein X_1 is X; X_2 is S, Q, A, or T; X_3 is Y, S, W, R; X_4 is A, D, R, T, or Y; X_5 is X; X_6 is X; X_7 is S, P, L, Y, G; X_8 is X or null; X_9 is X or null; X_{10} is L or null; X_{11} is X; and X_{12} is V, T, or L. For example, in some instances, the antibody has a CDR-L3 comprising the amino acid sequence $X_1X_2X_3X_4X_5X6X_7X_8X_9X_{10}X_{11}X_{12}$ (SEQ ID NO: 114), wherein X_1 is S, G, T, A, Q, C or N; X_2 is S, Q, A, or T; X_3 is Y, S, W, R; X_4 is A, D, R, T, or Y; X_5 is A, S, P, G, N or D; X_6 is I, S, G, T, A, L, H, R, N; X_7 is S, P, L, Y, G; X_8 is P, T, S, Q, M, R, N or null; X_9 is S, L, N, A, M or null; X_{10} is L or null; X_{11} is Y, W, F, V, A or L; and X_{12} is V, T, or L

[0115] In some instances, in the CDR-L1, such as set forth in SEQ ID NO:110, 226 or 111, X_3 is I, T, or S; X_4 is S, T, or Q; X_8 is D, G, I, S, or null; X_9 is S, G, I, or null; X_{10} is H, Y, S, or N; X_{11} is R, N, D, or H; X_{12} is Y or D; and X_{13} is V or L; and/or in the CDR-L2, such as set forth in SEQ ID NO:227 or 112, X_1 is D; X_4 is K, V, N, Q, or R; X_6 is P, K, or A; and X_7 is S, A, or T ; and/or in the CDR-L3, such as set forth in SEQ ID NO:228, 114 or 115, X_1 is S, G, T, A, Q, C, or N; X_5 is A, S, P, G, N, or D; X_6 is I, S, G, T, A, L, H, R, or N; X_8 is P, T, S, Q, M, R, N or null; X_9 is S, L, N, A, M or null; and X_{11} is Y, W, F, V, A, or L. In some instances, in the CDR-L3, X_1 is S, G, Q, or N; X_2 is S, Q, or T; X_4 is A, D, T, or Y; X_5 is A, S, or G; and X_6 is I, S, N, R, A, H, or T.

[0116] In some instances, the antibody includes a sequence of amino acids that contains a CDR-L1 set forth in SEQ ID NO:83, a CDR-L2 set forth in SEQ ID NO:84 and/or a CDR-L3 set forth in SEQ ID NO:85.

[0117] In some instances, the antibody, e.g., the antibody fragment contains a CDR-L1 that contains the amino acid sequence set forth in SEQ ID NO: 21, 25, 28, or 31. In some instances, the antibody or fragment contains a CDR-L1 that contains the amino acid sequence set forth in SEQ ID NO: 80, 77, 74, 73, 75, 79, 78, 76, 21, 25, 28, 31 or 146 to 152, such as contains the amino acid sequence set forth in SEQ ID NO: 80, 77, 74, 73, 75, 79, 78, 76, 21, 25, 28, or 31. In some instances, the antibody or fragment contains a CDR-L1 that contains the amino acid sequence set forth in SEQ ID NO: 80, 77, 74, 73, 78, 21, or 28.

[0118] In some instances, the antibody or fragment contains a CDR-L2 that contains the amino acid sequence set forth in SEQ ID NO: 22, 26, 29, or 32. In some instances, the antibody or fragment contains a CDR-L2 that contains the amino acid sequence SEQ ID NO: 100, 97, 94, 93, 95, 99, 98, 96, 22, 26, 29, 32 or 153 to 157, such as contains the amino acid sequence set forth in SEQ ID NO: 100, 97, 94, 93, 95, 99, 98, 96, 22, 26, 29, or 32. In some instances, the antibody or fragment contains a CDR-L2 that contains the amino acid sequence set forth in SEQ ID NO: 100, 97, 94, 93, 98, 22, or 29.

[0119] In some instances, the antibody or fragment contains a CDR-L3 that includes the sequence set forth in SEQ ID NO: 23, 24, 27, 30, or 33. In some instances, the antibody or fragment contains a CDR-L3 that includes the sequence set forth in SEQ ID NO: 109, 106, 103, 101, 104, 108, 107, 105, 102, 23, 24, 27, 30, 33, 158 or 159, such as contains the amino acid sequence set forth in SEQ ID NO: 109, 106, 103, 101, 104, 108, 107, 105, 102, 23, 24, 27, 30, or 33. In some instances, the antibody or fragment contains a CDR-L3 that includes the sequence set forth in SEQ ID NO: 109, 106, 103, 101, 107, 24 or 30.

[0120] In some instances, the CDR-L1, CDR-L2, and CDR-L3 contain the sequences of SEQ ID NOs: 21, 22, and 23, respectively; the CDR-L1, CDR-L2, and CDR-L3 include the sequences of SEQ ID NOs: 21, 22, and 24, respectively; the CDR-L1, CDR-L2, and CDR-L3 include the sequences of SEQ ID NOs: 25, 26, and 27, respectively; the CDR-L1, CDR-L2, and CDR-L3 contain the sequences of SEQ ID NOs: 28, 29, and 30, respectively; or the CDR-L1, CDR-L2, and CDR-L3 contain the sequences of SEQ ID NOs: 31, 32, and 33, respectively.

[0121] In some instances, the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22, and 23, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22, and 24, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 25, 26, and 27, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 28, 29, and 30, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 31, 32, and 33, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 80, 100, and 109, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs:77, 97, and 106, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 74, 94, and 103, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 73, 93, and 101, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs:75, 95, and 104, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 79, 99, and 108, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 78, 98, and 107, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 76, 96, and 105, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 73, 93, and 102, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 77, 97, and 106, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 163, 164, and 165, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 80, 100, and 109, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 146, 97, and 106, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 28, 153 and 158, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 74, 94, and 103, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 147, 154 and 121, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 148, 94 and 103, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 75, 95 and 104, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 149, 155 and 119, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 150, 22, and 120, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 21, 22 and 159, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 151, 26 and 118, respectively; the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 28, 156 and 116, respectively; or the CDR-L1, CDR-L2, and CDR-L3 comprise the sequences of SEQ ID NOs: 152, 157 and 117, respectively.

[0122] Also provided are antibodies having sequences at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such sequences.

[0123] In some instances, the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 81, and 20, respectively; the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 19, and 20, respectively; the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 82, and 20, respectively; or the CDR-H1, CDR-H2, and CDR-H3 comprise the sequences of SEQ ID NOs: 18, 72, and 20, respectively.

[0124] Also provided are antibodies having sequences at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such sequences.

[0125] In some instances, the VH region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 11, 12, 60, 61, 6362, 167 or 185, such as SEQ ID NO: 11, 12, 60, 61, 63, or 62; and/or the VL region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 13, 14, 15, 16, 17, 71, 90, 91, 68, 65, 64, 66, 70, 69 67 or 187 to 205, such as SEQ ID NO: 13, 14, 15, 16, 17, 71, 90, 91, 68, 65, 64, 66, 70, 69, or 67. In some instances, the VH region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 11, 60, 63, or 62; and/or the VL region of the antibody or fragment comprises the amino acid sequence of SEQ ID NO: 14, 16, 71, 90, 65, 64, or 69.

[0126] Also provided are antibodies having sequences at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such sequences.

[0127] In some instances, the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 17, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 15, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 13, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 14, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 16, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 71, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 62 and 68, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 65, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 60 and 64, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 61 and 66, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 70, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 62 and 69, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 67, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 12 and 91, respectively; or the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 90, respectively. In some instances, the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 14, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 16, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 71, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 11 and 65, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 60 and 64, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 62 and 69, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 63 and 90, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 167 and 207, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 168 or 63 and 208, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 169 or 11 and 209, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 170 or 61 and 210, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 171 or 61 and 211, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 172 and 212, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 173 or 11 and 213, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 174 or 11 and 214, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 175 or 11 and 215, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 176 or 61 and 216, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 177 or 61 and 217, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 178 or 61 and 218, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 179 or 61 and 219, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 180 or 12 and 220, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 181 or 12 and 221, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 182 or 11 and 222, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 183 or 60 and 223, respectively; the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 184 or 11 and 224, respectively; or the VH and VL regions of the antibody or fragment comprise the amino acid sequences of SEQ ID NOs: 185 and 225, respectively..

[0128] Also provided are antibodies having sequences at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such sequences.

[0129] In some instances, the antibody or fragment contains a V_H region including the amino acid sequence of SEQ ID NO: 11 or 12 or residues 1-119 of such a sequence or a sequence having at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence.

[0130] In some instances, the antibodies include or further include a V_L region including the amino acid sequence of SEQ ID NO: 13, 14, 15, 16, 17, or a sequence having at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence.

[0131] In some instances, the antibody is a single-chain antibody fragment, such as an scFv or diabody. In some instances, the single-chain antibody includes one or more linkers joining two antibody domains or regions, such as a variable heavy chain (V_H) region and a variable light chain (V_L). The linker typically is a peptide linker, e.g., a flexible and/or soluble peptide linker. Among the linkers are those rich in glycine and serine and/or in some cases threonine. In some instances, the linkers further include charged residues such as lysine and/or glutamate, which can improve solubility. In some instances, the linkers further include one or more proline.

[0132] Accordingly, also provided are single-chain antibody fragments, such as scFvs and diabodies, particularly human single-chain fragments, typically comprising linker(s) joining two antibody domains or regions, such V_H and V_L domains. The linker typically is a peptide linker, e.g., a flexible and/or soluble peptide linker, such as one rich in glycine and serine.

[0133] In some aspects, the linkers rich in glycine and serine (and/or threonine) include at least 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% such amino acid(s). In some instances, they include at least at or about 50%, 55%, 60%, 70%, or 75%, glycine, serine, and/or threonine. In some instances, the linker is comprised substantially entirely of glycine, serine, and/or threonine. The linkers generally are between about 5 and about 50 amino acids in length, typically between at or about 10 and at or about 30, e.g., 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30, and in some examples between 10 and 25 amino acids in length. Exemplary linkers include linkers having various numbers of repeats of the sequence GGGGS (4GS; SEQ ID NO:123) or GGGS (3GS; SEQ ID NO:122), such as between 2, 3, 4, and 5 repeats of such a sequence. Exemplary linkers include those having or consisting of a sequence set forth in SEQ ID NO: 34 (GGGGSGGGGSGGGGS). Exemplary linkers further include those having or consisting of the sequence set forth in SEQ ID NO: 43 (GSTSGSGKPGSGEGSTKG).

[0134] Accordingly, in some instances, also provided are single-chain fragments, e.g., scFvs, comprising one or more of the aforementioned linkers, such as glycine/serine rich linkers, including linkers having repeats of GGGS (SEQ ID NO:122) or GGGGS (SEQ ID NO: 123), such as the linker set forth as SEQ ID NO: 34.In some instances, the linker has an amino acid sequence containing the sequence set forth SEQ ID NO: 34.

[0135] The fragment, e.g., scFv, may include a V_H region or portion thereof, followed by the linker, followed by a V_L or portions thereof. The fragment, e.g., the scFv, may include the V_L, followed by the linker, followed by the V_H.

[0136] In some aspects, the scFv has the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, or 10, or has a sequence at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence.

[0137] In some aspects, the scFv has the amino acid sequence set forth set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 47, 49, 51, 53, 55, 57, 59, 87, or 89, or has a sequence at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence.

[0138] In some aspects, the scFv has the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 47, 49, 51, 53, 55, 57, 59, 87, 89, or 207 to 225 or has a sequence at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence.

[0139] In some aspects, the scFv contains the VH, linker and VL as set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 47, 49, 51, 53, 55, 57, 59, 87 89 or 207 to 225, or a sequence at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identical to such a sequence, but in which the VH and VL are configured in the opposite orientation, i.e. VL-VH, as compared to such sequence.

[0140] The antibody, e.g., antibody fragment, may contain at least a portion of an immunoglobulin constant region, such as one or more constant region domain. In some instances, the constant regions include a light chain constant region and/or a heavy chain constant region 1 (CH1). In some instances, the antibody includes a CH2 and/or CH3 domain, such as an Fc region. In some instances, the Fc region is an Fc region of a human IgG, such as an IgG1 or IgG4.

[0141] In some instances, any of the above antibodies, e.g., antibody fragments is human. For example, provided herein are human anti-CD 19 antibodies that specifically bind CD19, such as specifically bind human CD19.

[0142] In some instances of a provided human anti-CD 19 antibody, the human antibody contains a V_H region that contains a portion having at least 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence encoded by a germline nucleotide human heavy chain V segment, a portion with at least 95%, 96%, 97%, 98%, 99%, or 100 % identity to an amino acid sequence encoded by a germline nucleotide human heavy chain D segment, and/or a portion having at least 95%, 96%, 97%, 98%, 99%, or 100 % identity to an amino acid sequence encoded by a germline nucleotide human heavy chain J segment; and/or contains a V_L region that contains a portion with at least 95%, 96%, 97%, 98%, 99%, or 100 % identity to an amino acid sequence encoded by a germline nucleotide human kappa or lambda chain V segment, and/or a portion with at least 95%, 96%, 97%, 98%, 99%, or 100 % identity to an amino acid sequence encoded by a germline nucleotide human kappa or lambda chain J segment. In some instances, the portion of the V_H region corresponds to the CDR-H1, CDR-H2 and/or CDR-H3. In some instances, the portion of the V_H region corresponds to the framework region 1 (FR1), FR2, FR2 and/or FR4. In some instances, the portion of the V_L region corresponds to the CDR-L1, CDR-L2 and/or CDR-L3. In some instances, the portion of the V_L region corresponds to the FR1, FR2, FR2 and/or FR4.

[0143] In some instances, the human antibody contains a CDR-H1 having at least 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence of the corresponding CDR-H1 region within a sequence encoded by a germline nucleotide human heavy chain V segment. For example, the human antibody in some instances contains a CDR-H1 having a sequence that is 100% identical or with no more than one, two or three amino acid differences as compared to the corresponding CDR-H1 region within a sequence encoded by a germline nucleotide human heavy chain V segment.

[0144] In some instances, the human antibody contains a CDR-H2 having at least 95%, 96%, 97%, 98%, 99%, or

100% sequence identity to an amino acid sequence of the corresponding CDR-H2 region within a sequence encoded by a germline nucleotide human heavy chain V segment. For example, the human antibody in some instances contains a CDR-H2 having a sequence that is 100% identical or with no more than one, two or three amino acid difference as compared to the corresponding CDR-H2 region within a sequence encoded by a germline nucleotide human heavy chain V segment.

[0145] In some instances, the human antibody contains a CDR-H3 having at least 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence of the corresponding CDR-H3 region within a sequence encoded by a germline nucleotide human heavy chain V segment, D segment and J segment. For example, the human antibody in some instances contains a CDR-H3 having a sequence that is 100% identical or with no more than one, two or three amino acid differences as compared to the corresponding CDR-H3 region within a sequence encoded by a germline nucleotide human heavy chain V segment, D segment and J segment.

[0146] In some instances, the human antibody contains a CDR-L1 having at least 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence of the corresponding CDR-L1 region within a sequence encoded by a germline nucleotide human light chain V segment. For example, the human antibody in some instances contains a CDR-L1 having a sequence that is 100% identical or with no more than one, two or three amino acid differences as compared to the corresponding CDR-L1 region within a sequence encoded by a germline nucleotide human light chain V segment.

[0147] In some instances, the human antibody contains a CDR-L2 having at least 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence of the corresponding CDR-L2 region within a sequence encoded by a germline nucleotide human light chain V segment. For example, the human antibody in some instances contains a CDR-L2 having a sequence that is 100% identical or with no more than one, two or three amino acid difference as compared to the corresponding CDR-L2 region within a sequence encoded by a germline nucleotide human light chain V segment.

[0148] In some instances, the human antibody contains a CDR-L3 having at least 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to an amino acid sequence of the corresponding CDR-L3 region within a sequence encoded by a germline nucleotide human light chain V segment and J segment. For example, the human antibody in some instances contains a CDR-L3 having a sequence that is 100% identical or with no more than one, two or three amino acid differences as compared to the corresponding CDR-L3 region within a sequence encoded by a germline nucleotide human light chain V segment and J segment.

[0149] In some instances, the human antibody contains a framework region that contains human germline gene segment sequences. For example, in some instances, the human antibody contains a V_H region in which the framework region, e.g. FR1, FR2, FR3 and FR4, has at least 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a framework region encoded by a human germline antibody segment, such as a V and/or J segment. In some instances, the human antibody contains a V_L region in which the framework region e.g. FR1, FR2, FR3 and FR4, has at least 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to a framework region encoded by a human germline antibody segment, such as a V and/or segment. For example, in some such instances, the framework sequence of the V_H and/or V_L sequence differs by no more than 10 amino acids, such as no more than 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid, compared to the framework region encoded by a human germline antibody segment.

[0150] The antibody, e.g., antibody fragment, may contain at least a portion of an immunoglobulin constant region, such as one or more constant region domain. In some instances, the constant regions include a light chain constant region and/or a heavy chain constant region 1 (CH1). In some instances, the antibody includes a CH2 and/or CH3 domain, such as an Fc region. In some instances, the Fc region is an Fc region of a human IgG, such as an IgG1 or IgG4.

[0151] Also provided are nucleic acids encoding the antibodies and/or portions, e.g., chains, thereof. Among the provided nucleic acids are those encoding the anti-CD19 antibodies described herein. The nucleic acids may include those encompassing natural and/or non-naturally occurring nucleotides and bases, e.g., including those with backbone modifications. The terms "nucleic acid molecule", "nucleic acid" and "polynucleotide" may be used interchangeably, and refer to a polymer of nucleotides. Such polymers of nucleotides may contain natural and/or non-natural nucleotides, and include, but are not limited to, DNA, RNA, and PNA. "Nucleic acid sequence" refers to the linear sequence of nucleotides that comprise the nucleic acid molecule or polynucleotide. Exemplary nucleic acids and vectors are those having the sequences set forth as SEQ ID NOs: 1, 3, 5, 7, 9, 44, 46, 48, 50, 52, 54, 56, 58, 86, and 88, and CDR-encoding portions thereof, as well as sequences containing at least at or about 90, 91, 92, 93, 94, 95, 96, 97, 98, or 99% identity thereto. The nucleic acid may encode an amino acid sequence comprising the V_L and/or an amino acid sequence comprising the V_H of the antibody (e.g., the light and/or heavy chains of the antibody).

[0152] Also provided are vectors containing the nucleic acids, host cells containing the vectors, e.g., for producing the antibodies. Also provided are methods for producing the antibodies. In a further instance, one or more vectors (e.g., expression vectors) comprising such nucleic acid are provided. In a further instance, a host cell comprising such nucleic acid is provided. In one such instance, a host cell comprises (e.g., has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the V_L of the antibody and an amino acid sequence comprising the V_H of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the V_L of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the V_H of the antibody. In some instances, a method of making the anti-CD19 antibody is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

[0153] Also provided are methods of making the anti-CD 19 antibodies (including antigen-binding fragments). For recombinant production of the anti-CD 19 antibody, nucleic acid encoding an antibody, e.g., as described above, may be isolated and inserted into one or more vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[0154] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been modified to mimic or approximate those in human cells, resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, Nat. Biotech. 22:1409-1414 (2004), and Li et al., Nat. Biotech. 24:210-215 (2006).

[0155] Exemplary eukaryotic cells that may be used to express polypeptides include, but are not limited to, COS cells, including COS 7 cells; 293 cells, including 293-6E cells; CHO cells, including CHO-S, DG44. Lec13 CHO cells, and FUT8 CHO cells; PER.C6® cells; and NSO cells. In some instances, the antibody heavy chains and/or light chains may be expressed in yeast. See, *e.g.*, U.S. Publication No. US 2006/0270045 A1. In some instances, a particular eukaryotic host cell is selected based on its ability to make desired post-translational modifications to the heavy chains and/or light chains. For example, in some instances, CHO cells produce polypeptides that have a higher level of sialylation than the same polypeptide produced in 293 cells.

[0156] In some instances, the antibody is produced in a cell-free system. Exemplary cell-free systems are described, *e.g.*, in Sitaraman et al., Methods Mol. Biol. 498: 229-44 (2009); Spirin, Trends Biotechnol. 22: 538-45 (2004); Endo et al., Biotechnol. Adv. 21: 695-713 (2003).

[0157] The provided instances further include vectors and host cells and other expression systems for expressing and producing the antibodies and other binding proteins, including eukaryotic and prokaryotic host cells, including bacteria, filamentous fungi, and yeast, as well as mammalian cells such as human cells, as well as cell-free expression systems.

Exemplary Features

[0158] In some aspects, the provided antibodies, including antigen-binding fragments, have one or more specified functional features, such as binding properties, including binding to particular epitopes, such as epitopes that are similar to or overlap with those of other antibodies, the ability to compete for binding with other antibodies, and/or particular binding affinities.

[0159] In some instances, the antibodies specifically bind to CD19 protein. In some aspects of any of the instances herein, CD19 refers to human CD19. Generally, the observation that an antibody or other binding molecule binds to CD19 or specifically binds to CD19 does not necessarily mean that it binds to CD19 of every species. For example, in some instances, features of binding to CD19, such as the ability to specifically bind thereto and/or to compete for binding thereto with a reference antibody, and/or to bind with a particular affinity or compete to a particular degree, in some instances, refers to the ability with respect to human CD19 protein and the antibody many not have this feature with respect to a CD19 of another species, such as monkey or mouse.

[0160] In some instances, the provided antibodies, including antigen-binding fragments, bind to human CD19, such as to an epitope or region of human CD19, such as to human CD19 set forth in 92 (Accession No. P15391), or an allelic variant or splice variant thereof. In certain instances, the anti-CD 19 antibody binds to an epitope of CD19 that is conserved among CD19 from different species. In some instances, the anti-CD19 antibody binds to an epitope of CD19 that is not conserved or not entirely conserved among CD19 from different species, such as among human and *Macaca mulatta* (rhesus macaque (rhesus)) CD19.

[0161] In some instances, the antibody binds to an epitope containing one or more amino acids within (or is entirely within) an extracellular domain of a CD19 and/or within (or is entirely within) a membrane-proximal region of the extracellular portion of CD19. In some instances, the antibody binds to an epitope containing one or more amino acids within, or is entirely within, the Ig-like domain 2 of CD19, a portion encoded by the fourth exon of the CD19, a portion corresponding to positions 176-277 of the human CD19 sequence set forth in SEQ ID NO: 92, and/or the membrane-proximal-most 100, 90, 80, 75, 70, 65, 60, 55, 50, 45, 44, 43, 43, 41, or 40 amino acid portion of the extracellular portion of the CD19. In some instances, such a portion or domain is required for binding of the antibody to CD19. In some instances, the epitope contains (or further contains) one or more amino acids that is within, or is entirely within, the Ig-like domain 1 of CD19, a portion encoded by the second exon of the CD19 and/or a portion corresponding to positions 20-117 of the human CD19 sequence set forth in SEQ ID NO: 92. In some instances, such a portion or domain is required for binding of the antibody to CD19. In some instances, the antibody specifically binds to a peptide comprising or consisting of or consisting essentially of the sequence of such a portion, and not containing the entire sequence of full-length CD19.

[0162] In some instances, the epitope contains one or more amino acids within, is within, or includes a portion of CD19 corresponding to residues 218-249 of the human CD19 sequence set forth in SEQ ID NO: 92, such as a portion having the sequence set forth in SEQ ID NO: 143.

[0163] In some instances, the epitope includes an amino acid at a position corresponding to one or more of the positions of CD19 corresponding to the following amino acids at the following positions of the human CD19 sequence set forth in SEQ ID NO: 92: the histidine (H) at position 218, the alanine (A) at position 236, the methionine (M) at position 242, the glutamate (E) at position 243, the proline (P) at position 249, and/or the lysine (K) and/or serine (S) at positions 223 and 224. In some instances, an amino acid at one or more such a position is important or necessary for binding of the antibody to CD19. In some instances, the amino acid in the epitope at such one or more position corresponds to the amino acid at the respective position in the human CD19 sequence set forth in SEQ ID NO: 92.

[0164] In some instances, the epitope includes an amino acid (such as a histidine) at a position of CD19 corresponding to the histidine at position 218 of the human CD19 sequence set forth in SEQ ID NO: 92; in some instances, such amino acid is important for binding of the antibody to CD19.

[0165] In some instances, the epitope includes an amino acid (such as an alanine) at a position of CD19 corresponding to the alanine at position 236 of the human CD19 sequence set forth in SEQ ID NO: 92; in some instances, such amino acid is important for binding of the antibody to CD19.

[0166] In some instances, the epitope includes an amino acid (such as a methionine) at a position of CD19 corresponding to the methionine at position 242 of the human CD19 sequence set forth in SEQ ID NO: 92; in some instances, such amino acid is important for binding of the antibody to CD19.

[0167] In some instances, the epitope includes an amino acid (such as a glutamate) at a position of CD19 corresponding to the glutamate at position 243 of the human CD19 sequence set forth in SEQ ID NO: 92; in some instances, such amino acid is important for binding of the antibody to CD19.

[0168] In some instances, the epitope includes an amino acid (such as a proline) at a position of CD19 corresponding to the proline at position 249 of the human CD19 sequence set forth in SEQ ID NO: 92; in some instances, such amino acid is important for binding of the antibody to CD19.

[0169] In some instances, the epitope contains amino acid(s) (such as lysine and/or serine) at one or two positions corresponding to the lysine and/or serine at positions 223 and 224 of the human CD19 sequence set forth in SEQ ID NO: 92; in some instances, such amino acid(s) are important for binding of the antibody to CD19.

[0170] In some instances, the epitope is the same as, similar to, overlapping with, or contains one or more of the same amino acids as an epitope that is specifically bound to by a reference antibody, such as FMC63 or SJ25C1. In some instances, the same one or more amino acids is important for the binding of the provided antibody and the reference antibody.

[0171] In some instances, the extent of binding of an anti-CD 19 antibody to an unrelated, non-CD19 protein, such as non-human CD19 or other non-CD19 protein, is less than about 40% of the binding of the antibody to human CD19 as measured, for example, by a radioimmunoassay (RIA). In some instances, among provided antibodies are antibodies in which binding to a non-human CD19 or other non-CD19 protein is less than or about 30%, less than or about 20% or less than or about 10% of the binding of the antibody to human CD19.

[0172] In some instances, such properties of provided antibodies, including antigen-binding fragments, are described in relation to properties observed for another antibody, e.g., a reference antibody. In some instances, the reference antibody is a non-human anti-CD 19 antibody, such as a murine or chimeric or humanized anti-CD 19 antibody. In some aspects, the reference antibody is the antibody designated FMC63 or the antibody designated SJ25C1 (see, e.g., Zola H et al., Immunol Cell Biol. 1991 Dec; 69 (Pt 6):411-22; U.S. Patent 7,446,190), and/or a fragment derived therefrom such as an scFv fragment thereof, and/or an antibody containing the V_H and V_L sequences of such an antibody and/or the heavy and light chain CDRs of such an antibody.

[0173] For example, in some instances, the reference antibody has a V_H region containing the sequence set forth in SEQ ID NO: 39 or 41, or comprises CDR1, CDR2, and/or CDR3 within such a sequence, and/or has a V_L containing the sequence set forth in SEQ ID NO: 40 or 42, or comprises CDR1, CDR2, and/or CDR3 within such a sequence. Thus, in some instances, the antibody competes for binding with, and/or binds to the same or an overlapping epitope of CD19 as, FMC63 or SJ25C1 or an antigen-binding fragment thereof.

[0174] In some instances, the reference antibody has a sequence present in an antibody or portion thereof as described herein. For example, in some instances, the reference antibody has a light chain variable (V_L) region amino acid sequence set forth in SEQ ID NO: 13, 14, 15, 16, or 17 and/or set forth in SEQ ID NO: 13, 14, 15, 16, 17, 71, 90, 91, 68, 65, 64, 66, 70, 69, or 67, and/or has a heavy chain variable (VH) region set forth in SEQ ID NO: 11, 12, 60, 61, 63, or 62. In some instances, the antibody has heavy and/or light chain CDRs 1, 2, and/or 3 as present in such an antibody. In some instances, the reference antibody can be an scFv that contains the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10, 45, 47, 49, 51, 53,55, 57, 59, 87 or 89.

[0175] In some instances, the antibody nonetheless contains heavy and light chain CDRs that are distinct from the CDRs present in the reference antibody or antibodies, such as FMC63 and SJ25C1. For example, among the provided antibodies are those that compete for binding with and/or bind to the same or overlapping epitopes of CD19 as those bound by a reference antibody or antibody, but nonetheless contain distinct CDRs, e.g., distinct heavy and/or light chain CDR1, CDR2, and CDR3. In some instances, the provided antibody contains heavy and light chain CDRs that are distinct from the CDRs present in the antibody designated FMC63, such as present in the VH region set forth in SEQ ID NO:39 and/or the VL region set forth in SEQ ID NO:40. In some instances, the provided antibody contains heavy and light chain CDRs that are distinct from the CDRs present in the antibody designated SJ25C1, such as present in the VH region set forth in SEQ ID NO:41 and/or the VL region set forth in SEQ ID NO:42.

[0176] For example, in some instances, the antibody specifically binds to an epitope that overlaps with the epitope of CD19 bound by a reference antibody, such as antibodies that bind to the same or a similar epitope as the reference antibody. In some instances, the antibody competes for binding to CD19 with the reference antibody.

[0177] In some instances, the antibodies display a binding preference for CD19-expressing cells as compared to CD19-negative cells, such as particular cells known in the art and/or described herein. In some instances, the binding preference is observed where a significantly greater degree of binding is measured to the CD19-expressing, as compared to the non-expressing, cells. In some instances, the fold change in degree of binding detected, for example, as measured by mean fluorescence intensity in a flow cytometry-based assay and/or dissociation constant or EC50, to the CD19-expressing cells as compared to the non-CD 19-expressing cells, is at least at or about 1.5, 2, 3, 4, 5, 6, or more, and/or is about as great, about the same, at least as great or at least about as great, or greater, than the fold change observed for the reference antibody, such as the corresponding form of the reference antibody. In some cases, the total degree of observed binding to CD19 or to the CD19-expressing cells is approximately the same, at least as great, or greater than that observed for the reference antibody. In any of the provided instances, comparison of binding properties, such as affinities or competition, may be via measurement by the same or similar assay.

[0178] An antibody "competes for binding" to CD19 with a reference antibody if it competitively inhibits binding of the reference antibody to CD19, and/or if the reference antibody competitively inhibits binding of the antibody to CD19. An antibody competitively inhibits binding of a reference antibody to an antigen if the presence of the antibody in excess detectably inhibits (blocks) binding of the other antibody to its antigen. A particular degree of inhibition may be specified.

[0179] In some instances, addition of the provided antibody in excess, e.g., 1-, 2-, 5-, 10-, 50- or 100-fold excess, as compared to the amount or concentration of the reference antibody, inhibits binding to the antigen by the reference antibody (or vice versa). In some instances, the inhibition of binding is by at least 50%, and in some instances by at least 75%, 90% or 99%. In some aspects, the competitive inhibition is as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 1990:50:1495-1502).

[0180] In some instances, where the reference antibody is present at a concentration of 10 nM, the provided antibody inhibits binding of the reference antibody with an IC50 of less than at or about 100, 50, 40, 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, or 10 nM, or less than at or about 9, 8, 7, 6, or 5 nM. In some instances, where the provided antibody is present at a concentration of 10 nM, the reference antibody inhibits binding of the provided antibody with an IC50 of less than at or about 100, 50, 40, 30, 25, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, or 10 nM, or less than at or about 9, 8, 7, 6, or 5 nM.

[0181] In some instances, competitive inhibition of the reference antibody's binding by the provided antibody (or vice versa) is at or about or least at or about the same degree as the degree of competitive inhibition of the reference antibody's binding by the reference antibody itself, e.g., unlabeled reference antibody. In some instances, the provided antibody inhibits binding of the reference antibody, such as binding of FMC63 or SJ25C1, to human CD19 by at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%. Competitive inhibition assays are known and include ELISA-based, flow cytometry-based assays, and RIA-based assays. In some aspects, competitive inhibition assays are carried out by incorporating an excess of an unlabeled form of one of the antibodies and assessing its ability to block binding of the other antibody, which is labeled with a detectable marker, such that degree of binding and reduction thereof can be assessed by detection of the label or marker.

[0182] In some instances, two antibodies specifically bind to the same epitope if all or essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other antibody. In some instances, two antibodies specifically bind to an overlapping epitope if at least some of the amino acid mutations in the antigen that reduce binding or eliminate binding to the antigen by one antibody also reduce or eliminate binding to the antigen by the other antibody.

[0183] In some instances, the provided antibodies are capable of binding CD19, such as human CD19, with at least a certain affinity, as measured by any of a number of known methods. In some instances, the affinity is represented by a dissociation constant (Kd); in some instances, the affinity is represented by EC50. In certain instances, the binding affinity (EC50) and/or the dissociation constant of the antibody to CD19 is at or about or less than at or about 100 nM, 50 nM, 40 nM, 30 nM, 25 nM, 20 nM, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 nM, such as between at or about 1 nM and at or about 15 nM, e.g., between at or about 5 and at or about 10 nM. In one instance, the extent of binding of an anti-CD 19 antibody to an unrelated, non-CD19 protein is less than at or about 10% of the binding of the antibody to CD19 as measured, e.g., by a radioimmunoassay (RIA).

[0184] In some aspects, the affinity is at or about the same degree or substantially the same degree of affinity compared to the reference antibody, such as murine CD19 antibody, for example FMC63 or SJ25C1. In some aspects, the affinity is at least 80, 85, 90, 95, or 99% the same as that of the reference antibody. In some instances, binding affinity is compared with respect to the corresponding form of the reference antibody.

[0185] In some instances, the antibody has an affinity, e.g., EC50 or Kd, about the same as or lower than that of the reference antibody, such as of the corresponding form of the reference antibody, e.g., no more than about 1.5-fold or no more than about 2-fold greater, no more than 3-fold greater, and/or no more than 10-fold greater, than the EC50 of the reference antibody, e.g., as measured in the same or similar assay.

[0186] Anti-CD19 antibodies provided herein may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various known assays. In one aspect, the antibody is tested for its antigen binding activity, e.g., by known methods such as ELISA, Western blotting, and/or flow cytometric assays, including cell-based binding assays, for example, assessing binding of the antibody (e.g., conjugated to a fluorescent marker or tagged) to a cell expressing the target antigen, e.g., CD19, in some cases compared to results using cells that do not express the target antigen, e.g., CD19. Binding affinity may be measured as Kd or EC50.

[0187] Competition assays may be used to identify an antibody that competes with any of the antibodies described herein. Assays for mapping epitopes bound by the antibodies and reference antibodies also may be used and are known.

Immunoconjugates

[0188] In some instances, the antibody is or is part of an immunoconjugate, in which the antibody is conjugated to one or more heterologous molecule(s), such as, but not limited to, a cytotoxic agent, an imaging agent, a detectable moiety a multimerization domain or other heterologous molecule. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At211, I131, I125, Y90, Re186, Re188, Sm153, Bi212, P32, Pb212 and radioactive isotopes of Lu); chemotherapeutic agents (e.g., methotrexate, adriamicin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents); growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; antibiotics; toxins such as small molecule toxins or enzymatically active toxins. In some instances, the antibody is conjugated to one or more cytotoxic agents, such as chemotherapeutic agents or drugs, growth inhibitory agents, toxins (*e.g.*, protein toxins, enzymatically active toxins of bacterial, fungal, plant, or animal origin, or fragments thereof), or radioactive isotopes.

[0189] Among the immunoconjugates are antibody-drug conjugates (ADCs), in which an antibody is conjugated to one or more drugs, including but not limited to a maytansinoid (see U.S. Patent Nos. 5,208,020, 5,416,064 and European Patent EP 0 425 235 B1); an auristatin such as monomethylauristatin drug moieties DE and DF (MMAE and MMAF) (see U.S. Patent Nos. 5,635,483 and 5,780,588, and 7,498,298); a dolastatin; a calicheamicin or derivative thereof (see U.S. Patent Nos. 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, and 5,877,296; Hinman et al., Cancer Res. 53:3336-3342 (1993); and Lode et al., Cancer Res. 58:2925-2928 (1998)); an anthracycline such as daunomycin or doxorubicin (see Kratz et al., Current Med. Chem. 13:477-523 (2006); Jeffrey et al., Bioorganic & Med. Chem. Letters 16:358-362 (2006); Torgov et al., Bioconj. Chem. 16:717-721 (2005); Nagy et al., Proc. Natl. Acad. Sci. USA 97:829-834 (2000); Dubowchik et al., Bioorg. & Med. Chem. Letters 12:1529-1532 (2002); King et al., J. Med. Chem. 45:4336-4343 (2002); and U.S. Patent No. 6,630,579); methotrexate; vindesine; a taxane such as docetaxel, paclitaxel, larotaxel, tesetaxel, and ortataxel; a trichothecene; and CC1065.

[0190] Also among the immunoconjugates are those in which the antibody is conjugated to an enzymatically active toxin or fragment thereof, including but not limited to diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes.

[0191] Also among the immunoconjugates are those in which the antibody is conjugated to a radioactive atom to form a radioconjugate. Exemplary radioactive isotopes include At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu.

[0192] Conjugates of an antibody and cytotoxic agent may be made using any of a number of known protein coupling agents, e.g., linkers, (see Vitetta et al., Science 238:1098 (1987)), WO94/11026. The linker may be a "cleavable linker" facilitating release of a cytotoxic drug in the cell, such as acid-labile linkers, peptidase-sensitive linkers, photolabile linkers, dimethyl linkers, and disulfide-containing linkers (Chari et al., Cancer Res. 52:127-131 (1992); U.S. Patent No. 5,208,020).

[0193] Conjugates may also include fusion proteins such as Fc-fusions and chimeric molecules.

Multispecific Antibodies

[0194] In certain instances, the CD19-binding molecules, e.g., antibodies are multispecific. Among the multispecific binding molecules are multispecific antibodies, including, e.g. bispecific. Multispecific binding partners, e.g., antibodies, have binding specificities for at least two different sites, which may be in the same or different antigens. In certain instances, one of the binding specificities is for CD19 and the other is for another antigen. In certain instances, bispecific antibodies may bind to two different epitopes of CD19. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express CD19. Bispecific antibodies can be prepared as full length antibodies or antibody fragments. Among the bispecific antibodies are multispecific single-chain antibodies, e.g., diabodies, triabodies, and tetrabodies, tandem di-scFvs, and tandem tri-scFvs. Also provided are multispecific chimeric receptors, such as multispecific CARs, containing the antibodies.

[0195] Exemplary additional antigens include other B cell specific antigens and antigens expressed on T cells. Exemplary antigens include CD4, CD5, CD8, CD14, CD15, CD20, CD21, CD22, CD23, CD25, CD33, CD37, CD38, CD40, CD40L, CD46, CD52, CD54, CD74, CD80, CD126, CD138, B7, MUC-1, Ia, HM1.24, HLA-DR, tenascin, an angiogenesis factor, VEGF, PIGF, ED-B fibronectin, an oncogene, an oncogene product, CD66a-d, necrosis antigens, Ii, IL-2, T101, TAC, IL-6, TRAIL-R1 (DR4) and TRAIL-R2 (DR5).

Variants

[0196] In certain instances, the antibodies include one or more amino acid variations, e.g., substitutions, deletions, insertions, and/or mutations, compared to the sequence of an antibody described herein. Exemplary variants include those designed to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, e.g., antigen-binding.

[0197] In certain instances, the antibodies include one or more amino acid substitutions, e.g., as compared to an antibody sequence described herein and/or compared to a sequence of a natural repertoire, e.g., human repertoire. Sites of interest for substitutional mutagenesis include the CDRs and FRs. Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, e.g., retained/improved antigen binding, decreased immunogenicity, improved half-life, and/or improved effector function, such as the ability to promote antibody-dependent cellular cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC). In some instances, the variant antibody exhibits retained or improved binding to CD19.

[0198] In some instances, one or more residues within a CDR of a parent antibody (e.g. a humanized or human antibody) is/are substituted. In some instances, the substitution is made to revert a sequence or position in the sequence to a germline sequence, such as an antibody sequence found in the germline (e.g., human germline), for example, to reduce the likelihood of immunogenicity, e.g., upon administration to a human subject.

[0199] In some instances, alterations are made in CDR "hotspots," residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (see, e.g., Chowdhury, Methods Mol. Biol. 207:179-196 (2008)), and/or residues that contact antigen, with the resulting variant V_H or V_L being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, e.g., in Hoogenboom et al. in Methods in Molecular Biology 178:1-37 (O'Brien et al., ed., Human Press, Totowa, NJ, (2001)). In some instances of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a variety of methods (e.g., error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired affinity. Another method to introduce diversity involves CDR-directed approaches, in which several CDR residues (e.g., 4-6 residues at a time) are randomized. CDR residues involved in antigen binding may be specifically identified, e.g., using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

[0200] In certain instances, substitutions, insertions, or deletions may occur within one or more CDRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (e.g., conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made in CDRs. Such alterations may, for example, be outside of antigen contacting residues in the CDRs. In certain instances of the variant V_H and V_L sequences provided above, each CDR either is unaltered, or contains no more than one, two or three amino acid substitutions.

[0201] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme or a polypeptide which increases the serum half-life of the antibody.

Modifications

[0202] In certain instances, the antibody is altered to increase or decrease the extent to which the antibody is glycosylated, for example, by removing or inserting one or more glycosylation sites by altering the amino acid sequence and/or by modifying the oligosaccharide(s) attached to the glycosylation sites, e.g., using certain cell lines. Glycosylation sites include asparagine 297 of the heavy chain (according to Kabat numbering).

[0203] Exemplary modifications, variants, and cell lines are described, e.g., in Patent Publication Nos. US 2003/0157108, US 2004/0093621, US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; WO2002/031140; Okazaki et al. J. Mol. Biol. 336:1239-1249 (2004); Yamane-Ohnuki et al. Biotech. Bioeng. 87: 614 (2004). Ripka et al. Arch. Biochem. Biophys. 249:533-545 (1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Yamane-Ohnuki et al. Biotech. Bioeng. 87: 614 (2004); Kanda, Y. et al., Biotechnol. Bioeng., 94(4):680-688 (2006); and WO2003/085107); WO 2003/011878 (Jean-Mairet et al.); US Patent No. 6,602,684 (Umana et al.); and US 2005/0123546 (Umana et al.); WO 1997/30087 (Patel et al.); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

[0204] Among the modified antibodies are those having one or more amino acid modifications in the Fc region, such as those having a human Fc region sequence or other portion of a constant region (e.g., a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (e.g. a substitution) at one or more amino acid positions.

[0205] Such modifications can be made, e.g., to improve half-life, alter binding to one or more types of Fc receptors, and/or alter effector functions.

[0206] Also among the variants are cysteine engineered antibodies such as "thioMAbs" and other cysteine engineered variants, in which one or more residues of an antibody are substituted with cysteine residues, in order to generate reactive thiol groups at accessible sites, e.g., for use in conjugation of agents and linker-agents, to produce immunoconjugates. Cysteine engineered antibodies are described, e.g., in U.S. Patent Nos. 7,855,275 and 7,521,541.

[0207] In some instances, the antibodies are modified to contain additional nonproteinaceous moieties, including water soluble polymers. Exemplary polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propropylene glycol homopolymers, prolypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (e.g., glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one polymer is attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, whether the antibody derivative will be used in a therapy under defined conditions, etc.

B. Recombinant Receptors

[0208] Among the provided CD19 binding molecules are recombinant receptors, such as antigen receptors and other chimeric receptors, that specifically bind to CD19, such as receptors containing the provided anti-CD19 antibodies, e.g., antibody fragments. Among the antigen receptors are functional non-TCR antigen receptors, such as chimeric antigen receptors (CARs). Also provided are cells expressing the recombinant receptors and uses thereof in adoptive cell therapy, such as treatment of diseases and disorders associated with CD19 expression.

[0209] Exemplary antigen receptors, including CARs, and methods for engineering and introducing such receptors into cells, include those described, for example, in international patent application publication numbers WO200014257, WO2013126726, WO2012/129514, WO2014031687, WO2013/166321, WO2013/071154, WO2013/123061 U.S. patent application publication numbers US2002131960, US2013287748, US20130149337, U.S. Patent Nos.: 6,451,995, 7,446,190, 8,252,592, , 8,339,645, 8,398,282, 7,446,179, 6,410,319, 7,070,995, 7,265,209, 7,354,762, 7,446,191, 8,324,353, and 8,479,118, and European patent application number EP2537416,and/or those described by Sadelain et al., Cancer Discov. 2013 April; 3(4): 388-398; Davila et al. (2013) PLoS ONE 8(4): e61338; Turtle et al., Curr. Opin. Immunol., 2012 October; 24(5): 633-39; Wu et al., Cancer, 2012 March 18(2): 160-75. In some aspects, the antigen receptors include a CAR as described in U.S. Patent No.: 7,446,190, and those described in International Patent Application Publication No.: WO/2014055668 A1. Exemplary of the CARs include CARs as disclosed in any of the aforementioned publications, such as WO2014031687, US 8,339,645, US 7,446,179, US 2013/0149337, U.S. Patent No.:

7,446,190, US Patent No.: 8,389,282, e.g., and in which the antigen-binding portion, e.g., scFv, is replaced by an antibody, e.g., as provided herein.

[0210] Among the chimeric receptors are chimeric antigen receptors (CARs). The chimeric receptors, such as CARs, generally include an extracellular antigen binding domain that includes, is, or is comprised within, one of the provided anti-CD19 antibodies. Thus, the chimeric receptors, e.g., CARs, typically include in their extracellular portions one or more CD19-binding molecules, such as one or more antigen-binding fragment, domain, or portion, or one or more antibody variable domains, and/or antibody molecules, such as those described herein. In some instances, the CAR includes a CD19-binding portion or portions of the antibody molecule, such as a variable heavy (V_H) chain region and/or variable light (V_L) chain region of the antibody, e.g., an scFv antibody fragment.

[0211] CD19-targeting CARs are described, for example, by Kochenderfer et al., 2013, Nature Reviews Clinical Oncology, 10, 267-276 (2013); Wang et al. (2012) J. Immunother. 35(9): 689-701; and Brentjens et al., Sci Transl Med. 2013 5(177). See also WO2014031687, US 8,339,645, US 7,446,179, US 2013/0149337, U.S. Patent No.: 7,446,190, and US Patent No.: 8,389,282.

[0212] In some instances, the recombinant receptor, such as a CAR, such as the antibody portion thereof, further includes a spacer, which may be or include at least a portion of an immunoglobulin constant region or variant or modified version thereof, such as a hinge region, e.g., an IgG4 hinge region, and/or a CH1/CL and/or Fc region. In some aspects, the portion of the constant region serves as a spacer region between the antigen-recognition component, e.g., scFv, and transmembrane domain. The spacer can be of a length that provides for increased responsiveness of the cell following antigen binding, as compared to in the absence of the spacer. In some examples, the spacer is at or about 12 amino acids in length or is no more than 12 amino acids in length. Exemplary spacers include those having at least about 10 to 229 amino acids, about 10 to 200 amino acids, about 10 to 175 amino acids, about 10 to 150 amino acids, about 10 to 125 amino acids, about 10 to 100 amino acids, about 10 to 75 amino acids, about 10 to 50 amino acids, about 10 to 40 amino acids, about 10 to 30 amino acids, about 10 to 20 amino acids, or about 10 to 15 amino acids, and including any integer between the endpoints of any of the listed ranges. In some instances, a spacer region has about 12 amino acids or less, about 119 amino acids or less, or about 229 amino acids or less. Exemplary spacers include IgG4 hinge alone, IgG4 hinge linked to CH2 and CH3 domains, or IgG4 hinge linked to the CH3 domain. Exemplary spacers include, but are not limited to, those described in Hudecek et al. (2013) Clin. Cancer Res., 19:3153, international patent application publication number WO2014031687, U.S. Patent No. 8,822,647 or published app. No. US2014/0271635..

[0213] In some instances, the constant region or portion is of a human IgG, such as IgG4 or IgG1. In some instances, the spacer has the sequence ESKYGPPCPPCP (set forth in SEQ ID NO: 124), and is encoded by the sequence set forth in SEQ ID NO: 125. In some instances, the spacer has the sequence set forth in SEQ ID NO: 126. In some instances, the spacer has the sequence set forth in SEQ ID NO: 127. In some instances, the constant region or portion is of IgD. In some instances, the spacer has the sequence set forth in SEQ ID NO:128. In some instances, the spacer has a sequence of amino acids that exhibits at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to any of SEQ ID NOS: 124, 126, 127 or 128.

[0214] The antigen recognition domain generally is linked to one or more intracellular signaling components, such as signaling components that mimic activation through an antigen receptor complex, such as a TCR complex, in the case of a CAR, and/or signal via another cell surface receptor. Thus, in some instances, the CD19-specific binding component (e.g., antibody) is linked to one or more transmembrane and intracellular signaling domains. In some instances, the transmembrane domain is fused to the extracellular domain. In one instance, a transmembrane domain that naturally is associated with one of the domains in the receptor, e.g., CAR, is used. In some instances, the transmembrane domain is selected or modified by amino acid substitution to avoid binding of such domains to the transmembrane domains of the same or different surface membrane proteins to minimize interactions with other members of the receptor complex.

[0215] The transmembrane domain in some instances is derived either from a natural or from a synthetic source. Where the source is natural, the domain in some aspects is derived from any membrane-bound or transmembrane protein. Transmembrane regions include those derived from (i.e. comprise at least the transmembrane region(s) of) the alpha, beta or zeta chain of the T-cell receptor, CD28, CD3 epsilon, CD45, CD4, CD5, CD8, CD9, CD 16, CD22, CD33, CD37, CD64, CD80, CD86, CD 134, CD137, CD 154, and/or transmembrane regions containing functional variants thereof such as those retaining a substantial portion of the structural, e.g., transmembrane, properties thereof. In some instances, the transmembrane domain is a transmembrane domain derived from CD4, CD28, or CD8, e.g., CD8alpha, or functional variant thereof. In some instances the transmembrane domain in some instances is synthetic. In some aspects, the synthetic transmembrane domain comprises predominantly hydrophobic residues such as leucine and valine. In some aspects, a triplet of phenylalanine, tryptophan and valine will be found at each end of a synthetic transmembrane domain. In some instances, the linkage is by linkers, spacers, and/or transmembrane domain(s).

[0216] Among the intracellular signaling domains are those that mimic or approximate a signal through a natural antigen receptor, a signal through such a receptor in combination with a costimulatory receptor, and/or a signal through a costimulatory receptor alone. In some instances, a short oligo- or polypeptide linker, for example, a linker of between

2 and 10 amino acids in length, such as one containing glycines and serines, e.g., glycine-serine doublet, is present and forms a linkage between the transmembrane domain and the cytoplasmic signaling domain of the CAR.

[0217] The receptor, e.g., the CAR, generally includes at least one intracellular signaling component or components. In some instances, the receptor includes an intracellular component of a TCR complex, such as a TCR CD3 chain that mediates T-cell activation and cytotoxicity, e.g., CD3 zeta chain. Thus, in some aspects, the CD19-binding antibody is linked to one or more cell signaling modules. In some instances, cell signaling modules include CD3 transmembrane domain, CD3 intracellular signaling domains, and/or other CD transmembrane domains. In some instances, the receptor, e.g., CAR, further includes a portion of one or more additional molecules such as Fc receptor γ, CD8, CD4, CD25, or CD16. For example, in some aspects, the CAR includes a chimeric molecule between CD3-zeta (CDS-ζ) or Fc receptor γ and CD8, CD4, CD25 or CD16.

[0218] In some instances, upon ligation of the CAR, the cytoplasmic domain or intracellular signaling domain of the CAR activates at least one of the normal effector functions or responses of the immune cell, e.g., T cell engineered to express the CAR. For example, in some contexts, the CAR induces a function of a T cell such as cytolytic activity or T-helper activity, such as secretion of cytokines or other factors. In some instances, a truncated portion of an intracellular signaling domain of an antigen receptor component or costimulatory molecule is used in place of an intact immunostimulatory chain, for example, if it transduces the effector function signal. In some instances, the intracellular signaling domain or domains include the cytoplasmic sequences of the T cell receptor (TCR), and in some aspects also those of co-receptors that in the natural context act in concert with such receptor to initiate signal transduction following antigen receptor engagement, and/or any derivative or variant of such molecules, and/or any synthetic sequence that has the same functional capability.

[0219] In the context of a natural TCR, full activation generally requires not only signaling through the TCR, but also a costimulatory signal. Thus, in some instances, to promote full activation, a component for generating secondary or co-stimulatory signal is also included in the CAR. In other instances, the CAR does not include a component for generating a costimulatory signal. In some aspects, an additional CAR is expressed in the same cell and provides the component for generating the secondary or costimulatory signal.

[0220] T cell activation is in some aspects described as being mediated by two classes of cytoplasmic signaling sequences: those that initiate antigen-dependent primary activation through the TCR (primary cytoplasmic signaling sequences), and those that act in an antigen-independent manner to provide a secondary or co-stimulatory signal (secondary cytoplasmic signaling sequences). In some aspects, the CAR includes one or both of such signaling components.

[0221] In some aspects, the CAR includes a primary cytoplasmic signaling sequence that regulates primary activation of the TCR complex. Primary cytoplasmic signaling sequences that act in a stimulatory manner may contain signaling motifs which are known as immunoreceptor tyrosine-based activation motifs or ITAMs. Examples of ITAM containing primary cytoplasmic signaling sequences include those derived from TCR zeta, FcR gamma, FcR beta, CD3 gamma, CD3 delta, CD3 epsilon, CD8, CD22, CD79a, CD79b, and CD66d. In some instances, cytoplasmic signaling molecule(s) in the CAR contain(s) a cytoplasmic signaling domain, portion thereof, or sequence derived from CD3 zeta.

[0222] In some instances, the CAR includes a signaling domain and/or transmembrane portion of a costimulatory receptor, such as CD28, 4-1BB, OX40, DAP10, or ICOS, or CD27. In some aspects, the same CAR includes both the activating and costimulatory components.

[0223] In some instances, the activating domain (e.g. CD3 zeta) is included within one CAR, whereas the costimulatory component (e.g. CD28 or 4-1BB) is provided by another CAR recognizing another antigen. In some instances, the CARs include activating or stimulatory CARs, costimulatory CARs, both expressed on the same cell (*see* WO2014/055668). In some aspects, the CD19-targeting CAR is the stimulatory or activating CAR; in other aspects, it is the costimulatory CAR. In some instances, the cells further include inhibitory CARs (iCARs, *see* Fedorov et al., Sci. Transl. Medicine, 5(215) (December, 2013), such as a CAR recognizing an antigen other than CD19, whereby an activating signal delivered through the CD19-targeting CAR is diminished or inhibited by binding of the inhibitory CAR to its ligand, e.g., to reduce off-target effects.

[0224] In some instances, the intracellular signaling component of the recombinant receptor, such as CAR, comprises a CD3 zeta intracellular domain and a costimulatory signaling region. In certain instances, the intracellular signaling domain comprises a CD28 transmembrane and signaling domain linked to a CD3 (e.g., CD3-zeta) intracellular domain. In some instances, the intracellular signaling domain comprises a chimeric CD28 and/or CD137 (4-1BB, TNFRSF9) co-stimulatory domains, linked to a CD3 zeta intracellular domain.

[0225] In some instances, the CAR encompasses one or more, e.g., two or more, costimulatory domains and an activation domain, e.g., primary activation domain, in the cytoplasmic portion. Exemplary CARs include intracellular components of CD3-zeta, CD28, and 4-1BB.

[0226] In some instances, the CAR or other antigen receptor further includes a marker, such as a cell surface marker, which may be used to confirm transduction or engineering of the cell to express the receptor, such as a truncated version of a cell surface receptor, such as truncated EGFR (tEGFR). In some aspects, the marker includes all or part (e.g., truncated form) of CD34, a NGFR, or epidermal growth factor receptor (e.g., tEGFR) or a functional variant thereof. In some instances, the nucleic acid encoding the marker is operably linked to a polynucleotide encoding for a linker sequence, such as a cleavable linker sequence, e.g., T2A. For example, a marker, and optionally a linker sequence, can be any as disclosed in published patent application No. WO2014031687. For example, the marker can be a truncated EGFR (tEGFR) that is, optionally, linked to a linker sequence, such as a T2A cleavable linker sequence. An exemplary polypeptide for a truncated EGFR (e.g. tEGFR) comprises the sequence of amino acids set forth in SEQ ID NO: 138 or a sequence of amino acids that exhibits at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to SEQ ID NO:138. An exemplary T2A linker sequence comprises the sequence of amino acids set forth in SEQ ID NO:137 or a sequence of amino acids that exhibits at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to SEQ ID NO:137.

[0227] In some instances, the marker is a molecule, e.g., cell surface protein, not naturally found on T cells or not naturally found on the surface of T cells, or a portion thereof.

[0228] In some instances, the molecule is a non-self molecule, e.g., non-self protein, i.e., one that is not recognized as "self' by the immune system of the host into which the cells will be adoptively transferred.

[0229] In some instances, the marker serves no therapeutic function and/or produces no effect other than to be used as a marker for genetic engineering, e.g., for selecting cells successfully engineered. In other instances, the marker may be a therapeutic molecule or molecule otherwise exerting some desired effect, such as a ligand for a cell to be encountered in vivo, such as a costimulatory or immune checkpoint molecule to enhance and/or dampen responses of the cells upon adoptive transfer and encounter with ligand.

[0230] In some cases, CARs are referred to as first, second, and/or third generation CARs. In some aspects, a first generation CAR is one that solely provides a CD3-chain induced signal upon antigen binding; in some aspects, a second-generation CARs is one that provides such a signal and costimulatory signal, such as one including an intracellular signaling domain from a costimulatory receptor such as CD28 or CD137; in some aspects, a third generation CAR in some aspects is one that includes multiple costimulatory domains of different costimulatory receptors.

[0231] In some instances, the chimeric antigen receptor includes an extracellular portion containing the antibody or fragment described herein. In some aspects, the chimeric antigen receptor includes an extracellular portion containing the antibody or fragment described herein and an intracellular signaling domain. In some instances, the antibody or fragment includes an scFv and the intracellular domain contains an ITAM. In some aspects, the intracellular signaling domain includes a signaling domain of a zeta chain of a CD3-zeta (CD3ζ) chain. In some instances, the chimeric antigen receptor includes a transmembrane domain linking the extracellular domain and the intracellular signaling domain. In some aspects, the transmembrane domain contains a transmembrane portion of CD28. The extracellular domain and transmembrane domain can be linked directly or indirectly. In some instances, the extracellular domain and transmembrane are linked by a spacer, such as any described herein. In some instances, the receptor contains extracellular portion of the molecule from which the transmembrane domain is derived, such as a CD28 extracellular portion. In some instances, the chimeric antigen receptor contains an intracellular domain derived from a T cell costimulatory molecule or a functional variant thereof, such as between the transmembrane domain and intracellular signaling domain. In some aspects, the T cell costimulatory molecule is CD28 or 41BB.

[0232] For example, in some instances, the CAR contains an antibody, e.g., an antibody fragment, as provided herein, a transmembrane domain that is or contains a transmembrane portion of CD28 or a functional variant thereof, and an intracellular signaling domain containing a signaling portion of CD28 or functional variant thereof and a signaling portion of CD3 zeta or functional variant thereof. In some instances, the CAR contains an antibody, e.g.,antibody fragment, as provided herein, a transmembrane domain that is or contains a transmembrane portion of CD28 or a functional variant thereof, and an intracellular signaling domain containing a signaling portion of a 4-1BB or functional variant thereof and a signaling portion of CD3 zeta or functional variant thereof. In some such instances, the receptor further includes a spacer containing a portion of an Ig molecule, such as a human Ig molecule, such as an Ig hinge, e.g. an IgG4 hinge, such as a hinge-only spacer.

[0233] In some instances, the transmembrane domain of the recombinant receptor, e.g., the CAR, is or includes a transmembrane domain of human CD28 (e.g. Accession No. P01747.1) or variant thereof, such as a transmembrane domain that comprises the sequence of amino acids set forth in SEQ ID NO: 129 or a sequence of amino acids that exhibits at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to SEQ ID NO:129; in some instances, the transmembrane-domain containing portion of the recombinant receptor comprises the sequence of amino acids set forth in SEQ ID NO: 130 or a sequence of amino acids having at least at or about 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity thereto.

[0234] In some instances, the intracellular signaling component(s) of the recombinant receptor, *e.g.* the CAR, contains an intracellular costimulatory signaling domain of human CD28 or a functional variant or portion thereof, such as a domain with an LL to GG substitution at positions 186-187 of a native CD28 protein. For example, the intracellular signaling domain can comprise the sequence of amino acids set forth in SEQ ID NO:131 or 132 or a sequence of amino acids that exhibits at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to SEQ ID NO:131 or 132. In some instances, the intracellular domain comprises an intracellular costimulatory signaling domain of 4-1BB (e.g. (Accession No. Q07011.1) or functional variant or portion thereof, such as the sequence of amino acids set forth in SEQ ID NO:133 or a sequence of amino acids that exhibits at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to SEQ ID NO: 133.

[0235] In some instances, the intracellular signaling domain of the recombinant receptor, *e.g.* the CAR, comprises a human CD3 zeta stimulatory signaling domain or functional variant thereof, such as an 112 AA cytoplasmic domain of isoform 3 of human CD3ζ (Accession No.: P20963.2) or a CD3 zeta signaling domain as described in U.S. Patent No.: 7,446,190 or U.S. Patent No. 8,911,993. For example, in some instances, the intracellular signaling domain comprises the sequence of amino acids 134, 135 or 136 or a sequence of amino acids that exhibits at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to SEQ ID NO:134, 135 or 136.

[0236] In some aspects, the spacer contains only a hinge region of an IgG, such as only a hinge of IgG4 or IgG1, such as the hinge only spacer set forth in SEQ ID NO:124. In other instances, the spacer is or contains an Ig hinge, e.g., an IgG4-derived hinge, optionally linked to a CH2 and/or CH3 domains. In some instances, the spacer is an Ig hinge, e.g., an IgG4 hinge, linked to CH2 and CH3 domains, such as set forth in SEQ ID NO:127. In some instances, the spacer is an Ig hinge, e.g., an IgG4 hinge, linked to a CH3 domain only, such as set forth in SEQ ID NO:126. In some instances, the spacer is or comprises a glycine-serine rich sequence or other flexible linker such as known flexible linkers.

[0237] For example, in some instances, the CAR includes an anti-CD 19 antibody such as an anti-CD19 antibody fragment, such as any of the provided human anti-CD19 antibodies, e.g., single-chain antibodies including scFvs, described herein, a spacer, such as a spacer containing a portion of an immunoglobulin molecule, such as a hinge region and/or one or more constant regions of a heavy chain molecule, such as an Ig-hinge containing spacer, a transmembrane domain containing all or a portion of a CD28-derived transmembrane domain, a CD28-derived intracellular signaling domain, and a CD3 zeta signaling domain. In some instances, the CAR includes an anti-CD19 antibody or fragment, such as any of the human anti-CD 19 antibodies, including scFvs described herein, a spacer such as any of the Ig-hinge containing spacers, a CD28-derived transmembrane domain, a 4-1BB-derived intracellular signaling domain, and a CD3 zeta-derived signaling domain.

[0238] In some instances, such CAR constructs further includes a T2A ribosomal skip element and/or a tEGFR sequence, e.g., downstream of the CAR, such as set forth in SEQ ID NO: 137 and/or 138, respectively, or a sequence of amino acids that exhibits at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more sequence identity to SEQ ID NO: 137 or 138

C. Engineered Cells

[0239] Also provided are cells, cell populations, and compositions containing the cells, e.g., the engineered cells, e.g. that contain an engineered antigen receptor, e.g., that contains an extracellular domain including the anti-CD19 antibody or fragment, described herein. Among the compositions are pharmaceutical compositions and formulations for administration, such as for adoptive cell therapy. Also provided are therapeutic methods for administering the cells and compositions to subjects, e.g., patients.

[0240] Thus also provided are genetically engineered cells expressing the recombinant receptors containing the antibodies, e.g., cells containing the CARs. The cells generally are eukaryotic cells, such as mammalian cells, and typically are human cells. In some instances, the cells are derived from the blood, bone marrow, lymph, or lymphoid organs, are cells of the immune system, such as cells of the innate or adaptive immunity, *e.g.*, myeloid or lymphoid cells, including lymphocytes, typically T cells and/or NK cells. Other exemplary cells include stem cells, such as multipotent and pluripotent stem cells, including induced pluripotent stem cells (iPSCs). The cells typically are primary cells, such as those isolated directly from a subject and/or isolated from a subject and frozen. In some instances, the cells include one or more subsets of T cells or other cell types, such as whole T cell populations, CD4+ cells, CD8+ cells, and subpopulations thereof, such as those defined by function, activation state, maturity, potential for differentiation, expansion, recirculation, localization, and/or persistence capacities, antigen-specificity, type of antigen receptor, presence in a particular organ or compartment, marker or cytokine secretion profile, and/or degree of differentiation. With reference to the subject to be treated, the cells may be allogeneic and/or autologous. Among the methods include off-the-shelf methods. In some aspects, such as for off-the-shelf technologies, the cells are pluripotent and/or multipotent, such as stem cells, such as induced pluripotent stem cells (iPSCs). In some instances, the methods include isolating cells from the subject, preparing, processing, culturing, and/or engineering them, as described herein, and reintroducing them into the same patient, before or after cryopreservation.

[0241] Among the sub-types and subpopulations of T cells and/or of CD4+ and/or of CD8+ T cells are naive T (T_N) cells, effector T cells (T_{EFF}), memory T cells and sub-types thereof, such as stem cell memory T (T_{SCM}), central memory T (T_{CM}), effector memory T (T_{EM}), or terminally differentiated effector memory T cells, tumor-infiltrating lymphocytes

(TIL), immature T cells, mature T cells, helper T cells, cytotoxic T cells, mucosa-associated invariant T (MAIT) cells, naturally occurring and adaptive regulatory T (Treg) cells, helper T cells, such as TH1 cells, TH2 cells, TH3 cells, TH17 cells, TH9 cells, TH22 cells, follicular helper T cells, alpha/beta T cells, and delta/gamma T cells.

[0242] In some instances, the cells are natural killer (NK) cells. In some instances, the cells are monocytes or granulocytes, e.g., myeloid cells, macrophages, neutrophils, dendritic cells, mast cells, eosinophils, and/or basophils.

[0243] In some instances, the cells include one or more nucleic acids introduced via genetic engineering, and thereby express recombinant or genetically engineered products of such nucleic acids. In some instances, the nucleic acids are heterologous, i.e., normally not present in a cell or sample obtained from the cell, such as one obtained from another organism or cell, which for example, is not ordinarily found in the cell being engineered and/or an organism from which such cell is derived. In some instances, the nucleic acids are not naturally occurring, such as a nucleic acid not found in nature, including one comprising chimeric combinations of nucleic acids encoding various domains from multiple different cell types.

Vectors and methods for genetic engineering

[0244] Also provided are methods, nucleic acids, compositions, and kits, for expressing the binding molecules, including receptors comprising the antibodies, and for producing the genetically engineered cells expressing such binding molecules. The genetic engineering generally involves introduction of a nucleic acid encoding the recombinant or engineered component into the cell, such as by retroviral transduction, transfection, or transformation.

[0245] In some instances, gene transfer is accomplished by first stimulating the cell, such as by combining it with a stimulus that induces a response such as proliferation, survival, and/or activation, e.g., as measured by expression of a cytokine or activation marker, followed by transduction of the activated cells, and expansion in culture to numbers sufficient for clinical applications.

[0246] In some contexts, overexpression of a stimulatory factor (for example, a lymphokine or a cytokine) may be toxic to a subject. Thus, in some contexts, the engineered cells include gene segments that cause the cells to be susceptible to negative selection in vivo, such as upon administration in adoptive immunotherapy. For example in some aspects, the cells are engineered so that they can be eliminated as a result of a change in the in vivo condition of the patient to which they are administered. The negative selectable phenotype may result from the insertion of a gene that confers sensitivity to an administered agent, for example, a compound. Negative selectable genes include the Herpes simplex virus type I thymidine kinase (HSV-I TK) gene (Wigler et al., Cell II :223, I977) which confers ganciclovir sensitivity; the cellular hypoxanthine phosphribosyltransferase (HPRT) gene, the cellular adenine phosphoribosyltransferase (APRT) gene, bacterial cytosine deaminase, (Mullen et al., Proc. Natl. Acad. Sci. USA. 89:33 (1992)).

[0247] In some aspects, the cells further are engineered to promote expression of cytokines or other factors. Various methods for the introduction of genetically engineered components, e.g., antigen receptors, e.g., CARs, are well known and may be used with the provided methods and compositions. Exemplary methods include those for transfer of nucleic acids encoding the receptors, including via viral, e.g., retroviral or lentiviral, transduction, transposons, and electroporation.

[0248] In some instances, recombinant nucleic acids are transferred into cells using recombinant infectious virus particles, such as, e.g., vectors derived from simian virus 40 (SV40), adenoviruses, adeno-associated virus (AAV). In some instances, recombinant nucleic acids are transferred into T cells using recombinant lentiviral vectors or retroviral vectors, such as gamma-retroviral vectors (see, e.g., Koste et al. (2014) Gene Therapy 2014 Apr 3. doi: 10.1038/gt.2014.25; Carlens et al. (2000) Exp Hematol 28(10): 1137-46; Alonso-Camino et al. (2013) Mol Ther Nucl Acids 2, e93; Park et al., Trends Biotechnol. 2011 November 29(11): 550-557.

[0249] In some instances, the retroviral vector has a long terminal repeat sequence (LTR), e.g., a retroviral vector derived from the Moloney murine leukemia virus (MoMLV), myeloproliferative sarcoma virus (MPSV), murine embryonic stem cell virus (MESV), murine stem cell virus (MSCV), spleen focus forming virus (SFFV), or adeno-associated virus (AAV). Most retroviral vectors are derived from murine retroviruses. In some instances, the retroviruses include those derived from any avian or mammalian cell source. The retroviruses typically are amphotropic, meaning that they are capable of infecting host cells of several species, including humans. In one instance, the gene to be expressed replaces the retroviral gag, pol and/or env sequences. A number of illustrative retroviral systems have been described (e.g., U.S. Pat. Nos. 5,219,740; 6,207,453; 5,219,740; Miller and Rosman (1989) BioTechniques 7:980-990; Miller, A. D. (1990) Human Gene Therapy 1:5-14; Scarpa et al. (1991) Virology 180:849-852; Burns et al. (1993) Proc. Natl. Acad. Sci. USA 90:8033-8037; and Boris-Lawrie and Temin (1993) Cur. Opin. Genet. Develop. 3:102-109.

[0250] Methods of lentiviral transduction are known. Exemplary methods are described in, e.g., Wang et al. (2012) J. Immunother. 35(9): 689-701; Cooper et al. (2003) Blood. 101:1637-1644; Verhoeyen et al. (2009) Methods Mol Biol. 506: 97-114; and Cavalieri et al. (2003) Blood. 102(2): 497-505.

[0251] In some instances, recombinant nucleic acids are transferred into T cells via electroporation (*see,* e.g., Chicaybam et al, (2013) PLoS ONE 8(3): e60298 and Van Tedeloo et al. (2000) Gene Therapy 7(16): 1431-1437). In some instances, recombinant nucleic acids are transferred into T cells via transposition (see, e.g., Manuri et al. (2010) Hum Gene Ther 21(4): 427-437; Sharma et al. (2013) Molec Ther Nucl Acids 2, e74; and Huang et al. (2009) Methods Mol Biol 506: 115-126). Other methods of introducing and expressing genetic material in immune cells include calcium phosphate transfection (e.g., as described in Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.), protoplast fusion, cationic liposome-mediated transfection; tungsten particle-facilitated microparticle bombardment (Johnston, Nature, 346: 776-777 (1990)); and strontium phosphate DNA co-precipitation (Brash et al., Mol. Cell Biol., 7: 2031-2034 (1987)).

[0252] Other approaches and vectors for transfer of the nucleic acids encoding the recombinant products are those described, e.g., in international patent application, Publication No.: WO2014055668, and U.S. Patent No. 7,446,190.

[0253] Among additional nucleic acids, e.g., genes for introduction are those to improve the efficacy of therapy, such as by promoting viability and/or function of transferred cells; genes to provide a genetic marker for selection and/or evaluation of the cells, such as to assess *in vivo* survival or localization; genes to improve safety, for example, by making the cell susceptible to negative selection in vivo as described by Lupton S. D. et al., Mol. and Cell Biol., 11:6 (1991); and Riddell et al., Human Gene Therapy 3:319-338 (1992); see also the publications of PCT/US91/08442 and PCT/US94/05601 by Lupton et al. describing the use of bifunctional selectable fusion genes derived from fusing a dominant positive selectable marker with a negative selectable marker. *See,* e.g., Riddell et al., US Patent No. 6,040,177, at columns 14-17.

Preparation of cells for engineering

[0254] In some instances, preparation of the engineered cells includes one or more culture and/or preparation steps. The cells for introduction of the CD19-binding molecule, e.g., CAR, may be isolated from a sample, such as a biological sample, e.g., one obtained from or derived from a subject. In some instances, the subject from which the cell is isolated is one having the disease or condition or in need of a cell therapy or to which cell therapy will be administered. The subject in some instances is a human in need of a particular therapeutic intervention, such as the adoptive cell therapy for which cells are being isolated, processed, and/or engineered.

[0255] Accordingly, the cells in some instances are primary cells, e.g., primary human cells. The samples include tissue, fluid, and other samples taken directly from the subject, as well as samples resulting from one or more processing steps, such as separation, centrifugation, genetic engineering (e.g. transduction with viral vector), washing, and/or incubation. The biological sample can be a sample obtained directly from a biological source or a sample that is processed. Biological samples include, but are not limited to, body fluids, such as blood, plasma, serum, cerebrospinal fluid, synovial fluid, urine and sweat, tissue and organ samples, including processed samples derived therefrom.

[0256] In some aspects, the sample from which the cells are derived or isolated is blood or a blood-derived sample, or is or is derived from an apheresis or leukapheresis product. Exemplary samples include whole blood, peripheral blood mononuclear cells (PBMCs), leukocytes, bone marrow, thymus, tissue biopsy, tumor, leukemia, lymphoma, lymph node, gut associated lymphoid tissue, mucosa associated lymphoid tissue, spleen, other lymphoid tissues, liver, lung, stomach, intestine, colon, kidney, pancreas, breast, bone, prostate, cervix, testes, ovaries, tonsil, or other organ, and/or cells derived therefrom. Samples include, in the context of cell therapy, e.g., adoptive cell therapy, samples from autologous and allogeneic sources.

[0257] In some instances, the cells are derived from cell lines, e.g., T cell lines. The cells in some instances are obtained from a xenogeneic source, for example, from mouse, rat, non-human primate, and pig.

[0258] In some instances, isolation of the cells includes one or more preparation and/or non-affinity based cell separation steps. In some examples, cells are washed, centrifuged, and/or incubated in the presence of one or more reagents, for example, to remove unwanted components, enrich for desired components, lyse or remove cells sensitive to particular reagents. In some examples, cells are separated based on one or more property, such as density, adherent properties, size, sensitivity and/or resistance to particular components.

[0259] In some examples, cells from the circulating blood of a subject are obtained, e.g., by apheresis or leukapheresis. The samples, in some aspects, contain lymphocytes, including T cells, monocytes, granulocytes, B cells, other nucleated white blood cells, red blood cells, and/or platelets, and in some aspects contains cells other than red blood cells and platelets.

[0260] In some instances, the blood cells collected from the subject are washed, e.g., to remove the plasma fraction and to place the cells in an appropriate buffer or media for subsequent processing steps. In some instances, the cells are washed with phosphate buffered saline (PBS). In some instances, the wash solution lacks calcium and/or magnesium and/or many or all divalent cations. In some aspects, a washing step is accomplished a semi-automated "flow-through" centrifuge (for example, the Cobe 2991 cell processor, Baxter) according to the manufacturer's instructions. In some aspects, a washing step is accomplished by tangential flow filtration (TFF) according to the manufacturer's instructions. In some instances, the cells are resuspended in a variety of biocompatible buffers after washing, such as, for example, Ca^{++}/Mg^{++} free PBS. In certain instances, components of a blood cell sample are removed and the cells directly resuspended in culture media.

[0261] In some instances, the methods include density-based cell separation methods, such as the preparation of white blood cells from peripheral blood by lysing the red blood cells and centrifugation through a Percoll or Ficoll gradient.

[0262] In some instances, the isolation methods include the separation of different cell types based on the expression or presence in the cell of one or more specific molecules, such as surface markers, e.g., surface proteins, intracellular markers, or nucleic acid. In some instances, any known method for separation based on such markers may be used. In some instances, the separation is affinity- or immunoaffinity-based separation. For example, the isolation in some aspects includes separation of cells and cell populations based on the cells' expression or expression level of one or more markers, typically cell surface markers, for example, by incubation with an antibody or binding partner that specifically binds to such markers, followed generally by washing steps and separation of cells having bound the antibody or binding partner, from those cells having not bound to the antibody or binding partner.

[0263] Such separation steps can be based on positive selection, in which the cells having bound the reagents are retained for further use, and/or negative selection, in which the cells having not bound to the antibody or binding partner are retained. In some examples, both fractions are retained for further use. In some aspects, negative selection can be particularly useful where no antibody is available that specifically identifies a cell type in a heterogeneous population, such that separation is best carried out based on markers expressed by cells other than the desired population.

[0264] The separation need not result in 100% enrichment or removal of a particular cell population or cells expressing a particular marker. For example, positive selection of or enrichment for cells of a particular type, such as those expressing a marker, refers to increasing the number or percentage of such cells, but need not result in a complete absence of cells not expressing the marker. Likewise, negative selection, removal, or depletion of cells of a particular type, such as those expressing a marker, refers to decreasing the number or percentage of such cells, but need not result in a complete removal of all such cells.

[0265] In some examples, multiple rounds of separation steps are carried out, where the positively or negatively selected fraction from one step is subjected to another separation step, such as a subsequent positive or negative selection. In some examples, a single separation step can deplete cells expressing multiple markers simultaneously, such as by incubating cells with a plurality of antibodies or binding partners, each specific for a marker targeted for negative selection. Likewise, multiple cell types can simultaneously be positively selected by incubating cells with a plurality of antibodies or binding partners expressed on the various cell types.

[0266] For example, in some aspects, specific subpopulations of T cells, such as cells positive or expressing high levels of one or more surface markers, e.g., $CD28^+$, $CD62L^+$, $CCR7^+$, $CD27^+$, $CD127^+$, $CD4^+$, $CD8^+$, $CD45RA^+$, and/or $CD45RO^+$ T cells, are isolated by positive or negative selection techniques.

[0267] For example, $CD3^+$, $CD28^+$ T cells can be positively selected using CD3/CD28 conjugated magnetic beads (e.g., DYNABEADS® M-450 CD3/CD28 T Cell Expander).

[0268] In some instances, isolation is carried out by enrichment for a particular cell population by positive selection, or depletion of a particular cell population, by negative selection. In some instances, positive or negative selection is accomplished by incubating cells with one or more antibodies or other binding agent that specifically bind to one or more surface markers expressed or expressed ($marker^+$) at a relatively higher level ($marker^{high}$) on the positively or negatively selected cells, respectively.

[0269] In some instances, T cells are separated from a PBMC sample by negative selection of markers expressed on non-T cells, such as B cells, monocytes, or other white blood cells, such as CD14. In some aspects, a $CD4^+$ or $CD8^+$ selection step is used to separate $CD4^+$ helper and $CD8^+$ cytotoxic T cells. Such $CD4^+$ and $CD8^+$ populations can be further sorted into sub-populations by positive or negative selection for markers expressed or expressed to a relatively higher degree on one or more naive, memory, and/or effector T cell subpopulations.

[0270] In some instances, $CD8^+$ cells are further enriched for or depleted of naive, central memory, effector memory, and/or central memory stem cells, such as by positive or negative selection based on surface antigens associated with the respective subpopulation. In some instances, enrichment for central memory T (T_{CM}) cells is carried out to increase efficacy, such as to improve long-term survival, expansion, and/or engraftment following administration, which in some aspects is particularly robust in such sub-populations. *See* Terakuraet al. (2012) Blood. 1:72-82; Wang et al. (2012) J Immunother. 35(9):689-701. In some instances, combining T_{CM}-enriched $CD8^+$ T cells and $CD4^+$T cells further enhances efficacy.

[0271] In instances, memory T cells are present in both $CD62L^+$ and $CD62L^-$ subsets of $CD8^+$ peripheral blood lymphocytes. PBMC can be enriched for or depleted of $CD62L^-CD8^+$ and/or $CD62L^+CD8^+$ fractions, such as using anti-CD8 and anti-CD62L antibodies.

[0272] In some instances, the enrichment for central memory T (T_{CM}) cells is based on positive or high surface expression of CD45RO, CD62L, CCR7, CD28, CD3, and/or CD 127; in some aspects, it is based on negative selection for cells expressing or highly expressing CD45RA and/or granzyme B. In some aspects, isolation of a $CD8^+$ population enriched for T_{CM} cells is carried out by depletion of cells expressing CD4, CD14, CD45RA, and positive selection or enrichment for cells expressing CD62L. In one aspect, enrichment for central memory T (T_{CM}) cells is carried out starting with a negative fraction of cells selected based on CD4 expression, which is subjected to a negative selection based on expression of CD14 and CD45RA, and a positive selection based on CD62L. Such selections in some aspects are carried out simultaneously and in other aspects are carried out sequentially, in either order. In some aspects, the same CD4 expression-based selection step used in preparing the $CD8^+$ cell population or subpopulation, also is used to generate the $CD4^+$ cell population or sub-population, such that both the positive and negative fractions from the CD4-based separation are retained and used in subsequent steps of the methods, optionally following one or more further positive or negative selection steps.

[0273] In a particular example, a sample of PBMCs or other white blood cell sample is subjected to selection of $CD4^+$ cells, where both the negative and positive fractions are retained. The negative fraction then is subjected to negative selection based on expression of CD14 and CD45RA or CD19, and positive selection based on a marker characteristic of central memory T cells, such as CD62L or CCR7, where the positive and negative selections are carried out in either order.

[0274] $CD4^+$ T helper cells are sorted into naive, central memory, and effector cells by identifying cell populations that have cell surface antigens. $CD4^+$ lymphocytes can be obtained by standard methods. In some instances, naive $CD4^+$ T lymphocytes are $CD45RO^-$, $CD45RA^+$, $CD62L^+$, $CD4^+$ T cells. In some instances, central memory $CD4^+$ cells are $CD62L^+$ and $CD45RO^+$. In some instances, effector $CD4^+$ cells are $CD62L^-$ and $CD45RO^-$.

[0275] In one example, to enrich for $CD4^+$ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8. In some instances, the antibody or binding partner is bound to a solid support or matrix, such as a magnetic bead or paramagnetic bead, to allow for separation of cells for positive and/or negative selection. For example, in some instances, the cells and cell populations are separated or isolated using immunomagnetic (or affinitymagnetic) separation techniques (reviewed in Methods in Molecular Medicine, vol. 58: Metastasis Research Protocols, Vol. 2: Cell Behavior In Vitro and In Vivo, p 17-25 Edited by: S. A. Brooks and U. Schumacher © Humana Press Inc., Totowa, NJ).

[0276] In some aspects, the sample or composition of cells to be separated is incubated with small, magnetizable or magnetically responsive material, such as magnetically responsive particles or microparticles, such as paramagnetic beads (e.g., such as Dynalbeads or MACS beads). The magnetically responsive material, e.g., particle, generally is directly or indirectly attached to a binding partner, e.g., an antibody, that specifically binds to a molecule, e.g., surface marker, present on the cell, cells, or population of cells that it is desired to separate, e.g., that it is desired to negatively or positively select.

[0277] In some instances, the magnetic particle or bead comprises a magnetically responsive material bound to a specific binding member, such as an antibody or other binding partner. There are many well-known magnetically responsive materials used in magnetic separation methods. Suitable magnetic particles include those described in Molday, U.S. Pat. No. 4,452,773, and in European Patent Specification EP 452342 B. Colloidal sized particles, such as those described in Owen U.S. Pat. No. 4,795,698, and Liberti et al., U.S. Pat. No. 5,200,084 are other examples.

[0278] The incubation generally is carried out under conditions whereby the antibodies or binding partners, or molecules, such as secondary antibodies or other reagents, which specifically bind to such antibodies or binding partners, which are attached to the magnetic particle or bead, specifically bind to cell surface molecules if present on cells within the sample.

[0279] In some aspects, the sample is placed in a magnetic field, and those cells having magnetically responsive or magnetizable particles attached thereto will be attracted to the magnet and separated from the unlabeled cells. For positive selection, cells that are attracted to the magnet are retained; for negative selection, cells that are not attracted (unlabeled cells) are retained. In some aspects, a combination of positive and negative selection is performed during the same selection step, where the positive and negative fractions are retained and further processed or subject to further separation steps.

[0280] In certain instances, the magnetically responsive particles are coated in primary antibodies or other binding partners, secondary antibodies, lectins, enzymes, or streptavidin. In certain instances, the magnetic particles are attached to cells via a coating of primary antibodies specific for one or more markers. In certain instances, the cells, rather than the beads, are labeled with a primary antibody or binding partner, and then cell-type specific secondary antibody- or other binding partner (e.g., streptavidin)-coated magnetic particles, are added. In certain instances, streptavidin-coated magnetic particles are used in conjunction with biotinylated primary or secondary antibodies.

[0281] In some instances, the magnetically responsive particles are left attached to the cells that are to be subsequently incubated, cultured and/or engineered; in some aspects, the particles are left attached to the cells for administration to a patient. In some instances, the magnetizable or magnetically responsive particles are removed from the cells. Methods for removing magnetizable particles from cells are known and include, e.g., the use of competing non-labeled antibodies, magnetizable particles or antibodies conjugated to cleavable linkers, etc. In some instances, the magnetizable particles are biodegradable.

[0282] In some instances, the affinity-based selection is via magnetic-activated cell sorting (MACS) (Miltenyi Biotech, Auburn, CA). Magnetic Activated Cell Sorting (MACS) systems are capable of high-purity selection of cells having magnetized particles attached thereto. In certain instances, MACS operates in a mode wherein the non-target and target species are sequentially eluted after the application of the external magnetic field. That is, the cells attached to magnetized particles are held in place while the unattached species are eluted. Then, after this first elution step is completed, the species that were trapped in the magnetic field and were prevented from being eluted are freed in some manner such that they can be eluted and recovered. In certain instances, the non-target cells are labelled and depleted from the heterogeneous population of cells.

[0283] In certain instances, the isolation or separation is carried out using a system, device, or apparatus that carries out one or more of the isolation, cell preparation, separation, processing, incubation, culture, and/or formulation steps of the methods. In some aspects, the system is used to carry out each of these steps in a closed or sterile environment, for example, to minimize error, user handling and/or contamination. In one example, the system is a system as described in International Patent Application, Publication Number WO2009/072003, or US 20110003380 A1.

[0284] In some instances, the system or apparatus carries out one or more, e.g., all, of the isolation, processing, engineering, and formulation steps in an integrated or self-contained system, and/or in an automated or programmable fashion. In some aspects, the system or apparatus includes a computer and/or computer program in communication with the system or apparatus, which allows a user to program, control, assess the outcome of, and/or adjust various aspects of the processing, isolation, engineering, and formulation steps.

[0285] In some aspects, the separation and/or other steps is carried out using CliniMACS system (Miltenyi Biotic), for example, for automated separation of cells on a clinical-scale level in a closed and sterile system. Components can include an integrated microcomputer, magnetic separation unit, peristaltic pump, and various pinch valves. The integrated computer in some aspects controls all components of the instrument and directs the system to perform repeated procedures in a standardized sequence. The magnetic separation unit in some aspects includes a movable permanent magnet and a holder for the selection column. The peristaltic pump controls the flow rate throughout the tubing set and, together with the pinch valves, ensures the controlled flow of buffer through the system and continual suspension of cells.

[0286] The CliniMACS system in some aspects uses antibody-coupled magnetizable particles that are supplied in a sterile, non-pyrogenic solution. In some instances, after labelling of cells with magnetic particles the cells are washed to remove excess particles. A cell preparation bag is then connected to the tubing set, which in turn is connected to a bag containing buffer and a cell collection bag. The tubing set consists of pre-assembled sterile tubing, including a pre-column and a separation column, and are for single use only. After initiation of the separation program, the system automatically applies the cell sample onto the separation column. Labelled cells are retained within the column, while unlabeled cells are removed by a series of washing steps. In some instances, the cell populations for use with the methods described herein are unlabeled and are not retained in the column. In some instances, the cell populations for use with the methods described herein are labeled and are retained in the column. In some instances, the cell populations for use with the methods described herein are eluted from the column after removal of the magnetic field, and are collected within the cell collection bag.

[0287] In certain instances, separation and/or other steps are carried out using the CliniMACS Prodigy system (Miltenyi Biotec). The CliniMACS Prodigy system in some aspects is equipped with a cell processing unity that permits automated washing and fractionation of cells by centrifugation. The CliniMACS Prodigy system can also include an onboard camera and image recognition software that determines the optimal cell fractionation endpoint by discerning the macroscopic layers of the source cell product. For example, peripheral blood is automatically separated into erythrocytes, white blood cells and plasma layers. The CliniMACS Prodigy system can also include an integrated cell cultivation chamber which accomplishes cell culture protocols such as, e.g., cell differentiation and expansion, antigen loading, and long-term cell culture. Input ports can allow for the sterile removal and replenishment of media and cells can be monitored using an integrated microscope. See, e.g., Klebanoff et al. (2012) J Immunother. 35(9): 651-660, Terakuraet al. (2012) Blood. 1:72-82, and Wang et al. (2012) J Immunother. 35(9):689-701.

[0288] In some instances, a cell population described herein is collected and enriched (or depleted) via flow cytometry, in which cells stained for multiple cell surface markers are carried in a fluidic stream. In some instances, a cell population described herein is collected and enriched (or depleted) via preparative scale (FACS)-sorting. In certain instances, a cell population described herein is collected and enriched (or depleted) by use of microelectromechanical systems (MEMS) chips in combination with a FACS-based detection system (see, e.g., WO 2010/033140, Cho et al. (2010) Lab Chip 10, 1567-1573; and Godin et al. (2008) J Biophoton. 1(5):355-376. In both cases, cells can be labeled with multiple markers, allowing for the isolation of well-defined T cell subsets at high purity.

[0289] In some instances, the antibodies or binding partners are labeled with one or more detectable marker, to facilitate separation for positive and/or negative selection. For example, separation may be based on binding to fluorescently labeled antibodies. In some examples, separation of cells based on binding of antibodies or other binding partners specific for one or more cell surface markers are carried in a fluidic stream, such as by fluorescence-activated cell sorting (FACS), including preparative scale (FACS) and/or microelectromechanical systems (MEMS) chips, e.g., in combination with a flow-cytometric detection system. Such methods allow for positive and negative selection based on multiple markers simultaneously.

[0290] In some instances, the preparation methods include steps for freezing, e.g., cryopreserving, the cells, either before or after isolation, incubation, and/or engineering. In some instances, the freeze and subsequent thaw step removes granulocytes and, to some extent, monocytes in the cell population. In some instances, the cells are suspended in a freezing solution, e.g., following a washing step to remove plasma and platelets. Any of a variety of known freezing solutions and parameters in some aspects may be used. One example involves using PBS containing 20% DMSO and 8% human serum albumin (HSA), or other suitable cell freezing media. This is then diluted 1:1 with media so that the final concentration of DMSO and HSA are 10% and 4%, respectively. The cells are then frozen to -80° C. at a rate of 1° per minute and stored in the vapor phase of a liquid nitrogen storage tank.

[0291] In some instances, the provided methods include cultivation, incubation, culture, and/or genetic engineering steps. For example, in some instances, provided are methods for incubating and/or engineering the depleted cell populations and culture-initiating compositions.

[0292] Thus, in some instances, the cell populations are incubated in a culture-initiating composition. The incubation and/or engineering may be carried out in a culture vessel, such as a unit, chamber, well, column, tube, tubing set, valve, vial, culture dish, bag, or other container for culture or cultivating cells.

[0293] In some instances, the cells are incubated and/or cultured prior to or in connection with genetic engineering. The incubation steps can include culture, cultivation, stimulation, activation, and/or propagation. In some instances, the compositions or cells are incubated in the presence of stimulating conditions or a stimulatory agent. Such conditions include those designed to induce proliferation, expansion, activation, and/or survival of cells in the population, to mimic antigen exposure, and/or to prime the cells for genetic engineering, such as for the introduction of a recombinant antigen receptor.

[0294] The conditions can include one or more of particular media, temperature, oxygen content, carbon dioxide content, time, agents, e.g., nutrients, amino acids, antibiotics, ions, and/or stimulatory factors, such as cytokines, chemokines, antigens, binding partners, fusion proteins, recombinant soluble receptors, and any other agents designed to activate the cells.

[0295] In some instances, the stimulating conditions or agents include one or more agent, e.g., ligand, which is capable of activating an intracellular signaling domain of a TCR complex. In some aspects, the agent turns on or initiates TCR/CD3 intracellular signaling cascade in a T cell. Such agents can include antibodies, such as those specific for a TCR component and/or costimulatory receptor, e.g., anti-CD3, anti-CD28, for example, bound to solid support such as a bead, and/or one or more cytokines. Optionally, the expansion method may further comprise the step of adding anti-CD3 and/or anti CD28 antibody to the culture medium (e.g., at a concentration of at least about 0.5 ng/ml). In some instances, the stimulating agents include IL-2 and/or IL-15, for example, an IL-2 concentration of at least about 10 units/mL.

[0296] In some aspects, incubation is carried out in accordance with techniques such as those described in US Patent No. 6,040,1 77 to Riddell et al., Klebanoff et al.(2012) J Immunother. 35(9): 651-660, Terakuraet al. (2012) Blood. 1:72-82, and/or Wang et al. (2012) J Immunother. 35(9):689-701.

[0297] In some instances, the T cells are expanded by adding to the culture-initiating composition feeder cells, such as non-dividing peripheral blood mononuclear cells (PBMC), (e.g., such that the resulting population of cells contains at least about 5, 10, 20, or 40 or more PBMC feeder cells for each T lymphocyte in the initial population to be expanded); and incubating the culture (e.g. for a time sufficient to expand the numbers of T cells). In some aspects, the non-dividing feeder cells can comprise gamma-irradiated PBMC feeder cells. In some instances, the PBMC are irradiated with gamma rays in the range of about 3000 to 3600 rads to prevent cell division. In some aspects, the feeder cells are added to culture medium prior to the addition of the populations of T cells.

[0298] In some instances, the stimulating conditions include temperature suitable for the growth of human T lymphocytes, for example, at least about 25 degrees Celsius, generally at least about 30 degrees, and generally at or about 37 degrees Celsius. Optionally, the incubation may further comprise adding non-dividing EBV-transformed lymphoblastoid cells (LCL) as feeder cells. LCL can be irradiated with gamma rays in the range of about 6000 to 10,000 rads. The LCL feeder cells in some aspects is provided in any suitable amount, such as a ratio of LCL feeder cells to initial T lymphocytes of at least about 10:1.

[0299] In instances, antigen-specific T cells, such as antigen-specific CD4+ and/or CD8+ T cells, are obtained by stimulating naive or antigen specific T lymphocytes with antigen. For example, antigen-specific T cell lines or clones can be generated to cytomegalovirus antigens by isolating T cells from infected subjects and stimulating the cells in vitro with the same antigen.

II. Compositions, Methods and Uses

[0300] Also provided are compositions including the CD19 binding molecules and engineered cells, including pharmaceutical compositions and formulations, and methods of using and uses of the molecules and compositions, such as in the treatment of diseases, conditions, and disorders in which CD19 is expressed, and/or detection, diagnostic, and prognostic methods.

A. Pharmaceutical Compositions and Formulations

[0301] Provided are pharmaceutical formulations including the CD19-binding molecule, e.g., antibody or chimeric receptor, and/or the engineered cells expressing the molecules. The pharmaceutical compositions and formulations generally include one or more optional pharmaceutically acceptable carrier or excipient. In some instances, the composition includes at least one additional therapeutic agent.

[0302] The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

[0303] A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[0304] In some aspects, the choice of carrier is determined in part by the particular cell, binding molecule, and/or antibody, and/or by the method of administration. Accordingly, there are a variety of suitable formulations. For example, the pharmaceutical composition can contain preservatives. Suitable preservatives may include, for example, methylparaben, propylparaben, sodium benzoate, and benzalkonium chloride. In some aspects, a mixture of two or more preservatives is used. The preservative or mixtures thereof are typically present in an amount of about 0.0001% to about 2% by weight of the total composition. Carriers are described, e.g., by Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980). Pharmaceutically acceptable carriers are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g. Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG).

[0305] Buffering agents in some aspects are included in the compositions. Suitable buffering agents include, for example, citric acid, sodium citrate, phosphoric acid, potassium phosphate, and various other acids and salts. In some aspects, a mixture of two or more buffering agents is used. The buffering agent or mixtures thereof are typically present in an amount of about 0.001% to about 4% by weight of the total composition. Methods for preparing administrable pharmaceutical compositions are known. Exemplary methods are described in more detail in, for example, Remington: The Science and Practice of Pharmacy, Lippincott Williams & Wilkins; 21st ed. (May 1, 2005).

[0306] Formulations of the antibodies can include lyophilized formulations and aqueous solutions.

[0307] The formulation or composition may also contain more than one active ingredients useful for the particular indication, disease, or condition being treated with the binding molecules or cells, preferably those with activities complementary to the binding molecule or cell, where the respective activities do not adversely affect one another. Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended. Thus, in some instances, the pharmaceutical composition further includes other pharmaceutically active agents or drugs, such as chemotherapeutic agents, e.g., asparaginase, busulfan, carboplatin, cisplatin, daunorubicin, doxorubicin, fluorouracil, gemcitabine, hydroxyurea, methotrexate, paclitaxel, rituximab, vinblastine, vincristine, etc. In some instances, the cells or antibodies are administered in the form of a salt, e.g., a pharmaceutically acceptable salt. Suitable pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, and sulphuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, and arylsulphonic acids, for example, p-toluenesulphonic acid.

[0308] Active ingredients may be entrapped in microcapsules, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. In certain instances, the pharmaceutical composition is formulated as an inclusion complex, such as cyclodextrin inclusion complex, or as a liposome. Liposomes can serve to target the host cells (e.g., T-cells or NK cells) to a particular tissue. Many methods are available for preparing liposomes, such as those described in, for example, Szoka et al., Ann. Rev. Biophys. Bioeng., 9: 467 (1980), and U.S. Patents 4,235,871, 4,501,728, 4,837,028, and 5,019,369.

[0309] The pharmaceutical composition in some aspects can employ time-released, delayed release, and sustained release delivery systems such that the delivery of the composition occurs prior to, and with sufficient time to cause, sensitization of the site to be treated. Many types of release delivery systems are available and known. Such systems can avoid repeated administrations of the composition, thereby increasing convenience to the subject and the physician.

[0310] The pharmaceutical composition in some instances contains the binding molecules and/or cells in amounts effective to treat or prevent the disease or condition, such as a therapeutically effective or prophylactically effective amount. Therapeutic or prophylactic efficacy in some instances is monitored by periodic assessment of treated subjects. For repeated administrations over several days or longer, depending on the condition, the treatment is repeated until a desired suppression of disease symptoms occurs. However, other dosage regimens may be useful and can be determined. The desired dosage can be delivered by a single bolus administration of the composition, by multiple bolus administrations of the composition, or by continuous infusion administration of the composition.

[0311] In certain instances, in the context of genetically engineered cells containing the binding molecules, a subject is administered the range of about one million to about 100 billion cells, such as, e.g., 1 million to about 50 billion cells (e.g., about 5 million cells, about 25 million cells, about 500 million cells, about 1 billion cells, about 5 billion cells, about 20 billion cells, about 30 billion cells, about 40 billion cells, or a range defined by any two of the foregoing values), such as about 10 million to about 100 billion cells (e.g., about 20 million cells, about 30 million cells, about 40 million cells, about 60 million cells, about 70 million cells, about 80 million cells, about 90 million cells, about 10 billion cells, about 25 billion cells, about 50 billion cells, about 75 billion cells, about 90 billion cells, or a range defined by any two of the foregoing values), and in some cases about 100 million cells to about 50 billion cells (e.g., about 120 million cells, about 250 million cells, about 350 million cells, about 450 million cells, about 650 million cells, about 800 million cells, about 900 million cells, about 3 billion cells, about 30 billion cells, about 45 billion cells) or any value in between these ranges, and/or such a number of cells per kilogram of body weight of the subject.

[0312] The may be administered using standard administration techniques, formulations, and/or devices. Provided are formulations and devices, such as syringes and vials, for storage and administration of the compositions. Administration of the cells can be autologous or heterologous. For example, immunoresponsive cells or progenitors can be obtained from one subject, and administered to the same subject or a different, compatible subject. Peripheral blood derived immunoresponsive cells or their progeny (e.g., in vivo, ex vivo or in vitro derived) can be administered via localized injection, including catheter administration, systemic injection, localized injection, intravenous injection, or parenteral administration. When administering a therapeutic composition (e.g., a pharmaceutical composition containing a genetically modified immunoresponsive cell), it will generally be formulated in a unit dosage injectable form (solution, suspension, emulsion).

[0313] Formulations include those for oral, intravenous, intraperitoneal, subcutaneous, pulmonary, transdermal, intramuscular, intranasal, buccal, sublingual, or suppository administration. In some instances, the cell populations are administered parenterally. The term "parenteral," as used herein, includes intravenous, intramuscular, subcutaneous, rectal, vaginal, and intraperitoneal administration. In some instances, the cell populations are administered to a subject using peripheral systemic delivery by intravenous, intraperitoneal, or subcutaneous injection.

[0314] Compositions in some instances are provided as sterile liquid preparations, e.g., isotonic aqueous solutions, suspensions, emulsions, dispersions, or viscous compositions, which may in some aspects be buffered to a selected pH. Liquid preparations are normally easier to prepare than gels, other viscous compositions, and solid compositions. Additionally, liquid compositions are somewhat more convenient to administer, especially by injection. Viscous compositions, on the other hand, can be formulated within the appropriate viscosity range to provide longer contact periods with specific tissues. Liquid or viscous compositions can comprise carriers, which can be a solvent or dispersing medium containing, for example, water, saline, phosphate buffered saline, polyoi (for example, glycerol, propylene glycol, liquid polyethylene glycol) and suitable mixtures thereof.

[0315] Sterile injectable solutions can be prepared by incorporating the binding molecule in a solvent, such as in admixture with a suitable carrier, diluent, or excipient such as sterile water, physiological saline, glucose, dextrose, or the like. The compositions can also be lyophilized. The compositions can contain auxiliary substances such as wetting, dispersing, or emulsifying agents (e.g., methylcellulose), pH buffering agents, gelling or viscosity enhancing additives, preservatives, flavoring agents, colors, and the like, depending upon the route of administration and the preparation desired. Standard texts may in some aspects be consulted to prepare suitable preparations.

[0316] Various additives which enhance the stability and sterility of the compositions, including antimicrobial preservatives, antioxidants, chelating agents, and buffers, can be added. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[0317] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g. films, or microcapsules.

[0318] The formulations to be used for in vivo administration are generally sterile. Sterility may be readily accomplished, e.g., by filtration through sterile filtration membranes.

B. Therapeutic and prophylactic methods and uses

[0319] Also provided are methods for using and uses of the CD19 binding molecules, including the anti-CD19 antibodies, e.g., antibody fragments, and/or engineered cells expressing the recombinant receptors. Such methods and uses include therapeutic methods and uses, for example, involving administration of the molecules, cells, or compositions containing the same, to a subject having a disease, condition, or disorder expressing or associated with CD19 expression, and/or in which cells or tissues express CD19. In some instances, the molecule, cell, and/or composition is administered in an effective amount to effect treatment of the disease or disorder. Uses include uses of the antibodies and cells in such methods and treatments, and in the preparation of a medicament in order to carry out such therapeutic methods. In some instances, the methods are carried out by administering the antibodies or cells, or compositions comprising the same, to the subject having or suspected of having the disease or condition. In some instances, the methods thereby treat the disease or condition or disorder in the subject.

[0320] As used herein, "treatment" (and grammatical variations thereof such as "treat" or "treating") refers to complete or partial amelioration or reduction of a disease or condition or disorder, or a symptom, adverse effect or outcome, or phenotype associated therewith. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. The terms do not imply complete curing of a disease or complete elimination of any symptom or effect(s) on all symptoms or outcomes.

[0321] As used herein, "delaying development of a disease" means to defer, hinder, slow, retard, stabilize, suppress and/or postpone development of the disease (such as cancer). This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease. For example, a late stage cancer, such as development of metastasis, may be delayed.

[0322] "Preventing," as used herein, includes providing prophylaxis with respect to the occurrence or recurrence of a disease in a subject that may be predisposed to the disease but has not yet been diagnosed with the disease. In some instances, the provided molecules and compositions are used to delay development of a disease or to slow the progression of a disease.

[0323] As used herein, to "suppress" a function or activity is to reduce the function or activity when compared to otherwise same conditions except for a condition or parameter of interest, or alternatively, as compared to another condition. For example, an antibody or composition or cell which suppresses tumor growth reduces the rate of growth of the tumor compared to the rate of growth of the tumor in the absence of the antibody or composition or cell.

[0324] An "effective amount" of an agent, *e.g.*, a pharmaceutical formulation, binding molecule, antibody, or cells, or composition, in the context of administration, refers to an amount effective, at dosages/amounts and for periods of time necessary, to achieve a desired result, such as a therapeutic or prophylactic result.

[0325] A "therapeutically effective amount" of an agent, *e.g.*, a pharmaceutical formulation, antibody, or cells, refers to an amount effective, at dosages and for periods of time necessary, to achieve a desired therapeutic result, such as for treatment of a disease, condition, or disorder, and/or pharmacokinetic or pharmacodynamic effect of the treatment. The therapeutically effective amount may vary according to factors such as the disease state, age, sex, and weight of the subject, and the populations of cells administered. In some instances, the provided methods involve administering the molecules, cells, and/or compositions at effective amounts, e.g., therapeutically effective amounts.

[0326] A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically but not necessarily, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

[0327] As used herein, a "subject" is a mammal, such as a human or other animal, and typically is human. The diseases and disorders include B cell malignancies, such as B cell leukemias and lymphomas, including B cell chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), pro-lymphocytic leukemias, hairy cell leukemias, common acute lymphocytic leukemias, Null-acute lymphoblastic leukemias, non-Hodgkin lymphomas, diffuse large B cell lymphomas (DLBCLs), multiple myelomas, follicular lymphoma, splenic, marginal zone lymphoma, mantle cell lymphoma, indolent B cell lymphoma, Hodgkin lymphoma. Also among the diseases and conditions are autoimmune and inflammatory diseases, including those associated with inappropriate or enhanced B cell numbers and/or activation. Exemplary diseases and conditions include multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus (SLE).

[0328] In some instances, the subject has persistent or relapsed disease, e.g., following treatment with another CD19-specific antibody and/or cells expressing a CD19-targeting chimeric receptor and/or other therapy, including chemotherapy, radiation, and/or hematopoietic stem cell transplantation (HSCT), e.g., allogenic HSCT. In some instances, the administration effectively treats the subject despite the subject having become resistant to another CD19-targetetd therapy. In some instances, the subject has not relapsed but is determined to be at risk for relapse, such as at a high risk of relapse, and thus the compound or composition is administered prophylactically, e.g., to reduce the likelihood of or prevent relapse.

[0329] In some instances, the treatment does not induce an immune response by the subject to the therapy, and/or does not induce such a response to a degree that prevents effective treatment of the disease or condition. In some aspects, the degree of immunogenicity and/or graft versus host response is less than that observed with a different but comparable treatment. For example, in the case of adoptive cell therapy using cells expressing CARs including the provided anti-CD19 antibodies, the degree of immunogenicity is reduced compared to CARs including a different antibody that binds to a similar, e.g., overlapping epitope and/or that competes for binding to CD19 with the provided antibody, such as a mouse antibody.

[0330] In some instances, the methods include adoptive cell therapy, whereby genetically engineered cells expressing the provided anti-CD19-containing receptors (e.g., CD19-targeted CARs) are administered to subjects. Such administration can promote activation of the cells (e.g., T cell activation) in a CD19-targeted manner, such that the cells of the disease or disorder are targeted for destruction.

[0331] Thus, the provided methods and uses include methods and uses for adoptive cell therapy. In some instances, the methods include administration of the cells or a composition containing the cells to a subject, tissue, or cell, such as one having, at risk for, or suspected of having the disease, condition or disorder. In some instances, the cells, populations, and compositions are administered to a subject having the particular disease or condition to be treated, e.g., via adoptive cell therapy, such as adoptive T cell therapy. In some instances, the cells or compositions are administered to the subject, such as a subject having or at risk for the disease or condition. In some aspects, the methods thereby treat, e.g., ameliorate one or more symptom of the disease or condition, such as by lessening tumor burden in a CD19-expressing cancer.

[0332] Methods for administration of cells for adoptive cell therapy are known and may be used in connection with the provided methods and compositions. For example, adoptive T cell therapy methods are described, e.g., in US Patent Application Publication No. 2003/0170238 to Gruenberg et al; US Patent No. 4,690,915 to Rosenberg; Rosenberg (2011) Nat Rev Clin Oncol. 8(10):577-85). See, e.g., Themeli et al. (2013) Nat Biotechnol. 31(10): 928-933; Tsukahara et al. (2013) Biochem Biophys Res Commun 438(1): 84-9; Davila et al. (2013) PLoS ONE 8(4): e61338.

[0333] In some instances, the cell therapy, e.g., adoptive cell therapy, e.g., adoptive T cell therapy, is carried out by autologous transfer, in which the cells are isolated and/or otherwise prepared from the subject who is to receive the cell therapy, or from a sample derived from such a subject. Thus, in some aspects, the cells are derived from a subject, e.g., patient, in need of a treatment and the cells, following isolation and processing are administered to the same subject.

[0334] In some instances, the cell therapy, e.g., adoptive cell therapy, e.g., adoptive T cell therapy, is carried out by allogeneic transfer, in which the cells are isolated and/or otherwise prepared from a subject other than a subject who is to receive or who ultimately receives the cell therapy, e.g., a first subject. In such instances, the cells then are administered to a different subject, e.g., a second subject, of the same species. In some instances, the first and second subjects are genetically identical. In some instances, the first and second subjects are genetically similar. In some instances, the second subject expresses the same HLA class or supertype as the first subject.

[0335] In some instances, the subject, to whom the cells, cell populations, or compositions are administered is a primate, such as a human. In some instances, the primate is a monkey or an ape. The subject can be male or female and can be any suitable age, including infant, juvenile, adolescent, adult, and geriatric subjects. In some instances, the subject is a non-primate mammal, such as a rodent. In some examples, the patient or subject is a validated animal model for disease, adoptive cell therapy, and/or for assessing toxic outcomes such as cytokine release syndrome (CRS).

[0336] The CD19-binding molecules, such as antibodies and chimeric receptors containing the antibodies and cells expressing the same, can be administered by any suitable means, for example, by injection, e.g., intravenous or subcutaneous injections, intraocular injection, periocular injection, subretinal injection, intravitreal injection, trans-septal injection, subscleral injection, intrachoroidal injection, intracameral injection, subconjectval injection, subconjuntival injection, sub-Tenon's injection, retrobulbar injection, peribulbar injection, or posterior juxtascleral delivery. In some instances, they are administered by parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing and administration may depend in part on whether the administration is brief or chronic. Various dosing schedules include but are not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion.

[0337] For the prevention or treatment of disease, the appropriate dosage of the binding molecule or cell may depend on the type of disease to be treated, the type of binding molecule, the severity and course of the disease, whether the binding molecule is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the binding molecule, and the discretion of the attending physician. The compositions and molecules and cells are in some instances suitably administered to the patient at one time or over a series of treatments.

[0338] Depending on the type and severity of the disease, dosages of antibodies may include about 1 μg/kg to 15 mg/kg (*e.g.* 0.1mg/kg-10mg/kg), about 1 μg/kg to 100 mg/kg or more, about 0.05 mg/kg to about 10 mg/kg, 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg or 10 mg/kg. Multiple doses may be administered intermittently, e.g. every week or every three weeks. An initial higher loading dose, followed by one or more lower doses may be administered.

[0339] In certain instances, in the context of genetically engineered cells containing the binding molecules, a subject is administered the range of about one million to about 100 billion cells and/or that amount of cells per kilogram of body weight, such as, e.g., 1 million to about 50 billion cells (e.g., about 5 million cells, about 25 million cells, about 500 million cells, about 1 billion cells, about 5 billion cells, about 20 billion cells, about 30 billion cells, about 40 billion cells, or a range defined by any two of the foregoing values), such as about 10 million to about 100 billion cells (e.g., about 20 million cells, about 30 million cells, about 40 million cells, about 60 million cells, about 70 million cells, about 80 million cells, about 90 million cells, about 10 billion cells, about 25 billion cells, about 50 billion cells, about 75 billion cells, about 90 billion cells, or a range defined by any two of the foregoing values), and in some cases about 100 million cells to about 50 billion cells (e.g., about 120 million cells, about 250 million cells, about 350 million cells, about 450 million cells, about 650 million cells, about 800 million cells, about 900 million cells, about 3 billion cells, about 30 billion cells, about 45 billion cells) or any value in between these ranges and/or per kilogram of body weight. Again, dosages may vary depending on attributes particular to the disease or disorder and/or patient and/or other treatments.

[0340] In some instances, the cells or antibodies are administered as part of a combination treatment, such as simultaneously with or sequentially with, in any order, another therapeutic intervention, such as another antibody or engineered cell or receptor or agent, such as a cytotoxic or therapeutic agent.

[0341] The cells or antibodies in some instances are co-administered with one or more additional therapeutic agents or in connection with another therapeutic intervention, either simultaneously or sequentially in any order. In some contexts, the cells are co-administered with another therapy sufficiently close in time such that the cell populations enhance the effect of one or more additional therapeutic agents, or vice versa. In some instances, the cells or antibodies are administered prior to the one or more additional therapeutic agents. In some instances, the cells or antibodies are administered after to the one or more additional therapeutic agents.

[0342] Once the cells are administered to a mammal (e.g., a human), the biological activity of the engineered cell populations and/or antibodies in some aspects is measured by any of a number of known methods. Parameters to assess include specific binding of an engineered or natural T cell or other immune cell to antigen, in vivo, e.g., by imaging, or ex vivo, e.g., by ELISA or flow cytometry. In certain instances, the ability of the engineered cells to destroy target cells can be measured using any suitable method known in the art, such as cytotoxicity assays described in, for example, Kochenderfer et al., J. Immunotherapy, 32(7): 689-702 (2009), and Herman et al. J. Immunological Methods, 285(1): 25-40 (2004). In certain instances, the biological activity of the cells also can be measured by assaying expression and/or secretion of certain cytokines, such as CD 107a, IFNγ, IL-2, and TNF. In some aspects the biological activity is measured by assessing clinical outcome, such as reduction in tumor burden or load.

[0343] In certain instances, engineered cells are modified in any number of ways, such that their therapeutic or prophylactic efficacy is increased. For example, the engineered CAR or TCR expressed by the population can be conjugated either directly or indirectly through a linker to a targeting moiety. The practice of conjugating compounds, e.g., the CAR or TCR, to targeting moieties is known in the art. See, for instance, Wadwa et al., J. Drug Targeting 3: 1 1 1 (1995), and U.S. Patent 5,087,616.

C. Diagnostic and Detection Methods

[0344] Also provided are methods involving use of the provided binding molecules, e.g., antibodies, including antibody fragments, and molecules (such as conjugates and complexes) containing one or more of such antibodies, for detection, prognosis, diagnosis, staging, determining binding of a particular treatment to one or more tissues or cell types, and/or informing treatment decisions in a subject, such as by the detection of CD19 and/or the presence of an epitope thereof recognized by the antibody. In some instances, the methods are diagnostic and/or prognostic methods in association with a CD19-expressing disease or condition. The methods in some instances include incubating and/or probing a biological sample with the antibody and/or administering the antibody to a subject. In certain instances, a biological sample includes a cell or tissue or portion thereof, such as tumor or cancer tissue or biopsy or section thereof. In certain instances, the contacting is under conditions permissive for binding of the anti-CD 19 antibody to CD19 present in the sample. In some instances, the methods further include detecting whether a complex is formed between the anti-CD 19 antibody and CD19 in the sample, such as detecting the presence or absence or level of such binding. Such a method may be an in vitro or in vivo method. In one instance, an anti-CD 19 antibody is used to select subjects eligible for therapy with an anti-CD19 antibody or engineered antigen receptor, e.g. where CD19 is a biomarker for selection of patients.

[0345] In some instances, a sample, such as a cell, tissue sample, lysate, composition, or other sample derived therefrom is contacted with the anti-CD19 antibody and binding or formation of a complex between the antibody and the sample (e.g., CD19 in the sample) is determined or detected. When binding in the test sample is demonstrated or detected as compared to a reference cell of the same tissue type, it may indicate the presence of an associated disease or condition, and/or that a therapeutic containing the antibody (e.g., antibody fragment) will specifically bind to a tissue or cell that is the same as or is of the same type as the tissue or cell or other biological material from which the sample is derived. In some instances, the sample is from human tissues and may be from diseased and/or normal tissue, e.g., from a subject having the disease or condition to be treated and/or from a subject of the same species as such subject but that does not have the disease or condition to be treated. In some cases, the normal tissue or cell is from a subject having the disease or condition to be treated but is not itself a diseased cell or tissue, such as a normal tissue from the same or a different organ than a cancer that is present in a given subject.

[0346] Various methods known in the art for detecting specific antibody-antigen binding can be used. Exemplary immunoassays include fluorescence polarization immunoassay (FPIA), fluorescence immunoassay (FIA), enzyme immunoassay (EIA), nephelometric inhibition immunoassay (NIA), enzyme linked immunosorbent assay (ELISA), and radioimmunoassay (RIA). An indicator moiety, or label group, can be attached to the subject antibodies and is selected so as to meet the needs of various uses of the method which are often dictated by the availability of assay equipment and compatible immunoassay procedures. Exemplary labels include radionuclides (*e.g.* ^{125}I, ^{131}I, ^{35}S, ^{3}H, or ^{32}P and/or chromium (^{51}Cr), cobalt (^{57}Co), fluorine (^{18}F), gadolinium (^{153}Gd, ^{159}Gd), germanium (^{68}Ge), holmium (^{166}Ho), indium (^{115}In, ^{113}In, ^{112}In, ^{111}In), iodine (^{125}I, ^{123}I ^{121}I), lanthanium (^{140}La), lutetium (^{177}Lu), manganese (^{54}Mn), molybdenum (^{99}Mo), palladium (^{103}Pd), phosphorous (^{32}P), praseodymium (^{142}Pr), promethium (^{149}Pm), rhenium (186Re, 188Re), rhodium (105Rh), rutheroium (97Ru), samarium (^{153}Sm), scandium (^{47}Sc), selenium (^{75}Se), (^{85}Sr), sulphur (^{35}S), technetium (^{99}Tc), thallium (^{201}Ti), tin (^{113}Sn, ^{117}Sn), tritium (3H), xenon (^{133}Xe), ytterbium (^{169}Yb, ^{175}Yb), yttrium (^{90}Y),), enzymes (*e.g*., alkaline phosphatase, horseradish peroxidase, luciferase, or β-glactosidase), fluorescent moieties or proteins (*e.g*., fluorescein, rhodamine, phycoerythrin, GFP, or BFP), or luminescent moieties (*e.g*., Qdot™ nanoparticles supplied by the Quantum Dot Corporation, Palo Alto, Calif.). Various general techniques to be used in performing the various immunoassays noted above are known.

[0347] For purposes of diagnosis, the antibodies can be labeled with a detectable moiety including but not limited to radioisotopes, fluorescent labels, and various enzyme-substrate labels know in the art. Methods of conjugating labels to an antibody are known in the art.

[0348] In some instances, antibodies need not be labeled, and the presence thereof can be detected using a labeled antibody which binds to any of the antibodies.

[0349] The antibodies provided herein can be employed in any known assay method, such as competitive binding assays, direct and indirect sandwich assays, and immunoprecipitation assays. Zola, Monoclonal Antibodies: A Manual of Techniques, pp. 147-158 (CRC Press, Inc. 1987).

[0350] The antibodies and polypeptides can also be used for *in vivo* diagnostic assays, such as *in vivo* imaging. Generally, the antibody is labeled with a radionuclide (such as ^{111}In, ^{99}Tc, ^{14}C, ^{131}I, ^{125}I, or ^{3}H) so that the cells or tissue of interest can be localized *in vivo* following administration to a subject.

[0351] The antibody may also be used as staining reagent in pathology, e.g., using known techniques.

III. Articles of Manufacture

[0352] Also provided are articles of manufacture containing the provided binding molecules, e.g., antibodies and CARs and/or genetically engineered cells, and/or compositions. The articles of manufacture may include a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container in some instances holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition. In some instances, the container has a sterile access port. Exemplary containers include an intravenous solution bags, vials, including those with stoppers pierceable by a needle for injection. The label or package insert may indicate that the composition is used for treating the CD19-expressing or -associated disease or condition. The article of manufacture may include (a) a first container with a composition contained therein, wherein the composition includes the antibody or engineered antigen receptor; and (b) a second container with a composition contained therein, wherein the composition includes a further agent, such as a cytotoxic or otherwise therapeutic agent. The article of manufacture may further include a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture may further include another or the same container comprising a pharmaceutically-acceptable buffer. It may further include other materials such as other buffers, diluents, filters, needles, and/or syringes.

[0353] As used herein, reference to a "corresponding form" of an antibody means that when comparing a property or activity of two antibodies, the property is compared using the same form of the antibody. For example, if it is stated that an antibody has greater activity compared to the activity of the corresponding form of a first antibody, that means that a particular form, such as a scFv of that antibody, has greater activity compared to the scFv form of the first antibody.

[0354] As used herein, recitation that nucleotides or amino acid positions "correspond to" nucleotides or amino acid positions in a disclosed sequence, such as set forth in the Sequence listing, refers to nucleotides or amino acid positions identified upon alignment with the disclosed sequence to maximize identity using a standard alignment algorithm, such as the GAP algorithm. For example, in some instances, exemplary corresponding residues of a CD19 protein, such as a human CD19 protein, can be identified by alignment of a sequence with an exemplary Vpx sequence set forth in SEQ ID NO:92. By aligning the sequences, one skilled in the art can identify corresponding residues, for example, using conserved and identical amino acid residues as guides. In general, to identify corresponding positions, the sequences of amino acids are aligned so that the highest order match is obtained (see, e.g. : Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York, 1988; Biocomputing: Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part I, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New.Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987; and Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; Carrillo et al. (1988) SIAM J Applied Math 48: 1073).

[0355] "Effector functions" refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g. B cell receptor); and B cell activation.

[0356] The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. In one instance, a human IgG heavy chain Fc region extends from Cys226, or from Pro230, to the carboxyl-terminus of the heavy chain. However, the C-terminal lysine (Lys447) of the Fc region may or may not be present. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991.

[0357] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.

[0358] An "isolated" antibody is one which has been separated from a component of its natural environment. In some instances, an antibody is purified to greater than 95% or 99% purity as determined by, for example, electrophoretic (e.g., SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis) or chromatographic (e.g., ion exchange or reverse phase HPLC). For review of methods for assessment of antibody purity, see, e.g., Flatman et al., J. Chromatogr. B 848:79-87 (2007).

[0359] An "isolated" nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0360] "Isolated nucleic acid encoding an anti-CD 19 antibody" refers to one or more nucleic acid molecules encoding antibody heavy and light chains (or fragments thereof), including such nucleic acid molecule(s) in a single vector or separate vectors, and such nucleic acid molecule(s) present at one or more locations in a host cell.

[0361] The terms "host cell," "host cell line," and "host cell culture" are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include "transformants" and "transformed cells," which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

[0362] As used herein, "percent (%) amino acid sequence identity" and "percent identity" when used with respect to an amino acid sequence (reference polypeptide sequence) is defined as the percentage of amino acid residues in a candidate sequence (e.g., the subject antibody or fragment) that are identical with the amino acid residues in the reference polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[0363] An amino acid substitution may include replacement of one amino acid in a polypeptide with another amino acid. Exemplary substitutions are shown in Table 1. Amino acid substitutions may be introduced into a binding molecule, e.g., antibody, of interest and the products screened for a desired activity, *e.g.*, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

[0364] Amino acids generally can be grouped according to the following common side-chain properties:

(1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;
(2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;
(3) acidic: Asp, Glu;
(4) basic: His, Lys, Arg;

(5) residues that influence chain orientation: Gly, Pro;
(6) aromatic: Trp, Tyr, Phe.

[0365] Non-conservative amino acid substitutions will involve exchanging a member of one of these classes for another class.

[0366] The term "vector," as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as "expression vectors."

[0367] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

[0368] As used herein, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. For example, "a" or "an" means "at least one" or "one or more." It is understood that aspects and variations described herein include "consisting" and/or "consisting essentially of' aspects and variations.

[0369] Throughout this disclosure, various aspects of the claimed subject matter are presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the claimed subject matter. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range. For example, where a range of values is provided, it is understood that each intervening value, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the claimed subject matter. The upper and lower limits of these smaller ranges may independently be included in the smaller ranges, and are also encompassed within the claimed subject matter, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the claimed subject matter. This applies regardless of the breadth of the range.

[0370] The term "about" as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to "about" a value or parameter herein includes (and describes) instances that are directed to that value or parameter *per se.* For example, description referring to "about X" includes description of "X".

[0371] As used herein, a composition refers to any mixture of two or more products, substances, or compounds, including cells. It may be a solution, a suspension, liquid, powder, a paste, aqueous, non-aqueous or any combination thereof.

[0372] As used herein, a statement that a cell or population of cells is "positive" for a particular marker refers to the detectable presence on or in the cell of a particular marker, typically a surface marker. When referring to a surface marker, the term refers to the presence of surface expression as detected by flow cytometry, for example, by staining with an antibody that specifically binds to the marker and detecting said antibody, wherein the staining is detectable by flow cytometry at a level substantially above the staining detected carrying out the same procedure with an isotype-matched control under otherwise identical conditions and/or at a level substantially similar to that for cell known to be positive for the marker, and/or at a level substantially higher than that for a cell known to be negative for the marker.

[0373] As used herein, a statement that a cell or population of cells is "negative" for a particular marker refers to the absence of substantial detectable presence on or in the cell of a particular marker, typically a surface marker. When referring to a surface marker, the term refers to the absence of surface expression as detected by flow cytometry, for example, by staining with an antibody that specifically binds to the marker and detecting said antibody, wherein the staining is not detected by flow cytometry at a level substantially above the staining detected carrying out the same procedure with an isotype-matched control under otherwise identical conditions, and/or at a level substantially lower than that for cell known to be positive for the marker, and/or at a level substantially similar as compared to that for a cell known to be negative for the marker.

[0374] Unless defined otherwise, all terms of art, notations and other technical and scientific terms or terminology used herein are intended to have the same meaning as is commonly understood by one of ordinary skill in the art to which the claimed subject matter pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art.

[0375] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

V. EXAMPLES

[0376] The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

Example 1: Generation and assessment of anti-CD19 antibodies

[0377] Exemplary anti-CD 19 antibodies that specifically bind to CD19-expressing cells with similar binding properties to murine anti-CD 19 reference antibodies, and/or compete for binding with murine anti-CD19 reference antibodies were generated and assessed.

1A. Library Selection, Antibody Generation

[0378] Exemplary anti-CD19 antibodies (scFvs) were generated through a series of selection steps carried out on dsDNA-encoded human naive antibody libraries displayed in a cell-free system. Members of a V_H library were selected for binding to live cells through three successive rounds, enriching for members that bind specifically to stably-transfected CD19-expressing HEK293 cells, but not parental HEK293 cells and/or to CHOK1 cells that did not expresses CD19. At the end of each selection round, three separate elution pools were generated by (a) surface stripping to recover binders from target cells, (b) competitive elution using a murine anti-CD19 antibody, FMC63 IgG, and (c) competitive elution using another murine anti-CD19 antibody, SJ25C1 ((b) and (c) carried out to enrich for binders that compete with FMC63 and/or SJ25C1 for binding to CD19).

[0379] At end of 3 rounds of selections, these enriched V_H libraries were then converted to scFv libraries by shuffling V_H members of these respective pools and a naive human V_L library in V_H-(G4S)$_3$-V_L format. The resulting scFv libraries were subjected to a fourth round, enriching for members that bound specifically to CD19-expressing HEK293 cells and not to parental cells, followed by surface stripping.

[0380] A fifth round was carried out to further enrich for members that bound to other CD19-expressing cells (CD19/K562). Selections were followed by the generation of separate elution pools using either (a) surface stripping, (b) FMC63 competitive elution, or (c) SJ25C1 competitive elution. In a sixth round, these three pools were individually further enriched by negative selection for members that did not bind parental cells (HEK293, twice, K562), followed by positive selection for members that bound CD19-expressing HEK293 cells and immunoprecipitation with an anti-Myc antibody that recognized a C-terminal tag on CD19 expressed on HEK293 cells.

[0381] In one study, forty-eight (48) clones from each of the three R6 scFv resulting pools were sequenced using forward and reverse primers to determine amino acid sequences. 130 of the determined scFv sequences showed full length reading. Convergence was observed among the sequences. Eighteen (18) replicates were identified among the 130 scFv sequences (representing forty-six (46) of the 130 clones). In this study, one V_H portion sequence containing CDRs 1-3 and FRs 1-3 was detected fourteen (14) times in two of the different pools (10 copies from one and 4 copies from another), paired with 5 different V_Ls. Other replicates were identified between 2 and 5 times in different pools; others were single-copy sequences. In another study, additional CD19-binding clones were identified and sequenced. The same V_H portion appeared among them, with different V_L sequences.

1B. Specific Binding to CD19-Expressing Cells

[0382] Binding of the sequenced clones to CD19-expressing and control HEK293 cells, as compared to cells that did not express CD19, was assessed by flow cytometry either with *in vitro* translated crude cell lysate or with bacterially-produced supernatant. Briefly, RNA of each clone was normalized and *in vitro* translated as crude scFv with a C-terminal FLAG tag. CD19-expressing HEK293 and control (mock transfected) HEK293 cells were used in the assay. Binding of the individual scFvs to CD19 and control cells was measured with a secondary anti-FLAG-Alexa647 conjugate. Alternatively, scFv binding pools were cloned into *E.coli* expression vectors and were produced as HIS-tagged scFvs which were detected with anti-HIS-Alexa647 conjugate in flow-cytometric assays. Murine anti-CD19 antibodies (FMC63 scFv and FMC63 IgG) were used as positive controls; a control scFv also was used. Mean fluorescence intensity (MFI) was assessed by flow cytometry. The results are shown in Figures 1A and 1B, demonstrating binding of identified clones to CD19-expressing cells. Among the clones assessed were scFvs, including clones 5, 17, 18 (identified with *in vitro* translated lysates), and 76 (identified with bacterial supernatant), that displayed clear binding preference for CD19-expressing cells as compared to CD19-negative cells.

[0383] As shown in Figures 1A and 1B, for some clones, the fold change in degree of binding detected, in this case as measured by mean fluorescence intensity, to the CD19-expressing cells as compared to the non-CD 19-expressing cells, was about as great, at least as great, or greater than the fold change observed for the positive control reference antibodies, murine anti-CD19 antibodies FMC63 scFv and/or FMC63 IgG. In some cases, the total degree of observed binding to the CD19-expressing cells was approximately the same, at least as great, or greater than that observed for one or more of the positive control reference antibody.

[0384] Four (4) scFv clones that displayed clear binding preference for CD19-expressing cells compared to non-CD19-expressing cells ("clone 18," "clone 17," "clone 5," and "clone 76") were further analyzed. Sequencing revealed that the clones shared common CDR sequences within their V_H sequences, with different V_L sequences and different CDR-Ls. Sequence identifiers corresponding to sequences, including exemplary scFv, V_H, V_L, and CDR (Kabat) amino acid sequences and encoding nucleotide scFv sequences, for the four clones are listed Table 2. A germline variant of clone 18 (deemed "clone 18B") was generated by a cysteine (C) to serine (S) substitution at Kabat position 89; sequences for this clone also are listed in Table 2. Each of the clones had a V_H3 chain sequence. Clone 18 included a light chain framework derived from a Vλ2 sequence (with clone 18B having the Vλ2 germline framework sequence); clones 17 and 76 had Vλ1 sequences, and clone 5 included a Vλ3 sequence. Clones 18 and 17 were derived from multiple branches and libraries, including V_H-V_L shuffling and scFv. Clone 76 was derived from V_H-V_L SJ25C1 competitive elution (Round 6); clone 5 was derived from V_H-V_L FMC63 competitive elution (Round 6).

Table 2: Sequences for Exemplary Clones (SEQ ID NO.)

Clone #	Heavy Chain Variable (VH) Region (Amino Acid)	Light Chain Variable (VL) Region (Amino Acid)	ScFv Sequence (Amino Acid, Nucleotide)	CDR-H (1,2,3) (Kabat) (Amino Acid)	CDR-L (1,2,3) (Kabat) (Amino Acid)
5	12	17	10	18, 19, 20	31, 32, 33
17	12	15	6	18, 19, 20	25, 26, 27
18	11	13	2	18, 19, 20	21, 22, 23
18B	11	14	4	18, 19, 20	21, 22, 24
76	11	16	8	18, 19, 20	28, 29, 30

1C. Binding Affinities, Competition with Reference Antibodies

[0385] Clones 5, 17, 18, 18B, and 76, were purified by single-step purification and purification assessed via SDS gel. A gel from an exemplary study is shown in Figure 2 (lanes 1 and 2=clone 5, non-reduced, reduced; lanes 3 and 4=clone 17, non-reduced, reduced; lanes 5 and 6=clone 18, non-reduced and reduced; lanes 7 and 8=clone 76, non-reduced and reduced). In this study, isoelectric points were measured as 5.36, 5.32, 7.11, and 5.32, respectively for clones 5, 17, 18, and 76.

[0386] Melting temperature (T_m) measurements were made using BioTad CFX96 instrument to analyze sypro orange protein incorporation at incremental temperatures, revealing similar T_m values as those observed for the reference antibody FMC63 scFv. The results are presented in Table 3.

Table 3: Assessment of T_m

Clone, Condition	T_m (°C)
5, Imidazole	53
5, pH 6	61
5, pH 7	57
5, pH 8	57
17	51
18	59
18B	59
FMC63 scFv	56

[0387] Clones were titrated, and their binding affinities (EC_{50}) to CD19-expressing K562 cells assessed by flow cytometry, with a reference murine CD19 antibody, FMC63 scFv, used as a positive control. Results from three separate assays, each including and comparing other binding affinities to that for clone 18, are shown in Figures 3A-3C.

[0388] In the assay the results of which are shown in Figure 3A, EC_{50} values for clone 18, clone 17, another clone identified by the study (deemed clone 192; see sequences in Table 6), and the reference antibody (FMC63 scFv) were measured as 3.79 nM, 14.86 nM, 12.80 nM, and 7.37 nM, respectively. In the assay the results of which are shown in Figure 3B, EC_{50} values for clone 18, clone 18B, and clone 76 were measured as 7.1 nM and 9.3 nM, and 7.9 nM, respectively. In the assay the results of which are shown in Figure 3C, EC_{50} values for clone 18 and clone 76 were measured as 4.1 nM and 8.8 nM respectively.

[0389] Thus, each of the clones assayed specifically bound to the CD19-expressing cells with affinities similar to that of the reference antibody, e.g., having EC50s about the same as or lower than that of the reference antibody, or no more than about 1.5-fold or no more than about 2-fold, or no more than about 3-fold greater than the EC_{50} of the reference antibody.

[0390] In another assay, clones 18, 5, 17, other clones identified (161, 170, 1 (see sequence information in Table 6)), and the positive control reference antibody FMC63 scFv (one plate) and clone 18, other clones identified (177, 184, 192, 198), and the positive control reference antibody FMC63 scFv (another plate) were assessed by the same assay. Results are presented in Figure 4. EC_{50} values observed for the two plates are presented in Tables 4A and 4B. As shown, clones were observed to have comparable binding affinities with that of the reference antibody.

Table 4A

	Clone 18	Clone 5	Clone 17	Exemplary Additional Clones (clones 161,170, 1)	FMC63 scFv
EC_{50} (nM)	4.79	15.84	8.32	52.26, 96.68, 213.80	5.06

Table 4B

	Clone 18	Exemplary Additional Clones (clones 177, 184, 192, 198)	FMC63 scFv
EC_{50} (nM)	3.11	53.33, 113.90, 12.02, 13.21	5.83

[0391] Competition binding assays were performed to assess competition of various antibodies for binding to CD19-expressing cells. In one assay, binding of 0.5nM (~EC_{50}) FITC-labeled SJ25C1 to Ramos cells was assessed in the presence or absence of various concentrations of unconjugated competitor FMC63 IgG or a control IgG; binding was assessed by flow cytometry (mean fluorescence intensity). The results are shown in Figure 5A, indicating that FMC63 IgG competed for binding to CD19 with SJ25C1 IgG1 in this study, suggesting that SJ25C1 and FMC63 bound to overlapping epitopes e.g., a common epitope, of CD19. In another assay, CD19-expressing cells were incubated with labeled FMC63 IgG in the presence of various concentrations of (or absence of) clone 18 scFv, FMC63 scFv (positive control) and a control scFv (negative control). Results are shown in Figure 5B. As shown, both the clone 18 scFv and FMC63 scFv (but not the negative control scFv) were observed to compete with the FMC63 IgG for binding to CD19-expressing cells, with comparable IC_{50} values (24.0 nM and 19.8 nM, respectively), indicating that clone 18 bound to an epitope of CD19 that overlaps with the epitope recognized by FMC63, and competed for binding with the reference antibody to a similar degree.

[0392] In another assay, 10 nM (EC_{50}) Alexa647-labeled FMC63 scFv was incubated with CD19-expressing K562 cells in the presence or absence of varying concentrations of clone 18 scFv, clone 18B scFv, clone 17 scFv, clone 76 scFv, a reference antibody (FMC63 scFv) and a negative control antibody (R12). Results are presented in Figure 6. The clones and reference antibody, but not the negative control antibody, displayed competition for binding to CD19 with the FMC63 scFv, and competition by the reference antibody with itself was similar to competition observed for the tested clones.

[0393] Collectively, in a number of studies, the following EC_{50} (binding affinity) and IC_{50} (competition) values were observed for the various clones, as listed in Table 5. As shown, among the identified human CD19 antibodies were those having similar degrees of binding affinity for CD19 and similar degrees of competitive inhibition for a murine anti-CD 19 reference antibody, as compared to the reference antibody itself, for example, about the same, less than, or no more than 1.5-fold, 2-fold, or 3-fold greater EC_{50} and/or IC_{50}.

Table 5: Summary of Data from Exemplary Binding Studies		
Clone/Antibody	**EC_{50} (CD19-Expressing Cells) (nM)**	**IC_{50} (nM) (competition for binding with FMC63)**
Clone 18	4.1 ± .57 (n=7)	20.1 ± 9.8 (n=3)
Clone 18B	5.4 ± 1.3 (n=5)	28 (n=1)
Clone 76	8.04 ± 0.3	18.2 ± 1.5 (n=2)
Clone 17	11.7 ± 1.9	35.4 ± 3.9 (n=2)
Clone 5	15.8 (n=1)	50 (n=1)
FMC63	6.1 ± 1.2 (n=6)	20.5 ± 6.7 (n=3)

ID. Size Exclusion Chromatography

[0394] Biophysical properties of clone 18B were assessed via size-exclusion chromatography. A HiLoad 16/600 Superdex 200 column was calibrated and Bio-Rad gel filtration standard 150-1901 kDa proteins were injected, and fractions collected at 1.5 mL/min to generate references. 770 ug of clone 18B scFv was injected into the column and fraction collected under the same conditions. The results are shown in Figure 7 (Figure 7A=standard; Figure 7B=Clone 18B). The results for clone 18B scFv revealed a single peak, with minimal large size aggregates observed.

Example 2: Generation and assessment of additional anti-CD19 antibodies

[0395] Additional exemplary anti-CD19 antibodies (scFv fragments) having similar binding properties to (and/or that compete for binding with) murine anti-CD19 reference antibodies were generated and assessed.

2A. Library Selection, Antibody Generation

[0396] Additional exemplary anti-CD 19 scFvs were generated by two different selection approaches, each involving a series of selection steps carried out on dsDNA-encoded human antibody libraries displayed in a cell-free system.

[0397] In one approach (deemed "clone 18 CDR3 grafting"), a heavy chain CDR3 (CDR-H3) sequence present in clones identified in Example 1 (SEQ ID NO: 20, DQGYHYYDSAEHAFDI) was grafted into human naive V_H library frameworks. Members of the resulting CDR3-grafted V_H library were shuffled with members of a naive human V_L library to generate an scFv library as V_H-(G4S)3-V_L format. The resulting scFv library was subjected to three rounds of selection, to enrich for members that bound specifically to CD19-expressing HEK293 cells and not to parental cells, followed by surface stripping for round (R1), immunoprecipitation and off-rate for round 2 (R2).

[0398] In another approach (deemed "FMC63 guided selection"), two initial scFv libraries were generated, respectively, by (a) shuffling members of a naive V_H library with the V_L region of FMC63 and (b) shuffling members of a naive V_L library with the V_H region of FMC63. After two and three rounds of selection, respectively, to enrich the library members from (a) and (b) for CD19-binding with the guidance of the parental FMC63 V_H or V_L. The binding molecules were eluted off by surface stripping from CD19/HEK293 cells (R1) and FMC63 elution from CD19/K562 cells (R2 and R3). A third scFv library was generated by shuffling the V_H sequences from the selection in (a) with the V_L sequences resulting from the selection in (b). Three further rounds of selection were carried out on CD19/HEK293 cells with surface stripping (R1), followed by CD19/K562 cells with FMC63 elution (R2) and CD19/HEK293 cells with immunoprecipitation (R3). Binding by the selected scFv clones to CD19-expressing cells was confirmed by flow cytometry using bacterially-produced supernatant. The selected scFv pools were cloned into *E.coli* expression vectors and produced as HIS-tagged scFvs. Binding of individual clones to CD19-transfected HEK293 cells was detected with anti-HIS-Alexa647 conjugate by flow cytometry. Clone 18 or Clone 18B were used as positive controls, along with various negative controls. The results are shown in Figures 8A-C (MFI=mean fluorescence intensity).

[0399] The results shown in Figure 8D confirm CD19-specific binding by an exemplary twenty-three (23) of the hits (marked with asterisks in Figures 8A-C, representing 4 hits identified via the CDR3 grafting approach and 19 via FMC63-guided selection). Binding of *in vitro*-translated FLAG-tagged scFvs to CD19-expressing K562 cells, as compared to control (mock transfected) K562 cells, was assessed by flow cytometry as described in Example 1. As shown, the clones specifically bound to CD19-expressing cells.

[0400] These and additional CD19-specific scFv clones generated by the selection approaches in Examples 1 and 2 were further assessed. Sequencing revealed several CD19-specific binding antibodies (scFvs) with various different light chain sequences and sharing a common CDR-H3 sequence (SEQ ID NO: 20) also present in scFvs described in Example 1. Sequence identifiers corresponding to various sequences of additional CD19-binding scFvs are listed in

Table 6, including for scFv, V_H, V_L, and CDR (Kabat) amino acid sequences (and the encoding scFv nucleotide sequences). Among the CD19-specific scFv clones were those having several different light chain variable and CDR sequences, some of which had CDR-H1, CDR-H2, and/or CDR-H3 present in SEQ ID NO: 11, CDR-H1, CDR-H2, and/or CDR-H3 having sequences of SEQ ID NOs: 18,19, and/or 20, and/or CDR-H1, CDR-H2, and/or CDR-H3 having sequences of 18, 72, and 20. Each of the clones listed in Table 6 was derived from a human V_H3 framework (with kappa and lambda gene V segments from which the clones are derived indicated).

Table 6: Sequences for Exemplary Clones (SEQ ID NO.)						
Clone #	**Heavy Chain Variable (V_H) Region (Amino Acid)**	**Light Chain Variable (V_L) Region (Amino Acid)**	**ScFv Sequence (Amino Acid, Nucleotide)**	**CDR-H (1,2,3) (Kabat) (Amino Acid)**	**CDR-L (1,2,3) (Kabat) (Amino Acid)**	**Light Chain Framework Derived From**
488	63	71	45, 44	18, 72, 20	80, 100, 109	Vκ3
1304	62	68	47, 46	18, 72, 20	77, 97, 106	Vκ1
285	11	65	49, 48	18, 19, 20	74, 94, 103	Vλ2
192B	60	64	51,50	18, 19, 20	73, 93, 101	Vλ2
328	61	66	53, 52	18, 19, 20	75, 95, 104	V12
227	63	70	55, 54	18, 72, 20	79, 99, 108	Vκ1
1300	62	69	57, 56	18, 72, 20	78, 98, 107	Vκ1
1	12	67	59, 58	18, 19, 20	76, 96, 105	Vλ1
192	12	91	87, 86	18, 19, 20	73, 93, 102	Vλ2
241	63	90	89, 88	18, 72, 20	77, 97, 106	Vκ1

2B. Purification and Assessment

[0401] Clones described above, including clones listed in Table 6 and/or described in Example 1, were purified by single-step purification and purification assessed via SDS gel. The results are presented in Figure 9 (lane 1=MW marker; lanes 2, 9, and 10=clone 5 (1530, 2880, 1130 μg/mL); lane 3=clone 18B (660 μg/mL); lanes 4, 11, 12, and 13=clone 17 (300, 1060, 180, 1440 μg/mL); lane 5=clone 192B (1580 μg/mL); lanes 6 and 14=clone 76 (1340, 3220 μg/mL); lane 7=clone 835 (470 μg/mL); lane 8=clone 488 (340 μg/mL)). Melting temperature (T_m) measurements were made as described in Example 1, revealing similar T_m values as those observed for the reference antibody and clones in Example 1 (Table 7).

Table 7: Assessment of T_m	
Clone	**T_m (°C)**
5	58
18B	57
17	52
192B	64
76	51/59
488	63
285	68
227	60

[0402] Various clones were titrated and their binding affinity (EC50) to various CD19-expressing cells assessed by flow cytometry. The FMC63 scFv reference antibody was used as a positive control. The results from five separate assays assessing binding affinities for various CD19-specific scFv clones are shown in Figures 10A-10E. As shown, the selections resulted in several CD19-specific scFv clones with various binding affinities and a range of saturatable binding activity.

[0403] Competition binding assays were performed as described in Example 1 to assess the ability of various identified antibodies (scFv clones) to compete for binding with a murine reference antibody for binding to CD19-expressing cells. In one example, CD19-expressing cells were incubated with 10 nM labeled FMC63 scFv in the presence of various concentrations of the indicated scFv clones having different light chain sequences and sharing a common heavy chain CDR3 (or FMC63 scFv (positive control)). The results, shown in Figure 11, demonstrated that the clones competed with FMC63 scFv for binding to CD19-expressing cells, with various IC_{50} values. Similar studies were carried out to assess properties of other clones identified in the screening approaches described in Examples 1 and 2. EC_{50} (binding affinity) and IC_{50} (competition) values observed for various CD19-binding antibodies (scFvs) are listed in Table 8. CDR-L3 sequences for clones 79, 835, 184, 505, 506, and 305 are set forth as SEQ ID NOs: 116, 117, 118, 119, 120, 121, and respectively.

Table 8: Results from Various Binding and Competition Assays

Clone/Antibody	EC_{50} (CD19-Expressing Cells) (nM)	IC_{50} (nM) (competition for binding with FMC63)
Clone 18B	4.9 ± 0.8 (n=7)	32.9± 3.2 (n=3)
Clone 17	11.6 ± 1.1 (n=5)	35.4 ± 3.9 (n=2)
Clone 76	7.0 ± 1.4 (n=5)	18.2 ± 1.5 (n=2)
Clone 5	15.8 (n=1)	50 (n=1)
Clone 192B	7.7 ± 1.4 (n=3)	15.7 ± 2.5 (n=3)
Clone 488	2.9 ± 0.4 (n=4)	6.1 ± 0.7 (n=6)
Clone 79	65.7 (n=1)	102.5 (n=1)
Clone 835	71.8 (n=1)	>200
Clone 184	113.9 (n=1)	N/A
Clone 505	138.9 (n=1)	N/A
Clone 506	179.3 (n=1)	N/A
Clone 1	213.8 (n=1)	N/A
Clone241	5.2 ± 0.1 (n=2)	14.6 ± 2.7 (n=3)
1300	1.3 ± 0.1 (n=3)	3.9 ± 0.5 (n=2)
227	31.8 ± 5.3 (n=3)	56.1 ± 3.9 (n=2)
285	2.5 ± 0.5 (n=4)	9.4 ± 1.4 (n=3)
305	32.2 ± 6.9 (n=2)	> 500 (n=2)
328	10.9 ± 4.6 (n=4)	32.9 (n=1)
FMC63	6.0 ± 0.8 (n=9)	15.0 ± 2.8 (n=10)

[0404] Among the identified human CD19 antibodies (scFv fragments), many demonstrated similar or greater degrees of binding affinity (e.g., similar or lower EC_{50} values) for CD19 as compared to a murine anti-CD 19 reference antibody, FMC63. Many also demonstrated similar or greater degrees of competition (e.g., similar or lower IC_{50} values) with a murine anti-CD19 reference antibody for CD19 binding, as compared to the reference antibody's ability to compete with itself.

[0405] For example, clones were observed with EC_{50} values that were less than, about the same as, or no more than at or about 1.5-fold greater, 2-fold greater, or 3-fold greater than those for the reference antibody. Likewise, several of the identified anti-CD19 antibodies (scFvs) were observed to compete with labeled FMC63 scFv for binding to CD19-expressing cells with IC_{50} values that were lower than the IC_{50} values observed for FMC63 scFv, about the same as the IC_{50} values observed for FMC63, or no more than 1.5-fold or 2-fold or 3-fold higher (e.g., a degree of competition that is no more than 1.5-fold or 2-fold or 3-fold lower than the competition by the reference antibody). The results indicated that these studies identified a plurality of antibodies that bind to an epitope of CD19 that overlaps with the epitope specifically bound by FMC63.

Example 3: Generation of Chimeric Antigen Receptors (CARs) Against CD19 and Engineering of Cells Expressing Such CARs

[0406] Various exemplary chimeric antigen receptors (CARs) were generated, with antigen-binding regions containing human anti-CD 19 scFvs as described in Example 1. Specifically, nucleic acid molecules were generated that encoded CARs with scFvs (in the VH-VL format) derived from the following clones and having the amino acid sequences set forth in the indicated sequence identifiers: Clone 18 (SEQ ID NO:2), Clone 18B (SEQ ID NO:4), Clone 17 (SEQ ID NO:6), Clone 76 (SEQ ID NO: 8), and Clone 5 (SEQ ID NO: 10). Additionally, for each clone, constructs encoding a CAR having the same VH and VL sequences, but present in the reverse orientation (VL-VH), also were generated. A CAR containing a murine anti-CD19 scFv derived from FMC63 (in the VH-VL orientation) was used as a control. Each CAR further contained an Ig-derived spacer; a human CD28-derived transmembrane domain; a human 4-1BB-derived intracellular signaling domain; and a human CD3 zeta-derived signaling domain, a truncated EGFR (EGFRt) sequence, for use as a transduction marker, separated from the CAR sequence by a self-cleaving T2A sequence.

[0407] Primary human T cell populations expressing the various CARs were generated. Nucleic acid molecules encoding each CAR were individually cloned into a lentiviral vector, which was used to transduce CD4+ and CD8+ T cells in populations isolated from human PBMC samples obtained from healthy donors (essentially as described by Yam et al. (2002) Mol. Ther. 5:479; WO2015/095895).

[0408] After transduction and expansion, staining with anti-EGFR antibody was used to verify expression of the EGFRt transduction marker on the surface of CD4+ and CD8+ T cells by flow cytometry. Figure 12A provides representative results for expression of the various CARs in CD8+ cells; similar results were observed for CD4+ cells. CAR protein expression was confirmed by western blotting using an anti-CD247 (CD3 zeta) antibody (which in each case detected a band at approximately 50 kD, representing the CAR, and a band at approximately 18 kDa, representing the endogenous CD3 zeta chain present in the cells) (Figure 12B). The results demonstrated comparable degrees of transduction and CAR protein expression for each of the various human scFv-containing CAR constructs (including VH-VL and VL-VH orientations) and control (murine, FMC63-derived) CAR constructs in primary T cell populations. No EGFRt expression was detected in cells not subjected to transduction. Results from western blotting confirmed that the CAR derived from clone 76, in the VH-VL orientation, was present in different glycosylation forms.

[0409] As shown in Figure 12A, T cell populations were successfully enriched for transduced cells (at or close to 100 % EGFRt+ as confirmed by flow cytometry) by staining with an anti-EGFR antibody, sorting on a flow cytometer, and stimulation in the presence of irradiated (8,000 rad) cells from a CD19+ B-lymphoblastoid cell line (B-LCL) essentially as described by Yam et al. (2002) Mol. Ther. 5:479; WO2015/095895.

Example 4: Assessing Effector Functions of T cells Engineered to Express anti-CD19 Chimeric Antigen Receptor (CAR) In Vitro

[0410] Genetically engineered human T cells (either CD8+ or CD4+) expressing various CARs containing human anti-CD19 scFvs, produced as described in Example 3, were assessed for various responses following co-culture with CD19-expressing cells.

A. Cytolytic Activity

[0411] CD19-expressing target cells were incubated with CD8+ T cells expressing the various CARs and separately with cells transduced with EGFRt alone (negative control). Following incubation, lysis of target cells was monitored. Specifically, lysis of CD19-transduced K562 cells (K562/CD19), Raji (CD19+ B cell lymphoma line) cells, and non-transduced K562 control cells (negative control) (Figure 13A) and primary human chronic lymphocytic leukemia cells (CLL; Figure 13B) were tested.

[0412] The target cells (K562/CD19 Raji non-transduced K562 control cells or CLL) were labeled overnight with ^{51}Cr. Labeled cells were washed and incubated in triplicate with effector T cells (CAR-expressing and negative control CD8+ cells) at an effector to target (E:T) ratio of 30:1. To measure spontaneous lysis, target cells were incubated with an equal volume of media but without effector cells and maximum lysis was determined following incubation of target cells with detergent to completely lyse the target cells. Supernatants were harvested for γ-counting after a 4 hour incubation. The percent specific lysis for the experimental conditions was calculated as:

[(Experimental Release – Spontaneous Release)/ (Maximum Release – Spontaneous Release)] x 100.

[0413] The results are set forth in Figure 13A and 13B. As shown in Figure 13A, engineered CD8+ T cells expressing the various human anti-CD 19 scFv-containing CARs exhibited antigen-specific cytolytic activity against CD19+ cells, to a comparable degree as cells expressing CARs containing the murine anti-CD19 (FMC63) scFv. This cytotoxic activity was not observed against control K562 cells not expressing CD19. The degree of cytolytic activity observed for cells expressing CARs with the human scFvs in the VH-VL orientation (HL) was observed to be comparable or greater than that observed for cells expressing the murine scFv-containing CAR. The degree of cytolytic activity observed for cells expressing a CAR with a given human scFv in the VH-VL (HL) orientation was generally greater than that observed for cells expressing a CAR with the corresponding scFv in the reverse VL-VH orientation (LH). As shown in Figure 13B, the results also demonstrated antigen-specific cytolytic activity against the primary human CLL cells by the engineered CD8+ cells expressing the various human anti-CD19 scFv-containing CARs (VH-VL orientation) also was observed.

B. Cytokine Release

[0414] Cytokine release was assessed following incubation of the CAR-expressing cells with antigen-expressing and control target cells. Transduced CD8+ and CD4+ T cells were co-cultured in triplicate with target cells (K562, K562/CD19, Raji) at an effector to target (E:T) ratio of 2:1. Cytokine secretion following co-culture of transduced CD8+ cells with primary human chronic lymphocytic leukemia cells (CLL) also was similarly tested. The co-cultured cells were incubated for about 24 hours, and then supernatants were collected for measurement of IFN-γ (CD8+ cells) or IFN-γ, TNF-α, or IL-2 (CD4+ cells) using a multiplex cytokine immunoassay (Luminex®).

[0415] The results for CD8+ cells are set forth in Figures 14A and 14B. Engineered CD8+ T cells expressing the various human anti-CD19 scFv-containing CARs were observed to secrete IFN-γ in an antigen-specific manner following incubation with CD19+ cells, to a comparable degree as that observed for cells expressing CARs containing the murine anti-CD19 (FMC63) scFv. The cytokine secretion was not observed following incubation control K562 cells not expressing CD19. The levels of cytokine secretion observed for cells expressing CARs with the tested human anti-CD19 scFvs in the VH-VL orientation were comparable and in some cases greater than that observed for cells expressing the murine anti-CD19 scFv-containing CAR. The degree of IFNy secretion observed for cells expressing a CAR with a given human scFv in the VH-VL orientation was generally greater that observed for cells expressing a CAR with the corresponding scFv in the reverse (VL-VH) orientation. As shown in Figure 14B, antigen-specific cytokine secretion by CD8+ engineered T cells expressing the various human anti-CD19 scFv-containing CARs (VH-VL orientation) also was observed following co-culture with the CLL cells.

[0416] The results for CD4+ CAR-expressing T cells are set forth in Figure 15. Engineered CD4+ T cells expressing the various human anti-CD19 scFv-containing CARs (VH-VL orientation) were observed to secrete cytokines in an antigen-specific manner following incubation with CD19+ target cells, at levels comparable to and in general greater than those observed for cells expressing the murine-scFv (FMC63)-containing CAR. The cytokine secretion was not observed following CD19-negative control cells.

C. T Cell Proliferation

[0417] Proliferation of the various CAR-expressing T cells following incubation with CD19-expressing target cells was assessed by flow cytometry. CD8+ or CD4+ CAR-expressing T cells were labeled with 0.2 μM carboxyfluorescein succinmidyl ester (CFSE). Cells were washed and incubated for 72 hours in triplicate with target cells (K562, K562/CD19 or Raji) in serum-containing medium without exogenous cytokines. Division of live T cells was indicated by CFSE dilution, as assessed by flow cytometry.

[0418] The results are set forth in Figure 16A and 16B for CD8+ CAR-expressing T cells and CD4+ CAR-expressing T cells, respectively. As shown in Figure 16A, CD8+ T cells expressing each of the tested human anti-CD 19 scFv-containing CAR constructs proliferated after co-culture with CD19-expressing K562/CD19 or Raji target cells, but generally not with K562 control cells. The degree of proliferation observed for T cells expressing CARs with the tested human anti-CD 19 scFv was comparable to that observed for cells expressing the murine anti-CD19 scFv-containing CAR. The degree of proliferation of cells expressing a CAR with a given human scFv in the VH-VL orientation was generally observed to be greater than observed for cells expressing a CAR with the corresponding scFv in the reverse (VL-VH) orientation.

[0419] Antigen-specific proliferation of CAR-expressing T cells also was observed for CD4+ cells. As shown in Figure 16B, CD4+ T cell expressing each of the tested human anti-CD19 scFv-containing CAR constructs proliferated after co-culture with CD19-expressing K562/CD19 or Raji target cells. The degree of proliferation observed for CD4+ T cells expressing CARs with the tested human anti-CD19 scFv was comparable to that observed for cells expressing the murine anti-CD19 scFv-containing CAR.

Example 5: Anti-Tumor Effect of CAR-Expressing T cells After Adoptive Transfer *In Vivo*

[0420] The anti-tumor effects of CAR-expressing engineered primary human T cells was assessed by monitoring tumors following adoptive transfer of cells to patient-derived xenograft (PDX) tumor model animal subjects. Six- to eight-week old female NOD.Cg.Prkdc^{scid}IL2rg^{tm1Wjl}/SzJ (NSG) mice were injected intravenously (i.v.) with 0.5 x 10^6 Raji lymphoma tumor cells transfected with firefly luciferase (Raji-ffluc). Tumor engraftment was allowed to occur for 6 days and verified using bioluminescence imaging. On day 7, mice received a single intravenous (i.v.) injection of a sub-optimal dose (1 x 10^6 CAR-expressing T cells in this study) of the various engineered primary human T cells (CD8+ cells alone (Figure 17A) or combined CD4+ and CD8+ cells at a 1:1 ratio (Figure 17B)) described in Example 3. As a control, mice were administered cells that were transduced with EGFRt alone (negative control). The sub-optimal dose was used in order to better visualize differences in anti-tumor effects.

[0421] Anti-tumor activity of the adoptively transferred CAR-expressing cells was monitored by bioluminescence imaging on days 6, 9, 13, 20 27 and 34. For bioluminescence imaging, mice received intraperitoneal (i.p.) injections of luciferin substrate (CaliperLife Sciences, Hopkinton, MA) resuspended in PBS (15 μg/g body weight). Mice were anesthetized and imaged essentially as described in WO2015/095895. The average radiance (p/s/cm^2/sr) was determined.

[0422] As shown in Figures 17A and 17B, tumors in control mice continued to grow over the course of the study following adoptive transfer of control T cells (CD8+ cells alone (Figure 17A) or combination of CD4+ and CD8+ cells (Figure 17B) transduced with EGFRt alone). Compared to the control mice, mice having been administered adoptive transfer of engineered T cells expressing each of the various tested anti-CD19 scFv-containing CARs were observed to have a lower degree of bioluminescence signal, indicating a reduction in tumor size over time and/or a lower degree of tumor growth in the treated animals. In general, as shown in Figure 17A, adoptive transfer of CD8+ T cells expressing the tested human anti-CD 19 scFv CARs alone led to a comparative reduction in tumor size to at least the same degree as adoptive transfer of cells expressing a CAR containing the mouse anti-CD19 scFv (FMC63). As shown in Figure 17B, adoptive transfer of the combination of CD8+ and CD4+ T cells expressing the tested human anti-CD19 CARs was observed to reduce tumor size over time. Tumor size (as indicated by bioluminescence signal) following adoptive transfer of such human anti-CD19 CAR-expressing cells was observed to be comparatively lower than that detected following adoptive transfer of the mouse-scFv-derived CAR-expressing cells.

EXAMPLE 6: Identification of Region in Human CD19 Recognized by anti-CD19 antibodies

[0423] CARs containing certain anti-CD19 antibodies (scFvs) described in Example 1, or the murine anti-CD19 (FMC63) scFv, were assessed for binding to various CD19 molecules. K562 cells were engineered to express (a) a human CD19 (having the amino acid sequence set forth in SEQ ID NO:92), (b) a *Macaca mulatta* (rhesus macaque (rhesus)) CD19 (having the amino acid sequence set forth in SEQ ID NO:139; Accession No. F7F486), or (c) one the three different human/rhesus chimeric CD19 molecules, VI, V2, and V3, which contained membrane-proximal regions having the sequences depicted in Figure 18A. Aside from the region depicted in Figure 18A, the remaining regions of each chimeric molecule were identical in sequence to the corresponding regions of the rhesus CD19.

[0424] **Chimeric CD19 V1:** The 74-amino acid membrane-proximal region depicted in Figure 18A of the chimeric molecule designated V1 had the amino acid sequence set forth in SEQ ID NO: 140, which was identical to the sequence of the corresponding region (residues 218 to 291) of the human CD19 molecule having the sequence set forth in SEQ ID NO: 92.

[0425] **Chimeric CD19 V2:** The 75- amino acid membrane-proximal region depicted in Figure 18A of the chimeric CD19 molecule designated V2 had the amino acid sequence set forth in SEQ ID NO: 141. Within this region, the 27-amino acid membrane-proximal portion was identical in sequence to the corresponding portion (residues 265 to 291) of human CD19. The remaining portion of the shown region was identical in sequence to the corresponding portion of the rhesus CD19 sequence set forth in SEQ ID NO: 139. Positions in this remaining portion having a substitution or an insertion compared to the corresponding human sequence are underlined.

[0426] **Chimeric CD19 V3:** The 74- amino acid region depicted in Figure 18A of the chimeric CD19 molecule designated V3 had the amino acid sequence set forth in SEQ ID NO: 142. Within this depicted region, a 47-amino acid portion was identical in sequence to the corresponding portion (residues 218-264) of the human CD19 sequence set forth in SEQ ID NO: 92. The remaining 27-amino acid membrane-proximal portion was identical in sequence to the corresponding portion of rhesus CD19 sequence set forth in SEQ ID NO: 139. Positions in this remaining 27-amino acid portion having a substitution compared to the corresponding human sequence are underlined.

[0427] Primary human T cells expressing various human anti-CD19 scFv-containing CARs or a murine anti-CD19 scFv (FMC63)-containing CAR were generated as described in Example 3 and co-cultured with the various K562 target cells transfected with nucleic acid molecules encoding the various CD19 molecules, at an effector to target (E:T) ratio of 2:1. The cells were incubated for 24 hours, and supernatants were collected for measurement of IFN-γ, using a cytokine immunoassay, as an indicator of functional binding by the anti-CD 19 scFv-containing CARs to the respective CD19 molecules on the surface of the target cells. The results are shown in Figure 18B.

[0428] Each of the tested anti-CD19 CARs exhibited detectable levels of cytokine following co-culture with cells expressing the human CD19 molecule (indicating functional binding thereto), but not following co-culture with cells expressing the rhesus CD19. For each of the tested anti-CD19 CARs, detectable levels of secretion were observed following co-culture with cells expressing the rhesus/human chimeric molecules designated V1 (entire membrane-proximal 74-amino acid region human-derived) and V3 (27-amino acid membrane-proximal portion rhesus-derived), but not to cells expressing the rhesus/human chimeric molecule designated V2 (27-amino acid membrane-proximal portion human-derived).

[0429] These results indicated that at least part of a 32-amino acid portion (SEQ ID NO: 143 (HPKGPKSLLSLELKDDRPARDMWVMETGLLLP) of the human CD19 molecule (corresponding to residues 218-249 of SEQ ID NO: 92), was important for functional binding to CD19 by each of the tested anti-CD19 CARs. Specifically, whereas each of V1 and V3 contained this 32-amino acid sequence (set forth in bold in Figure 18A), the corresponding portion of V2 contained the 33-residue amino acid sequence set forth in SEQ ID NO: 144 (RPKGPKSSLLSLELKDDRPDRDMWVVDTGLLLT), which was identical in sequence to the corresponding portion of the rhesus CD19 molecule, but contained five amino acid substitutions (at positions 218, 236, 242, 243, and 249 of the human CD19 sequence of SEQ ID NO: 92) and one insertion (between positions 223 and 224 of the human CD19 sequence of SEQ ID NO: 92) compared with the corresponding human sequence, each underlined in Figure 18A. Thus, the results indicate that the amino acid(s) present at at least one of these position(s) in the human sequence (positions 218, 236, 242, 243, 249 and/or 223-224 of SEQ ID NO: 92) was important for the ability of each CAR tested to specifically bind to human CD19. Thus, the results support a conclusion that each of the tested human scFv-containing CARs bound to a similar and/or overlapping epitope as compared to the CAR containing the mouse scFv, FMC63.

SEQUENCES

TABLE 9

SEQ ID NO.	Sequence	Description
1	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGGATAGGCTATGCGGACTCTGTAAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTTTCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAGTGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGCAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCC GGCTTTCCTGGACAATCAGTCACCATCTCCTGCACTGGAACCACCAGTGAT GATGTCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAACTTATGCT TTATGATGTCAGTAAGCGGCCCTCCGGGGTCCCTCATCGCTTCTCTGGCTC CAGGTCTGGCAGAGCGGCCTCCCTGATCATCTCTGGGCTCCAGACTGAGG ATGAGGCTGATTATTTCTGCTGCTCATATGCAGGCCGATACAACTCTGTCC TTTTCGGCGGAGGGACCAAGCTGACCGTCCTA	Clone 18 scFv (nt)
2	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPRSVSGFP GQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSRSGR AASLIISGLQTEDEADYFCCSYAGRYNSVLFGGGTKLTVL	Clone 18 scFv (aa)

(continued)

TABLE 9		
SEQ ID NO.	Sequence	Description
3	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGGATAGGCTATGCGGACTCTGTAAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTTTCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAGTGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGCAGTCTGCCCTGACTCAGCCTCGCTCAGTGTCC GGCTTTCCTGGACAATCAGTCACCATCTCCTGCACTGGAACCACCAGTGAT GATGTCTCCTGGTACCAACAACACCCAGGCAAAGCCCCCAACTTATGCT TTATGATGTCAGTAAGCGGCCCTCCGGGGTCCCTCATCGCTTCTCTGGCTC CAGGTCTGGCAGAGCGGCCTCCCTGATCATCTCTGGGCTCCAGACTGAGG ATGAGGCTGATTATTTCTGCAGCTCATATGCAGGCCGATACAACTCTGTCC TTTTCGGCGGAGGGACCAAGCTGACCGTCCTA	Clone 18B scFv (nt)
4	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPRSVSGFP GQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSRSGR AASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTVL	Clone 18B scFv (aa)
5	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC	Clone 17 scFv

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
	CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCATGCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTATTAGTTGGAATAGTGGTAGGATAGGCTATGCGGACTCTGTAAAGGGCCGATTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTTTCTGCAAATGAACAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGGGGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAGGGACAATGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGCTCTGGCGGTGGCGGATCGCAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCTGGGTCTCCTGGACAGTCGATCACCATCTTCTGCACTGGAACCAGCAGTGACGTTGGTGGTTATAACTATGTCTCCTGGTACCAGCAGCTCCCAGGAACGGCCCCCAAACTCCTCATCTATAGTAATAATCAGCGGCCCTCAGGGGTCCCTGACCGATTCTCTGGCTCCAAGTCTGGCACCTCAGCCTCCCTGGCCATCAGTGGGCTCCGGTCCGAGGATGAGGCTGATTATTACTGTGCAGCATGGGATGACAGCCTGAGTGTGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTC	(nt)
6	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGYHYYDSAEHAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGSPGQSITIFCTGTSSDVGGYNYVSWYQQLPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSVVFGGGTKLTVL	Clone 17 scFv (aa)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
7	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGGATAGGCTATGCGGACTCTGTAAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTTTCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAGTGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGCAGTCTGTGCTGACGCAGCCGCCCTCAGTGTC TGCGGCCCCAGGACAGGAGGTCACCATCTCCTGCTCTGGAAGCAGCTCCA ACATTGGGAATAATTATGTATCCTGGTACCAGCAACTCCCAGGAACAGCC CCCAAACTCCTCATTTATGACAATGATAAGCGACCCTCAGGGATTCCTGA CCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCATCACCG GACTCCAGACTGGGGACGAGGCCGATTATTACTGCGGAACATGGGATGGC AATCTGAGTGCTGTATTCGGCGGAGGGACCAAGGTGACCGTCCTA	Clone 76 scFv (nt)
8	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSAA PGQEVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNDKRPSGIPDRFSGSK SGTSATLGITGLQTGDEADYYCGTWDGNLSAVFGGGTKVTVL	Clone 76 scFv (aa)
9	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGGATAGGCTATGCGGACTCTGTAAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTTTCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAATGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC	Clone 5 scFv (nt)

(continued)

TABLE 9		
SEQ ID NO.	Sequence	Description
	TCTGGCGGTGGCGGATCGTCCTATGAGCTGACTCAGGACCCTGCTGTGTCT GTGGCCTTGGGACAGACAGTCAGGATCACATGCCAAGGAGACAGCCTCAG AAGCTATTATGCAAGCTGGTACCAGCAGAAGCCAGGACAGGCCCCTGTAC TTGTCATCTATGATAAAAACAACCGGCCCTCAGGGATCCCAGACCGATTC TCTGGCTCCAGCTCAGGAAACACAGCTTCCTTGACCATCACTGGGGCTCA GGCGGAAGATGAGGCTGACTACTACTGCAACTCCCGGGACAGCAGTGGTA ACAATTGGGTGTTCGGCGGAGGGACCAAGCTGACCGTCCTA	
10	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSYELTQDPAVSVA LGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYDKNNRPSGIPDRFSGSSS GNTASLTITGAQAEDEADYYCNSRDSSGNNWVFGGGTKLTVL	Clone 5 scFv (aa)
11	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH (clones 18, 18B reversion, 76, 285) (aa)
12	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTMVTVSS	VH (clones 17, 5, 1, 192) (aa)
13	QSALTQPRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRP SGVPHRFSGSRSGRAASLIISGLQTEDEADYFCCSYAGRYNSVLFGGGTKLTV L	VL Clone 18 (aa)
14	QSALTQPRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRP SGVPHRFSGSRSGRAASLIISGLQTEDEADYFCSSYAGRYNSVLFGGGTKLTV L	VL, Clone 18B (aa)
15	QSALTQPASVSGSPGQSITIFCTGTSSDVGGYNYVSWYQQLPGTAPKLLIYSN NQRPSGVPDRFSGSKSGTSASLAISGLRSEDEADYYCAAWDDSLSVVFGGGT KLTVL	VL, Clone 17 (aa)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
16	QSVLTQPPSVSAAPGQEVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDND KRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDGNLSAVFGGGTK VTVL	VL, Clone 76 (aa)
17	SYELTQDPAVSVALGQTVRITCQGDSLRSYYASWYQQKPGQAPVLVIYDKNN RPSGIPDRFSGSSSGNTASLTITGAQAEDEADYYCNSRDSSGNNWVFGGGTKL TVL	VL, Clone 5 (aa)
18	DYAMH	CDR-H1 (aa)
19	GISWNSGRIGY ADSVKG	CDR-H2 (aa)
20	DQGYHYYDSAEHAFDI	CDR-H3 (aa)
21	TGTTSDDVS	Clones 18, 18B CDR-L1 (aa)
22	DVSKRPS	Clones 18, 18B CDR-L2 (aa)
23	CSYAGRYNSVL	Clone 18 CDR-L3 (aa)
24	SSYAGRYNSVL	Clone 18B CDR-L3 (aa)
25	TGTSSDVGGYNYVS	Clone 17 CDR-L1 (aa)
26	SNNQRPS	Clone 17 CDR-L2 (aa)
27	AAWDDSLSVV	Clone 17 CDR-L3 (aa)
28	SGSSSNIGNNYVS	Clone 76 CDR-L1 (aa)
29	DNDKRPS	Clone 76 CDR-L2 (aa)
30	GTWDGNLSAV	Clone 76 CDR-L3 (aa)
31	QGDSLRSYYAS	Clone 5 CDR-L1 (aa)
32	DKNNRPS	Clone 5 CDR-L2 (aa)
33	NSRDSSGNNWV	Clone 5 CDR-L3 (aa)
34	GGGGSGGGGSGGGGS	Linker (aa)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
35	GISWNSGRIGY	CDR-H2
36	$X_1GX_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}S$ X_1 = T, S, or Q; X_3 = T, S, or D; X_4 = T or S; X_5 = null or S; X_6 = null, D, or N; X_7 = null or V; X_8 = null, G, or I; X_9 = null, G, or R; X_{10} = S, Y, or N; X_{11} = D or N; X_{12}=D or Y; X_{13} = V or A	CDR-L1 consensus
37	$X_1X_2X_3X_4RPS$ X_1 = D or S; X_2 = V, N, or K; X_3 = S, N, or D; X_4 = K, Q, or N	CDR-L2 consensus
38	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ X_1 = C, S, A, G, or N; X_2 = S, A, or T; X_3= Y, W, or R; X_4 = A or D; X_5 = G, D, or S; X_6 = R, S, or N; X_7 = Y, L, or G; X_8 = N or S; X_9 = S or null; X_{10} = V, A, or N; X_{11} = W or null;X_{12} = L or V.	CDR-L3
39	EVKLQESGPGLVAPSQSLSVTCTVSGVSLPDYGVSWIRQPPRKGLEWLGVIW GSETTYYNSALKSRLTIIKDNSKSQVFLKMNSLQTDDTAIYYCAKHYYYGGS YAMDYWGQGTSVTVSS	FMC63 VH
40	DIQMTQTTSSLSASLGDRVTISCRASQDISKYLNWYQQKPDGTVKLLIYHTSR LHSGVPSRFSGSGSGTDYSLTISNLEQEDIATYFCQQGNTLPYTFGGGTKLEIT	FMC63VL
41	EVKLQQSGAELVRPGSSVKISCKASGYAFSSYWMNWVKQRPGQGLEWIGQI YPGDGDTNYNGKFKGQATLTADKSSSTAYMQLSGLTSEDSAVYFCARKTISS VVDFYFDYWGQGTTVTVSS	SJ25C1 VH
42	DIELTQSPKFMSTSVGDRVSVTCKASQNVGTNVAWYQQKPGQSPKPLIYSAT YRNSGVPDRFTGSGSGTDFTLTITNVQSKDLADYFCQQYNRYPYTSGGGTKL EI	SJ25C1 VL
43	GSTSGSGKPGSGEGSTKG	Linker
44	GAAGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGCATAGGCTATGCGGACTCTGTGAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGCAAATGAA	Clone 488 scFv (nt)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
	CAGTCTGAGAGCTGAGGACACCGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAGTGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGGAAATTGTGTTGACGCAGTCTCCAGCCACCCT GTCTTTGTCTCCAGGGGAGACCGCCACCCTCTCCTGCAGGGCCAGTCAGA GTATTAACCACTACTTAGCCTGGTACCAACAGAAACCTGGCCAGGCTCCC CGGCTCCTCATCTATGATGCCTCCAACAGGGCCACTGGCATCCCAGCCAG GTTCAGTGGCAGTGGGTCTGGGACAGACTTCACTCTCACCATCAGCAGCC TAGAGCCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTCACC CTCGAATGTACACTTTTGGCCAGGGGACCAAACTGGATATCAAA	
45	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSEIVLTQSPATLSLS PGETATLSCRASQSINHYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGS GTDFTLTISSLEPEDFATYYCQQSYSHPRMYTFGQGTKLDIK	Clone 488 scFv (aa)
46	CAGATGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGCATAGGCTATGCGGACTCTGTGAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAGTGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGGCCATCCGGATGACCCAGTCTCCATCCTCCCTG TCTGCATCTGTAGGAGACAGAGTCACCGTCACTTGCCAGGCGAGTCAGGA CATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGAAGAGCCCCTA AGCTCCTGATCTACGATGCATCCAATGTGAAAGCAGGGGTCCCATCAAGG TTCAGTGGGGGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTG CAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCT CAGGCGTACACTTTTGGCCAGGGGACCAAGCTGGAGATCAAA	Clone 1304 scFv (nt)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
47	QMQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSAIRMTQSPSSLSAS VGDRVTVTCQASQDISNYLNWYQQKPGRAPKLLIYDASNVKAGVPSRFSGG GSGTDFTLTISSLQPEDFATYYCQQSYSTPQAYTFGQGTKLEIK	Clone 1304 scFv (aa)
48	GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGGATAGGCTATGCGGACTCTGTAAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTTTCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAGTGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGCAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCT GGGTCTCCTGGACAGTCGATCACCATCTCCTGCACTGGAACCAGCAGTGA CCTTGGTGGTTACAATTATGTCTCCTGGTATCAACACCGCCCAGGCAAAGC CCCCAAACTCATCATTTATGATGTCACTGTTCGGCCCTCAGGGGTTTCTGA	Clone 285 scFv (nt)
	TCGCTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCTGG GCTCCAGGCTGAGGACGAGGCTGATTATTACTGCGGCTCATATACAAGCA GTAGCACTCTTCTTTGGGTGTTCGGCGGAGGGACCAAGCTCACCGTCCTA	
49	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGS PGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGS KSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	Clone 285 scFv (aa)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
50	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGGATAGGCTATGCGGACTCTGTAAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTTTCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAATGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGCAGGCTGTGCTGACTCAGCCTCGCTCAGTGTC CGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAATCAGCAGTG GTGTTGATAGTCATAGGTATGTCTCCTGGTACCAACACCACCCAGGCAAA GCCCCCAAACTCATGATTTATGATTTCAGTAAGCGGCCCTCAGGGGTCCCT GATCGTTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCT GGGCTCCAGGCTGAGGATGAGGCTGATTACTATTGCAGCTCATATGCAGC CATCTCCCCTAATTATGTCTTCGGAACTGGGACCAAGCTCACCGTCCTA	Clone 192B scFv (nt)
51	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQAVLTQPRSVSGS PGQSVTISCTGISSGVDSHRYVSWYQHHPGKAPKLMIYDFSKRPSGVPDRFSG SKSGNTASLTISGLQAEDEADYYCSSYAAISPNYVFGTGTKLTVL	Clone 192B scFv (aa)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
52	CAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGGATAGGCTATGCGGACTCTGTAAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTTTCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAGTGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGCAGTCTGCCCTGACTCAGCCTGCCTCCGTGTCT GGGTCTCCTGGACATTCGATCACCATCTCCTGCACTGGAACCAGAAGTGA CGTCGGTGGTTTTGATTATGTCTCCTGGTACCAGCATAACCCAGGCAAAGC CCCCAAACTCATAATTTATGATGTCACTAAGCGGCCCTCAGGGGTCTCTAA TCGCTTCTCTGGCGCCAAGTCTGGCATCACGGCCTCCCTGACCATCTCTGG GCTCCAGGCTGAGGACGAGGCTGATTATTACTGCACCTCATATAGACCCG GTCCAACATTTGTCTTCGGCACCGGGACCAAGCTCACCGTCCTA	Clone 328 scFv (nt)
53	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGS PGHSITISCTGTRSDVGGFDYVSWYQHNPGKAPKLIIYDVTKRPSGVSNRFSG	Clone 328 scFv (aa)
	AKSGITASLTISGLQAEDEADYYCTSYRPGPTFVFGTGTKLTVL	

(continued)

TABLE 9		
SEQ ID NO.	Sequence	Description
54	GAAGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGCATAGGCTATGCGGACTCTGTGAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAGTGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGGACATCCAGTTGACCCAGTCTCCTTCCACCCTG TCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGCCAGTCAGAG TATTAGTAGGTGGTTGGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTA AGCTCCTGATCTACGATGCATCCAATTTGGAAACAGGGGTCCCATCCAGG TTCAGTGGAAGTGGATCTGGGACAGATTTTACTTTCACCATCAGCAGCCTG CAGCCTGAAGATATTGCAACATATTACTGTCAACAGTATGATAATCTCCCT CTCACTTTCGGCGGAGGGACCAAGGTGGAGATCAAA	Clone 227 scFv (nt)
55	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSDIQLTQSPSTLSAS VGDRVTITCRASQSISRWLAWYQQKPGKAPKLLIYDASNLETGVPSRFSGSGS GTDFTFTISSLQPEDIATYYCQQYDNLPLTFGGGTKVEIK	Clone 227 scFv (aa)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
56	CAGATGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGCATAGGCTATGCGGACTCTGTGAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAGTGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGGCCATCCGGATGACCCAGTCTCCTTCCACCCTG TCTGCATCTGTGGGAGACAGAGTCACCATCACTTGCCGGGCCAGTCAGAG CATTAGTCACTACTTGGCCTGGTATCAACAGAAACCAGGGAAAGCCCCTA AGCTCCTGATCTTTGATGCCTCCCGTTTGGCAAGTGGGGTCCCATCAAGGT TCAGTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTGC AACCTGAAGATTTTGCGACATACTACTGTCAACAGAGTTACGGTGCCCCT ATGTTCACTTTCGGCCCTGGGACCAGAGTGGATCTCAAA	Clone 1300 scFv (nt)
57	QMQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSAIRMTQSPSTLSAS VGDRVTITCRASQSISHYLAWYQQKPGKAPKLLIFDASRLASGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQSYGAPMFTFGPGTRVDLK	Clone 1300 scFv (aa)
58	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGGATAGGCTATGCGGACTCTGTAAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTTTCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG	Clone 1 scFv (nt)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
	GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAATGGTCACAGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGCAGTCTGCCCTGACTCAGCCCGCCTCCGTGTCT GGGTCTCCTGGACAGTCGATCACCATCTCCTGCACTGGGACCAGCAGTGA CGTTGGTGCTTATAACTTTGTCTCCTGGTACCAGCAGCTCCCAGGAACAGC CCCCAAATTCCTCATTTATGACAATAATAAACGACCCCCAGGGATTCCTG ACCGATTCTCTGGCTCCAAGTCTGGCACGTCAGCCACCCTGGGCATCACC GGACTCCAGACTGGGGACGAGGCCGATTATTACTGCGCAACATGGGATAG CGGCCTGAGTGCTGTGGTATTCGGCGGAGGGACCAAGCTGACCGTCCTA	
59	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGS PGQSITISCTGTSSDVGAYNFVSWYQQLPGTAPKFLIYDNNKRPPGIPDRFSGS KSGTSATLGITGLQTGDEADYYCATWDSGLSAVVFGGGTKLTVL	Clone 1 scFv (aa)
60	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTMVTVSS	VH Clone 192B (aa)
61	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 328 (aa)
62	QMQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 1304 Clone 1300 (aa)
63	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clones 227, 488, 241 (aa)

(continued)

TABLE 9		
SEQ ID NO.	Sequence	Description
64	QAVLTQPRSVSGSPGQSVTISCTGISSGVDSHRYVSWYQHHPGKAPKLMIYDFSKRPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCSSYAAISPNYVFGTGTKLTVL	VL Clone 192B (aa)
65	QSALTQPASVSGSPGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	VL Clone 285 (aa)
66	QSALTQPASVSGSPGHSITISCTGTRSDVGGFDYVSWYQHNPGKAPKLIIYDVTKRPSGVSNRFSGAKSGITASLTISGLQAEDEADYYCTSYRPGPTFVFGTGTKLTVL	VL Clone 328 (aa)
67	QSALTQPASVSGSPGQSITISCTGTSSDVGAYNFVSWYQQLPGTAPKFLIYDNNKRPPGIPDRFSGSKSGTSATLGITGLQTGDEADYYCATWDSGLSAVVFGGGTKLTVL	VL Clone 1 (aa)
68	AIRMTQSPSSLSASVGDRVTVTCQASQDISNYLNWYQQKPGRAPKLLIYDASNVKAGVPSRFSGGGSGTDFTLTISSLQPEDFATYYCQQSYSTPQAYTFGQGTKLEIK	VL Clone 1304 (aa)
69	AIRMTQSPSTLSASVGDRVTITCRASQSISHYLAWYQQKPGKAPKLLIFDASRLASGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQSYGAPMFTFGPGTRVDLK	VL Clone 1300 (aa)
70	DIQLTQSPSTLSASVGDRVTITCRASQSISRWLAWYQQKPGKAPKLLIYDASN	VL
	LETGVPSRFSGSGSGTDFTFTISSLQPEDIATYYCQQYDNLPLTFGGGTKVEIK	Clone 227 (aa)
71	EIVLTQSPATLSLSPGETATLSCRASQSINHYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQQSYSHPRMYTFGQGTKLDIK	VL Clone 488 (aa)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
72	GISWNSGSIGYADSVKG	CDR-H2 Clone 1304 Clone 1300 Clone 227 Clone 488 Clone 241 (aa)
73	TGISSGVDSHRYVS	CDR-L1 Clone 192B Clone 192 (aa)
74	TGTSSDLGGYNYVS	CDR-L1 Clone 285 (aa)
75	TGTRSDVGGFDYVS	CDR-L1 Clone 328 (aa)
76	TGTSSDVGAYNFVS	CDR-L1 Clone 1 (aa)
77	QASQDISNYLN	CDR-L1 Clone 1304 Clone 241 (aa)
78	RASQSISHYLA	CDR-L1 Clone 1300 (aa)
79	RASQSISRWLA	CDR-L1 Clone 227 (aa)
80	RASQSINHYLA	CDR-L1 Clone 488 (aa)
81	GISWNSGRIG	CDR-H2
82	GISWNSGSIG	CDR-H2
83	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ X_1 = T, Q, or R; X_2 = G or A; X_3 = I, T, or S; X_4 = S, R, or Q; X_5 = null or S; X_6 = null, D, or G; X_7 = null, V, or L; X_8 = D, G, or S; X_9 = S, G, A, or I; X_{10} = H, Y, F, S, or N; X_{11} = R, N, D, or H; X_{12} = Y, F, or W; X_{13} = V or L; X_{14} = S, N, or A	CDR-L1 Consensus
84	$DX_2X_3X_4X_5X_6X_7$ X_2 = F, V, N, or A; X_3 = S, T, or N; X_4 = K, V, N, or R; X_5 =R, V, or L; X_6 = P, K, A, or E; X_7 = S, P, A, or T	CDR-L2 Consensus
85	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ X_1 = S, G, T, A, or Q; X_2 = S, T, or Q; X_3 = Y, W, or S; X_4 = A, T, R, D, or Y; X_5 = A, S, P, G, or N; X_6 = I, S, G, T, L, A, or H; X_7 = S, P, or L; X_8 = P, T, S, Q, M, R, or null; X_9 = N, L, A, M, or null; X_{10}= L or null; X_{11}= Y, W, F, V, or L; X_{12} = V or T	CDR-L3 Consensus

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
86	GAAGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGGATAGGCTATGCGGACTCTGTAAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTTTCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAATGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGCAGGCTGTGCTGACTCAGCCTCGCTCAGTGTC CGGGTCTCCTGGACAGTCAGTCACCATCTCCTGCACTGGAATCAGCAGTG GTGTTGATAGTCATAGGTATGTCTCCTGGTACCAACACCACCCAGGCAAA GCCCCCAAACTCATGATTTATGATTTCAGTAAGCGGCCCTCAGGGGTCCCT GATCGTTTCTCTGGCTCCAAGTCTGGCAACACGGCCTCCCTGACCATCTCT GGGCTCCAGGCTGAGGATGAGGCTGATTACTATTGCTGCTCATATGCAGC CATCTCCCCTAATTATGTCTTCGGAACTGGGACCAAGCTGACCGTCCTA	Clone 192 scFv (nt)
87	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQAVLTQPRSVSGS PGQSVTISCTGISSGVDSHRYVSWYQHHPGKAPKLMIYDFSKRPSGVPDRFSG SKSGNTASLTISGLQAEDEADYYCCSYAAISPNYVFGTGTKLTVL	Clone 192 scFv (aa)

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
88	GAAGTGCAGCTGGTGCAGTCTGGGGGAGGCTTGGTACAGCCTGGCAGGTC CCTGAGACTCTCCTGTGCAGCCTCTGGATTCACCTTTGATGATTATGCCAT GCACTGGGTCCGGCAAGCTCCAGGGAAGGGCCTGGAGTGGGTCTCAGGTA TTAGTTGGAATAGTGGTAGCATAGGCTATGCGGACTCTGTGAAGGGCCGA TTCACCATCTCCAGAGACAACGCCAAGAACTCCCTGTATCTGCAAATGAA CAGTCTGAGAGCTGAGGACACGGCCGTGTATTACTGTGCGAGAGATCAGG GGTATCATTACTATGATAGTGCCGAACATGCTTTTGATATCTGGGGCCAAG GGACAGTGGTCACCGTCTCCTCAGGTGGAGGCGGTTCAGGCGGAGGTGGC TCTGGCGGTGGCGGATCGGCCATCCGGATGACCCAGTCTCCATCCTCCCTG TCTGCATCTGTAGGAGACAGAGTCACCGTCACTTGCCAGGCGAGTCAGGA CATTAGCAACTATTTAAATTGGTATCAGCAGAAACCAGGGAGAGCCCCTA AGCTCCTGATCTACGATGCATCCAATGTGAAAGCAGGGGTCCCATCAAGG TTCAGTGGGGGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTCTG CAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTACCCCT CAGGCGTACACTTTTGGCCAGGGGACCAAGCTGGATATCAAA	Clone 241 scFv (nt)
89	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSAIRMTQSPSSLSAS VGDRVTVTCQASQDISNYLNWYQQKPGRAPKLLIYDASNVKAGVPSRFSGG GSGTDFTLTISSLQPEDFATYYCQQSYSTPQAYTFGQGTKLDIK	Clone 241 scFv (aa)
90	AIRMTQSPSSLSASVGDRVTVTCQASQDISNYLNWYQQKPGRAPKLLIYDAS NVKAGVPSRFSGGGSGTDFTLTISSLQPEDFATYYCQQSYSTPQAYTFGQGTK LDIK	VL Clone 241 (aa)
91	QAVLTQPRSVSGSPGQSVTISCTGISSGVDSHRYVSWYQHHPGKAPKLMIYDF SKRPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSYAAISPNYVFGTGT KLTVL	VL Clone 192

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
92	MPPPRLLFFLLFLTPMEVRPEEPLVVKVEEGDNAVLQCLKGTSDGPTQQLTW SRESPLKPFLKLSLGLPGLGIHMRPLAIWLFIFNVSQQMGGFYLCQPGPPSEKA WQPGWTVNVEGSGELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLMSPKLY VWAKDRPEIWEGEPPCLPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVSR GPLSWTHVHPKGPKSLLSLELKDDRPARDMWVMETGLLLPRATAQDAGKY YCHRGNLTMSFHLEITARPVLWHWLLRTGGWKVSAVTLAYLIFCLCSLVGIL HLQRALVLRRKRKRMTDPTRRFFKVTPPPGSGPQNQYGNVLSLPTPTSGLGR AQRWAAGLGGTAPSYGNPSSDVQADGALGSRSPPGVGPEEEEGEGYEEPDSE EDSEFYENDSNLGQDQLSQDGSGYENPEDEPLGPEDEDSFSNAESYENEDEEL TQPVARTMDFLSPHGSAWDPSREATSLGSQSYEDMRGILYAAPQLRSIRGQP GPNHEEDADSYENMDNPDGPDPAWGGGGRMGTWSTR	CD19 Accession No. P15391 Homo Sapiens
93	DFSKRPS	CDR-L2 Clone 192B, Clone 192
94	DVTVRPS	CDR-L2 Clone 285
95	DVTKRPS	CDR-L2 Clone 328
96	DNNKRPP	CDR-L2 Clone 1
97	DASNVKA	CDR-L2 Clone 1304 Clone 241
98	DASRLAS	CDR-L2 Clone 1300
99	DASNLET	CDR-L2 Clone 227
100	DASNRAT	CDR-L2 Clone 488
101	SSYAAISPNYV	CDR-L3 Clone 192B
102	CSYAAISPNYV	CDR-L3 Clone 192
103	GSYTSSSTLLWV	CDR-L3 Clone 285
104	TSYRPGPTFV	CDR-L3 Clone 328

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
105	ATWDSGLSAVV	CDR-L3 Clone 1
106	QQSYSTPQAYT	CDR-L3 Clone 1304
		Clone 241
107	QQSYGAPMFT	CDR-L3 Clone 1300
108	QQYDNLPLT	CDR-L3 Clone 227
109	QQSYSHPRMYT	CDR-L3 Clone 488
110	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ X_1 = T, Q, S, or R; X_2 = G or A; X_3 = I, T, D, or S; X_4 = S, R, T, or Q; X_5 = null or S; X_6 = null, D,D, or G; X_7 = null, V, or L; X_8 = X or null; X_9 = X or null; X_{10} = X; X_{11} = X; X_{12} = Y, F, D, or W; X_{13} = V, A, or L; X_{14} = S, N, or A	CDR-L1 consensus
111	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}$ X_1 = T, Q, S, or R; X_2 = G or A; X_3 = I, T, D, or S; X_4 = S, R, T, or Q; X_5 = null or S; X_6 = G, D, N, or null; X_7 = null, V, or L; X_8 = D, G, I, L, S, or null; X_9 = S, G, A, I, R, or null; X_{10} = H, Y, F, S, or N; X_{11} = R, N, D, H, or Y; X_{12} = Y, F, D, or W; X_{13} = V, A, or L; X_{14} = S, N, or A	CDR-L1 consensus
112	$X_1X_2X_3X_4X_5X_6X_7$ X_1=D or S; X_2 = F, V, N, K, or A; X_3 = S, T, D, or N; X_4= K, V, N, Q, or R; X_5 =R, V, or L; X_6 = P, K, A, or E; X_7 = S, P, A, or T	CDR-L2 Consensus
113	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ X_1 = C, S, A, G, or N;	CDR-L3
	X_2 = S, A, or T; X_3 = Y, W, or R; X_4 = A or D; X_5 = G, D, or S; X_6 = R, S, or N; X_7 = Y, L, or G; X_8 = N or S; X_9 = S, N, or null; X_{10} =null; X_{11}=V, A, or W; X_{12} = L or V.	
114	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ X_1= S, G, T, A, Q, C, or N; X_2= S, Q, A, or T; X_3= Y, S, W, R; X_4= A, D, R, T, or Y; X_5=A, S, P, G, N, or D; X_6= I, S, G, T, A, L, H, R, N; X_7= S, P, L, Y, G; X_8= P, T, S, Q, M, R, N or null X_9= S, L, N, A, M or null; X_{10}=L or null; X_{11}=Y, W, F, V, A, or L; X_{12}=V, T, or L	CDR-L3 consensus
115	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$ X_1= X; X_2= S, Q, A, or T; X_3= Y, S, W, R; X_4= A, D, R, T, or Y; X_5=X X_6= XX_7= S, P, L, Y, G; X_8=X or null X_9= X or null X_{10}=L or null; X_{11}=X X_{12}=V, T, or L	CDR-L3 consensus
116	GTWDISLRFGV	CDR-L3 Clone 79
117	CSYEAPTHTYV	CDR-L3 Clone 835
118	AAWDDSLNVV	CDR-L3 Clone 184
119	CSYAGSYTFEV	CDR-L3 Clone 505
120	CSFAGYYTYWL	CDR-L3 Clone 506

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
121	SSXAGRKYV	CDR-L3 Clone 305
122	GGGS	Linker artificial
123	GGGGS	Linker artificial
124	ESKYGPPCPPCP	spacer (IgG4hinge) (aa) homo sapien
125	GAATCTAAGTACGGACCGCCCTGCCCCCCTTGCCCT	spacer (IgG4hinge) (nt) homo sapien
126	ESKYGPPCPPCPGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALH NHYTQKSLSLSLGK	Hinge-CH3 spacer Homo sapien
127	ESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPE VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPS DIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLGK	Hinge-CH2-CH3 spacer Homo sapien
128	RWPESPKAQASSVPTAQPQAEGSLAKATTAPATTRNTGRGGEEKKKEKEKEE QEERETKTPECPSHTQPLGVYLLTPAVQDLWLRDKATFTCFVVGSDLKDAHL TWEVAGKVPTGGVEEGLLERHSNGSQSQHSRLTLPRSL WNAGTSVTCTLNHPSLPPQRLMALREPAAQAPVKLSLNLLASSDPPEAASWL LCEVSGFSPPNILLMWLEDQREVNTSGFAPARPPPQPGSTTFWAWSVLRVPAP PSPQPATYTCVVSHEDSRTLLNASRSLEVSYVTDH	IgD-hinge-Fc Homo sapien
129	FWVLVVVGGVLACYSLLVTVAFIIFWV	CD28 (amino acids 153-179 of Accession No. P10747) Homo sapien

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
130	IEVMYPPPYLDNEKSNGTIIHVKGKHLCPSPLFPGPSKP FWVLVVVGGVLACYSLLVTVAFIIFWV	CD28 (amino acids 114-179 of Accession No. P10747) Homo sapien Homo sapien
131	RSKRSRLLHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS	CD28 (amino
		acids 180-220 of P10747) Homo sapien
132	RSKRSRGGHSDYMNMTPRRPGPTRKHYQPYAPPRDFAAYRS	CD28 (LL to GG) Homo sapien
133	KRGRKKL L YIFKQPFMRPVQTTQEEDGCSCRFPEEEEGGCEL	4-1BB (amino acids 214-255 of Q07011.1) Homo sapien
134	RVKFSRSADAPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR RKNPQEGLYN ELQKDKMAEA YSEIGMKGER RRGKGHDGLY QGLSTATKDTYDALHMQALP PR	CD3 zeta Homo sapien
135	RVKFSRSAEPPAYQQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPRR KNPQEGLYN ELQKDKMAEA YSEIGMKGER RRGKGHDGLY QGLSTATKDTYDALHMQALP PR	CD3 zeta Homo sapien
136	RVKFSRSADAPAYKQGQNQLYNELNLGRREEYDVLDKRRGRDPEMGGKPR RKNPQEGLYN ELQKDKMAEA YSEIGMKGER RRGKGHDGLY QGLSTATKDTYDALHMQALP PR	CD3 zeta Homo sapien
137	LEGGGEGRGSLLTCGDVEENPGPR	T2A artificial

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
138	MLLLVTSLLLCELPHPAFLLIPRKVCNGIGIGEFKDSLSINATNIKHFKNCTSISG DLHILPVAFRGDSFTHTPPLDPQELDILKTVKEITGFLLIQAWPENRTDLHAFE NLEIIRGRTKQHGQFSLAVVSLNITSLGLRSLKEISDGDVIISGNKNLCYANTIN WKKLFGTSGQKTKIISNRGENSCKATGQVCHALCSPEGCWGPEPRDCVSCRN VSRGRECVDKCNLLEGEPREFVENSECIQCHPECLPQAMNITCTGRGPDNCIQ CAHYIDGPHCVKTCPAGVMGENNTLVWKYADAGHVCHLCHPNCTYGCTGP GLEGCPTNGPKIPSIATGMVGALLLLLVVALGIGLFM	tEGFR artificial
139	MPPPCLLFFLLFLTPMEVRPQEPLVVKVEEGDNAVLQCLEGTSDGPTQQLVW CRDSPFEPFLNLSLGLPGMGIRMGPLGIWLLIFNVSNQTGGFYLCQPGLPSEKA WQPGWTVSVEGSGELFRWNVSDLGGLGCGLKNRSSEGPSSPSGKLNSSQLY VWAKDRPEMWEGEPVCGPPRDSLNQSLSQDLTMAPGSTLWLSCGVPPDSVS RGPLSWTHVRPKGPKSSLLSLELKDDRPDRDMWVVDTGLLLTRATAQDAGK YYCHRGNWTKSFYLEITARPALWHWLLRIGGWKVPAVTLTYLIFCLCSLVGI LQLQRALVLRRKRKRMTDPTRRFFKVTPPPGSGPQNQYGNVLSLPTPTSGLG RAQRWAAGLGGTAPSYGNPSSDVQVDGAVGSRSPPGAGPEEEEGEGYEEPD SEEGSEFYENDSNFGQDQLSQDGSGYENPEDEPLGPEDEDSFSNAESYENEDE ELTQPVARTMDFLSPHGSAWDPSREATSLGSQSYEDMRGLLYAAPQLRTIRG QPGPNHEEDADSYENMDNPDGPDPAWGGGGRMGTWSAR	Rhesus macaque CD19 Accession No. F7F486
140	HPKGPKSLLSLELKDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNLT MSFHLEITARPVLWHWLLRTGGWK	V1 chimeric/rhesus human corresponding
		to residues 218 to 291 of human CD19
141	RPKGPKSSLLSLELKDDRPDRDMWVVDTGLLLTRATAQDAGKYYCHRGNLT MSFHLEITARPVLWHWLLRTGGWK	V2 chimeric/rhesus human corresponding to residues 218 to 291 of human CD19

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
142	HPKGPKSLLSLELKDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNWT KSFYLEITARPALWHWLLRIGGWK	V3 chimeric/rhesus human corresponding to residues 218 to 291 of human CD19
143	HPKGPKSLLSLELKDDRPARDMWVMETGLLLP	Artificial
144	RPKGPKSSLLSLELKDDRPDRDMWVVDTGLLLT	Artificial
145	DQGXHXYDSAEHAFXI	CDR-H3 clone 305
146	QASQDISNYLN	CDR-L1 Clone 255
147	TGTGRDIGAYDYVS	CDR-L1 Clone 305
148	TETSSDLGGYNYVS	CDR-L1 Clone 327
149	TGASTDVGGYNYVS	CDR-L1 Clone 505
150	TGASSDVGGYDHVS	CDR-L1 Clone 506
151	SGSSSNIGSNTVN	CDR-L1 Clone 184
152	TGPISGVGDYTSVS	CDR-L1 Clone 835
153	DNNKRPS	CDR-L2 Clone 272
154	GVNKRPS	CDR-L2 Clone 305
155	DVNKRPS	CDR-L2 Clone 505
156	DNNKRPS	CDR-L2 Clone 79
157	DVTQRPS	CDR-L2 Clone 835
158	GTWDSSLNRDWV	CDR-L3 Clone 272
159	CSYAGRYNSVP	CDR-L3 Clone 508
160	TSGVGVG	CDR-H1 Clone 1265
161	LIYWDDDKRYSPSLKS	CDR-H2 Clone 1265
162	IDYGSGSYSPRTSYYYYMSV	CDR-H3 Clone 1265

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
163	RASQGISSYLN	CDR-L1 Clone 1265
164	AASNLQS	CDR-L2 Clone 1265
165	QQGDAFPLT	CDR-L3 Clone 1265
166	QITLKESGPTLVKPTQTLTLTCTFSGFSLSTSGVGVGWIRQPPGKALEWLALIY WDDDKRYSPSLKSRLTITKDTSKNQVVLTMTNMDPVDTATYYCAHIDYGSG SYSPRTSYYYYMSVWGKGTTVTVSS	VH Clone 1265
167	QVQLVQSGGGVVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSG ISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 213
168	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 255
169	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 272
170	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 283
171	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 302
172	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSXXGRXXISRDNAKNSLFLQMNSLRAEDTAXYYCAXDQGX HXYDSAEHAFXIWGQGTVVTVSS	VH Clone 305

(continued)

TABLE 9		
SEQ ID NO.	Sequence	Description
173	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 314
174	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 379
175	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 324
176	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAXNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 327
177	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 336
178	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 440
179	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSS	VH Clone 448
180	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTMVTVSS	VH Clone 505

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
181	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGYHYYDSAEHAFDIWGQGTMVTVSS	VH Clone 506
182	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSS	VH Clone 508
183	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGYHYYDSAEHAFDIWGQGTMVTVSS	VH Clone 184
184	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSS	VH Clone 79
185	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRLAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAKDTAVYYCARDQGYHYYDSAEHAFDIWGQGTMVTVSS	VH Clone 835
186	AIQLTQSPSFLSASVGDRVTITCRASQGISSYLNWYQQRAGKAPELLIYAASNLQSGVPSRFSGSGSGTDFTLTITSVQPEDFATYFCQQGDAFPLTFGPGTKVTIR	VL Clone 1265
187	EIVLTQSPATLSLSPGETATLSCRASQSINHYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFATYYCQQSYSHPRMYTFGQGTKLEIK	VL Clone 213
188	AIRMTQSPSSLSASVGDRVTVTCQASQDISNYLNWYQQKPGRAPKLLIYDASNVKAGVPSRFSGGGSGTDFTLTISSLQPEDFATYYCQQSYSTPQAYTFGQGTKLDIK	VL Clone 255

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
189	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLNRDWVFGGGTKLTVL	VL Clone 272
190	QSALTQPASVSGSPGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	VL Clone 283
191	QSALTQPASVSGSPGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	VL Clone 302
192	QSVLXXPXXASGSPGQSVTVSCTGTGRDIGAYDYVSWYQQHPGKAPKLLIYGVNKRPSGVPDRFSGSKSDNTASLTVSGLQVEDEADYYCSSXAGRKYVFGTGXKVTVL	VL Clone 305
193	QSALTQPASVSGSPGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	VL Clone 314
194	QSALTQPASVSGSPGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	VL Clone 379
195	QSALTQPASVSGSPGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	VL Clone 324
196	QSALTQPASVSGSPGQSITISCTETSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVXDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	VL Clone 327

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
197	QSALTQPASVSGSPGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	VL Clone 336
198	QSALTQPASVSGSPGHSITISCTGTRSDVGGFDYVSWYQHNPGKAPKLIIYDVTKRPSGVSNRFSGAKSGITASLTISGLQAEDEADYYCTSYRPGPTFVFGTGTKLDIK	VL Clone 440
199	QSALTQPASVSGSPGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLDIK	VL Clone 448
200	QSVLTQPRSLSGSPGQSVTIACTGASTDVGGYNYVSWYQQHPGKAPKLMIYDVNKRPSGVPDRFSGSKSGNTAFLTISGLQAEDEADYYCCSYAGSYTFEVFGGGTKLTVL	VL Clone 505
201	QLVLTQPPSVSGSPGQSVTFSCTGASSDVGGYDHVSWYQHHPGKGPKLLIYDVSKRPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYCCSFAGYYTYWLFGGGTKVTVL	VL Clone 506
202	QSALTQPRSVSGFPGQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSRSGRAASLIISGLQTEDEADYFCCSYAGRYNSVPFGGGTKLTVL	VL Clone 508
203	SYVLTQPPSASGTPGQRVTISCSGSSSNIGSNTVNWYQQFPGTAPKLLIYSNNQRPSGVPDRFSGSKSGTSASLAISGLQSEDEAEYYCAAWDDSLNVV	VL Clone 184
204	QSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEGDYYCGTWDISLRFGVFGGGTKVTVL	VL Clone 79
205	QSVLTQPRSVSGSPGQSVTISCTGPISGVGDYTSVSWYQHYPGKTPKLIIYDVTQRPSGVPNRFSGSKSGNTASLTISGLQADDEADYYCCSYEAPTHTYVFGTGTKLTVL	VL Clone 835

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
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207	QVQLVQSGGGVVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSEIVLTQSPATLSLSPGETATLSCRASQSINHYLAWYQQKPGQAPRLLIYDASNRATGIPARFSGSGS	scFv Clone 213
	GTDFTLTISSLEPEDFATYYCQQSYSHPRMYTFGQGTKLEIK	
208	EVQLVQSGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSAIRMTQSPSSLSASVGDRVTVTCQASQDISNYLNWYQQKPGRAPKLLIYDASNVKAGVPSRFSGGGSGTDFTLTISSLQPEDFATYYCQQSYSTPQAYTFGQGTKLDIK	scFv Clone 255
209	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSAAPGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSKSGTSATLGITGLQTGDEADYYCGTWDSSLNRDWVFGGGTKLTVL	scFv Clone 272
210	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGISWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGYHYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGSPGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGSKSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	scFv Clone 283

(continued)

TABLE 9

SEQ ID NO.	Sequence	Description
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212	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSXXGRXXISRDNAKNSLFLQMNSLRAEDTAXYYCAXDQGX HXYDSAEHAFXIWGQGTVVTVSSGGGGSGGGGSGGGGSQSVLXXPXXASGS PGQSVTVSCTGTGRDIGAYDYVSWYQQHPGKAPKLLIYGVNKRPSGVPDRFS GSKSDNTASLTVSGLQVEDEADYYCSSXAGRKYVFGTGXKVTVL	scFv Clone 305
213	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGS PGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGS KSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	scFv Clone 314
214	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGS PGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGS KSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	scFv Clone 379
215	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGS PGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGS KSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	scFv Clone 324

(continued)

TABLE 9		
SEQ ID NO.	Sequence	Description
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217	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI	scFv
	SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGS PGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGS KSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLTVL	Clone 336
218	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGS PGHSITISCTGTRSDVGGFDYVSWYQHNPGKAPKLIIYDVTKRPSGVSNRFSG AKSGITASLTISGLQAEDEADYYCTSYRPGPTFVFGTGTKLDIK	scFv Clone 440
219	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPASVSGS PGQSITISCTGTSSDLGGYNYVSWYQHRPGKAPKLIIYDVTVRPSGVSDRFSGS KSGNTASLTISGLQAEDEADYYCGSYTSSSTLLWVFGGGTKLDIK	scFv Clone 448
220	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTMVTVSSQSVLTQPRSLSGSPGQSVTIACTGASTDV GGYNYVSWYQQHPGKAPKLMIYDVNKRPSGVPDRFSGSKSGNTAFLTISGLQ AEDEADYYCCSYAGSYTFEVFGGGTKLTVL	scFv Clone 505

(continued)

TABLE 9		
SEQ ID NO.	Sequence	Description
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222	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSALTQPRSVSGFP GQSVTISCTGTTSDDVSWYQQHPGKAPQLMLYDVSKRPSGVPHRFSGSRSGR AASLIISGLQTEDEADYFCCSYAGRYNSVPFGGGTKLTVL	scFv Clone 508
223	QVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSSYVLTQPPSASGT PGQRVTISCSGSSSNIGSNTVNWYQQFPGTAPKLLIYSNNQRPSGVPDRFSGSK SGTSASLAISGLQSEDEAEYYCAAWDDSLNVV	scFv Clone 184
224	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRQAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAEDTAVYYCARDQGY HYYDSAEHAFDIWGQGTVVTVSSGGGGSGGGGSGGGGSQSVLTQPPSVSAA PGQKVTISCSGSSSNIGNNYVSWYQQLPGTAPKLLIYDNNKRPSGIPDRFSGSK SGTSATLGITGLQTGDEGDYYCGTWDISLRFGVFGGGTKVTVL	scFv Clone 79
225	EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYAMHWVRLAPGKGLEWVSGI SWNSGRIGYADSVKGRFTISRDNAKNSLFLQMNSLRAKDTAVYYCARDQGY HYYDSAEHAFDIWGQGTMVTVSSGGGGSGGGGSGGGGSQSVLTQPRSVSGS PGQSVTISCTGPISGVGDYTSVSWYQHYPGKTPKLIIYDVTQRPSGVPNRFSGS KSGNTASLTISGLQADDEADYYCCSYEAPTHTYVFGTGTKLTVL	scFv Clone 835
226	X1X2X3X4X5X6X7X8X9X10X11X12X13X14 X1= T, Q, R, or S; X2= G, A, or E;	CDR-L1 consensus

(continued)

TABLE 9		
SEQ ID NO.	Sequence	Description
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227	X1X2X3X4X5X6X7 X1= D, S, or G; X2= F, V, N, K, or A; X3= S, T, N, or D; X4= K, V, N, R, or Q; X5= R, V, or L; X6= P, K, A, or E; X7= S, P, A, or T	CDR-L2 consensus
228	X1X2X3X4X5X6X7X8X9X10X11X12 X1= S, G, T, A, Q, C, or N; X2= S, Q, A, or T; X3= Y, S, W, or R; X4= A, D, R, T, or Y; X5= A, S, P, G, N, or D; X6= I, S, G, T, A, L, H, R, or N; X7= S, P, L, Y, or G; X8= P, T, S, Q, M, R, or N; X9= S, L, N, A, M, null, or R; X10= L, null, or D; X11= Y, W, F, V, A, or L; X12= V, T, L, or P	CDR-L3 consensus

SEQUENCE LISTING

[0430]

<110> Juno Therapeutics, Inc.
CHEN, Yan
SHAMAH, Steve
PAZMANY, Csaba
DUTTA-SIMMONS, Jui

<120> ANTIBODIES AND CHIMERIC ANTIGEN RECEPTORS SPECIFIC FOR CD19

<130> 735042000740

<140> Not Yet Assigned
<141> Concurrently Herewith

<150> US 62/043,273
<151> 2014-08-28

<150> US 62/078,942
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ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
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cagtctgccc tgactcagcc tcgctcagtg tccggctttc ctggacaatc agtcaccatc 480
tcctgcactg gaaccaccag tgatgatgtc tcctggtacc aacaacaccc aggcaaagcc 540
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<210> 2
<211> 246
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<220>
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<400> 2

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 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
                165                 170                 175
Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
            180                 185                 190
Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
        195                 200                 205
Ser Leu Ile Ile Ser Gly Leu Gln Thr Glu Asp Glu Ala Asp Tyr Phe
    210                 215                 220
Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu Phe Gly Gly Gly
225                 230                 235                 240
Thr Lys Leu Thr Val Leu
                245
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<211> 738
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<220>
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ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
gcggactctg taaagggccg attcaccatc tccagagaca acgccaagaa ctccctgttt 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacagtg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
cagtctgccc tgactcagcc tcgctcagtg tccggctttc ctggacaatc agtcaccatc 480
tcctgcactg gaaccaccag tgatgatgtc tcctggtacc aacaacaccc aggcaaagcc 540
ccccaactta tgctttatga tgtcagtaag cggccctccg gggtccctca tcgcttctct 600
ggctccaggt ctggcagagc ggcctccctg atcatctctg ggctccagac tgaggatgag 660
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accaagctga ccgtccta                                               738
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<213> Homo sapiens

<220>
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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
                165                 170                 175
Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
            180                 185                 190
Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
        195                 200                 205
Ser Leu Ile Ile Ser Gly Leu Gln Thr Glu Asp Glu Ala Asp Tyr Phe
    210                 215                 220
Cys Ser Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu Phe Gly Gly Gly
225                 230                 235                 240
Thr Lys Leu Thr Val Leu
                245
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<210> 5
<211> 750
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 17 scFv (nt)

<400> 5

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ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
gcggactctg taaagggccg attcaccatc tccagagaca acgccaagaa ctccctgttt 240
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cctgaccgat tctctggctc caagtctggc acctcagcct ccctggccat cagtgggctc 660
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            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160
Phe Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175
Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Ser
            180                 185                 190
Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Arg Ser Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu Ser Val Val
225                 230                 235                 240
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
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<210> 7
<211> 747

<212> DNA
<213> Homo sapiens

<220>
<223> Clone 76 scFv (nt)

<400> 7

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ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
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cagtctgtgc tgacgcagcc gccctcagtg tctgcggccc caggacagga ggtcaccatc 480
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gaccgattct ctggctccaa gtctggcacg tcagccaccc tgggcatcac cggactccag 660
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ggcggaggga ccaaggtgac cgtccta                                    747
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<210> 8
<211> 249
<212> PRT
<213> Homo sapiens

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<400> 8

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Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu
    130                 135                 140
Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Glu Val Thr Ile
145                 150                 155                 160
Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
                165                 170                 175
Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Asp Asn
            180                 185                 190
Asp Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205
Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
    210                 215                 220
Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Gly Asn Leu Ser Ala Val Phe
225                 230                 235                 240
Gly Gly Gly Thr Lys Val Thr Val Leu
                245
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<210> 9
<211> 744
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 5 scFv (nt)

<400> 9

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gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
gcggactctg taaagggccg attcaccatc tccagagaca acgccaagaa ctccctgttt 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacaatg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
tcctatgagc tgactcagga ccctgctgtg tctgtggcct tgggacagac agtcaggatc 480
acatgccaag gagacagcct cagaagctat tatgcaagct ggtaccagca gaagccagga 540
caggcccctg tacttgtcat ctatgataaa aacaaccggc cctcagggat cccagaccga 600
ttctctggct ccagctcagg aaacacagct tccttgacca tcactggggc tcaggcggaa 660
gatgaggctg actactactg caactcccgg gacagcagtg gtaacaattg ggtgttcggc 720
ggagggacca agctgaccgt ccta                                        744
```

<210> 10
<211> 248

<212> PRT
<213> Homo sapiens

<220>
<223> Clone 5 scFv (aa)

<400> 10

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Glu Leu
    130                 135                 140
Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln Thr Val Arg Ile
145                 150                 155                 160
Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser Trp Tyr Gln
                165                 170                 175
Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Asp Lys Asn Asn
            180                 185                 190
Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Ser Ser Gly Asn
        195                 200                 205
Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu Asp Glu Ala Asp
    210                 215                 220
Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn Asn Trp Val Phe Gly
225                 230                 235                 240
Gly Gly Thr Lys Leu Thr Val Leu
                245
```

<210> 11
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH (clones 18, 18B reversion, 76, 285) (aa)

<400> 11

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe

65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 12
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH (clones 17, 5, 1, 192) (aa)

<400> 12

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120                 125
```

<210> 13
<211> 106
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 18 (aa)

<400> 13

```
Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln
 1               5                  10                  15
Ser Val Thr Ile Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp
            20                  25                  30
Tyr Gln Gln His Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val
        35                  40                  45
Ser Lys Arg Pro Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser
    50                  55                  60
Gly Arg Ala Ala Ser Leu Ile Ile Ser Gly Leu Gln Thr Glu Asp Glu
65                  70                  75                  80
Ala Asp Tyr Phe Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu
                85                  90                  95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 14
<211> 106
<212> PRT
<213> Homo sapiens

<220>
<223> VL, Clone 18B (aa)

<400> 14

```
Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln
 1               5                  10                  15
Ser Val Thr Ile Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp
            20                  25                  30
Tyr Gln Gln His Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val
        35                  40                  45
Ser Lys Arg Pro Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser
    50                  55                  60
Gly Arg Ala Ala Ser Leu Ile Ile Ser Gly Leu Gln Thr Glu Asp Glu
65                  70                  75                  80
Ala Asp Tyr Phe Cys Ser Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu
                85                  90                  95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105
```

<210> 15
<211> 110
<212> PRT
<213> Homo sapiens

<220>
<223> VL, Clone 17 (aa)

<400> 15

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Phe Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu
35 40 45
Leu Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu
65 70 75 80
Arg Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ala Ala Trp Asp Asp Ser
85 90 95
Leu Ser Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 16
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<223> VL, Clone 76 (aa)

<400> 16

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
1 5 10 15

Glu Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
20 25 30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Asp Asn Asp Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
50 55 60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65 70 75 80
Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Gly Asn Leu
85 90 95
Ser Ala Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
100 105

<210> 17
<211> 108
<212> PRT
<213> Homo sapiens

<220>
<223> VL, Clone 5 (aa)

<400> 17

Ser Tyr Glu Leu Thr Gln Asp Pro Ala Val Ser Val Ala Leu Gly Gln
1   5   10   15
Thr Val Arg Ile Thr Cys Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala
            20   25   30
Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr
        35   40   45
Asp Lys Asn Asn Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser
    50   55   60
Ser Ser Gly Asn Thr Ala Ser Leu Thr Ile Thr Gly Ala Gln Ala Glu
65   70   75   80
Asp Glu Ala Asp Tyr Tyr Cys Asn Ser Arg Asp Ser Ser Gly Asn Asn
                85   90   95
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100   105

<210> 18
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-H1 (aa)

<400> 18

Asp Tyr Ala Met His
1   5

<210> 19
<211> 17
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-H2 (aa)

<400> 19

Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val Lys
1   5   10   15
Gly

<210> 20
<211> 16
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-H3 (aa)

<400> 20

Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe Asp Ile
1 5 10 15

<210> 21
<211> 9
<212> PRT
<213> Homo sapiens

<220>
<223> Clones 18, 18B CDR-L1 (aa)

<400> 21

Thr Gly Thr Thr Ser Asp Asp Val Ser
1 5

<210> 22
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> Clones 18, 18B CDR-L2 (aa)

<400> 22

Asp Val Ser Lys Arg Pro Ser
1 5

<210> 23
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 18 CDR-L3 (aa)

<400> 23

Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu
1 5 10

<210> 24
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 18B CDR-L3 (aa)

<400> 24

Ser Ser Tyr Ala Gly Arg Tyr Asn Ser Val Leu
1 5 10

<210> 25
<211> 14
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 17 CDR-L1 (aa)

<400> 25

Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 26
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 17 CDR-L2 (aa)

<400> 26

Ser Asn Asn Gln Arg Pro Ser
1 5

<210> 27
<211> 10
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 17 CDR-L3 (aa)

<400> 27

Ala Ala Trp Asp Asp Ser Leu Ser Val Val
1 5 10

<210> 28
<211> 13
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 76 CDR-L1 (aa)

<400> 28

Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser
1 5 10

<210> 29
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 76 CDR-L2 (aa)

<400> 29

Asp Asn Asp Lys Arg Pro Ser
1 5

<210> 30
<211> 10
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 76 CDR-L3 (aa)

<400> 30

Gly Thr Trp Asp Gly Asn Leu Ser Ala Val
1 5 10

<210> 31
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 5 CDR-L1 (aa)

<400> 31

Gln Gly Asp Ser Leu Arg Ser Tyr Tyr Ala Ser
1 5 10

<210> 32
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 5 CDR-L2 (aa)

<400> 32

Asp Lys Asn Asn Arg Pro Ser
1 5

<210> 33
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 5 CDR-L3 (aa)

<400> 33

Asn Ser Arg Asp Ser Ser Gly Asn Asn Trp Val
1 5 10

<210> 34
<211> 15
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> Linker (aa)

<400> 34

Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser
1 5 10 15

<210> 35
<211> 11
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-H2

<400> 35

Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr
1 5 10

<210> 36
<211> 14
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<220>
<223> CDR-L1 consensus

<220>
<221> VARIANT
<222> 1
<223> Xaa = Thr, Ser or Gln

<220>
<221> VARIANT
<222> 3
<223> Xaa = Thr, Ser or Asp

<220>
<221> VARIANT
<222> 4
<223> Xaa = Thr or Ser

<220>
<221> VARIANT
<222> 5
<223> Xaa = null or Ser

<220>
<221> VARIANT
<222> 6
<223> Xaa = null, Asp or Asn

<220>
<221> VARIANT
<222> 7
<223> Xaa = null or Val

<220>
<221> VARIANT
<222> 8
<223> Xaa = null, Gly or Ile

<220>
<221> VARIANT
<222> 9
<223> Xaa = null, Gly or Arg

<220>
<221> VARIANT
<222> 10
<223> Xaa = Ser, Tyr or Asn

<220>
<221> VARIANT
<222> 11
<223> Xaa = Asp or Asn

<220>
<221> VARIANT
<222> 12

<223> Xaa = Asp or Tyr

<220>
<221> VARIANT
<222> 13
<223> Xaa = Val or Ala

<400> 36

```
Xaa Gly Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ser
 1               5                  10
```

<210> 37
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-L2 consensus

<220>
<221> VARIANT
<222> 1
<223> Xaa = Asp or Ser

<220>
<221> VARIANT
<222> 2
<223> Xaa = Val, Asn or Lys

<220>
<221> VARIANT
<222> 3
<223> Xaa = Ser, Asn or Asp

<220>
<221> VARIANT
<222> 4
<223> Xaa = Lys, Gln or Asn

<400> 37

```
Xaa Xaa Xaa Xaa Arg Pro Ser
 1               5
```

<210> 38
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-L3

<220>
<221> VARIANT
<222> 1
<223> Xaa = Cys, Ser, Ala, Gly or Asn

<220>
<221> VARIANT
<222> 2
<223> Xaa = Ser, Ala or Thr

<220>
<221> VARIANT
<222> 3
<223> Xaa = Tyr, Trp or Arg

<220>
<221> VARIANT
<222> 4
<223> Xaa = Ala or Asp

<220>
<221> VARIANT
<222> 5
<223> Xaa = Gly, Asp or Ser

<220>
<221> VARIANT
<222> 6
<223> Xaa = Arg, Ser or Asn

<220>
<221> VARIANT
<222> 7
<223> Xaa = Tyr, Leu or Gly

<220>
<221> VARIANT
<222> 8
<223> Xaa = Asn or Ser

<220>
<221> VARIANT
<222> 9
<223> Xaa = Ser or null

<220>
<221> VARIANT
<222> 10
<223> Xaa = Val, Ala or Asn

<220>
<221> VARIANT
<222> 11
<223> Xaa = Trp or null

<220>
<221> VARIANT
<222> 12
<223> Xaa = Leu or Val

<400> 38

```
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1               5                  10
```

<210> 39
<211> 120
<212> PRT
<213> Mus musculus

<220>
<223> FMC63 VH

<400> 39

```
Glu Val Lys Leu Gln Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
 1               5                  10                  15
Ser Leu Ser Val Thr Cys Thr Val Ser Gly Val Ser Leu Pro Asp Tyr
            20                  25                  30
Gly Val Ser Trp Ile Arg Gln Pro Pro Arg Lys Gly Leu Glu Trp Leu
        35                  40                  45
Gly Val Ile Trp Gly Ser Glu Thr Thr Tyr Tyr Asn Ser Ala Leu Lys
    50                  55                  60
Ser Arg Leu Thr Ile Ile Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65                  70                  75                  80
Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Ile Tyr Tyr Cys Ala
                85                  90                  95
Lys His Tyr Tyr Tyr Gly Gly Ser Tyr Ala Met Asp Tyr Trp Gly Gln
            100                 105                 110
Gly Thr Ser Val Thr Val Ser Ser
        115                 120
```

<210> 40
<211> 107
<212> PRT
<213> Mus musculus

<220>
<223> FMC63VL

<400> 40

```
Asp Ile Gln Met Thr Gln Thr Thr Ser Ser Leu Ser Ala Ser Leu Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Ser Cys Arg Ala Ser Gln Asp Ile Ser Lys Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Asp Gly Thr Val Lys Leu Leu Ile
        35                  40                  45
Tyr His Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Tyr Ser Leu Thr Ile Ser Asn Leu Glu Gln
65                  70                  75                  80
Glu Asp Ile Ala Thr Tyr Phe Cys Gln Gln Gly Asn Thr Leu Pro Tyr
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile Thr
            100                 105
```

<210> 41
<211> 122
<212> PRT
<213> Mus musculus

<220>
<223> SJ25C1VH

<400> 41

```
Glu Val Lys Leu Gln Gln Ser Gly Ala Glu Leu Val Arg Pro Gly Ser
 1               5                  10                  15
Ser Val Lys Ile Ser Cys Lys Ala Ser Gly Tyr Ala Phe Ser Ser Tyr
            20                  25                  30
Trp Met Asn Trp Val Lys Gln Arg Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45
Gly Gln Ile Tyr Pro Gly Asp Gly Asp Thr Asn Tyr Asn Gly Lys Phe
    50                  55                  60
Lys Gly Gln Ala Thr Leu Thr Ala Asp Lys Ser Ser Ser Thr Ala Tyr

65                  70                  75                  80
Met Gln Leu Ser Gly Leu Thr Ser Glu Asp Ser Ala Val Tyr Phe Cys
                85                  90                  95
Ala Arg Lys Thr Ile Ser Ser Val Val Asp Phe Tyr Phe Asp Tyr Trp
            100                 105                 110
Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> 42
<211> 106
<212> PRT
<213> Mus musculus

<220>
<223> SJ25C1 VL

<400> 42

```
Asp Ile Glu Leu Thr Gln Ser Pro Lys Phe Met Ser Thr Ser Val Gly
 1               5                  10                  15
Asp Arg Val Ser Val Thr Cys Lys Ala Ser Gln Asn Val Gly Thr Asn
            20                  25                  30
Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Lys Pro Leu Ile
        35                  40                  45
Tyr Ser Ala Thr Tyr Arg Asn Ser Gly Val Pro Asp Arg Phe Thr Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Asn Val Gln Ser
65                  70                  75                  80
Lys Asp Leu Ala Asp Tyr Phe Cys Gln Gln Tyr Asn Arg Tyr Pro Tyr
                85                  90                  95
Thr Ser Gly Gly Gly Thr Lys Leu Glu Ile
            100                 105
```

<210> 43
<211> 18
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> Linker

<400> 43

```
Gly Ser Thr Ser Gly Ser Gly Lys Pro Gly Ser Gly Glu Gly Ser Thr
 1               5                  10                  15
Lys Gly
```

<210> 44
<211> 747
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 488 scFv (nt)

<400> 44

```
gaagtgcagc tggtgcagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cataggctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaatga acagtctgag agctgaggac accgccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacagtg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
gaaattgtgt tgacgcagtc tccagccacc ctgtctttgt ctccagggga gaccgccacc 480
ctctcctgca gggccagtca gagtattaac cactacttag cctggtacca acagaaacct 540
ggccaggctc cccggctcct catctatgat gcctccaaca gggccactgg catcccagcc 600
aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 660
gaagattttg caacttacta ctgtcaacag agttacagtc accctcgaat gtacactttt 720
ggccagggga ccaaactgga tatcaaa                                     747
```

<210> 45
<211> 249
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 488 scFv (aa)

<400> 45

```
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
    130                 135                 140
Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Thr Ala Thr
145                 150                 155                 160
Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn His Tyr Leu Ala Trp Tyr
                165                 170                 175
Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser
            180                 185                 190
Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205
Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
    210                 215                 220
Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser His Pro Arg Met Tyr Thr Phe
225                 230                 235                 240
Gly Gln Gly Thr Lys Leu Asp Ile Lys
                245
```

<210> 46
<211> 747
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 1304 scFv (nt)

<400> 46

```
cagatgcagc tggtgcagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cataggctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacagtg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
gccatccgga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 480
gtcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 540
ggaagagccc ctaagctcct gatctacgat gcatccaatg tgaaagcagg ggtcccatca 600
aggttcagtg gggtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 660
gaagattttg caacttacta ctgtcaacag agttacagta cccctcaggc gtacactttt 720
ggccagggga ccaagctgga gatcaaa                                      747
```

<210> 47
<211> 249
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 1304 scFv (aa)

<400> 47

```
Gln Met Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
    130                 135                 140
Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160
Val Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn Trp Tyr
                165                 170                 175
Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser
            180                 185                 190
Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly
        195                 200                 205
Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220
Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr Phe
225                 230                 235                 240
Gly Gln Gly Thr Lys Leu Glu Ile Lys
                245
```

<210> 48
<211> 756

<212> DNA
<213> Homo sapiens

<220>
<223> Clone 285 scFv (nt)

<400> 48

```
gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
gcggactctg taaagggccg attcaccatc tccagagaca acgccaagaa ctccctgttt 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacagtg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacagtc gatcaccatc 480
tcctgcactg gaaccagcag tgaccttggt ggttacaatt atgtctcctg gtatcaacac 540
cgcccaggca aagcccccaa actcatcatt tatgatgtca ctgttcggcc ctcaggggtt 600
tctgatcgct tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 660
caggctgagg acgaggctga ttattactgc ggctcatata caagcagtag cactcttctt 720
tgggtgttcg gcggagggac caagctcacc gtccta                           756
```

<210> 49
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 285 scFv (aa)

<400> 49

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 50
<211> 753
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 192B scFv (nt)

<400> 50

```
caggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
gcggactctg taaagggccg attcaccatc tccagagaca acgccaagaa ctccctgttt 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacaatg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
caggctgtgc tgactcagcc tcgctcagtg tccgggtctc ctggacagtc agtcaccatc 480
tcctgcactg gaatcagcag tggtgttgat agtcataggt atgtctcctg gtaccaacac 540
cacccaggca aagcccccaa actcatgatt tatgatttca gtaagcggcc ctcaggggtc 600
cctgatcgtt tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 660
caggctgagg atgaggctga ttactattgc agctcatatg cagccatctc ccctaattat 720
gtcttcggaa ctgggaccaa gctcaccgtc cta                              753
```

<210> 51
<211> 251

<212> PRT
<213> Homo sapiens

<220>
<223> Clone 192B scFv (aa)

<400> 51

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ala Val Leu
    130                 135                 140
Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His Arg Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
            180                 185                 190
Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ala Ile Ser Pro Asn Tyr
225                 230                 235                 240
Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 52
<211> 750
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 328 scFv (nt)

<400> 52

```
caggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
gcggactctg taaagggccg attcaccatc tccagagaca acgccaagaa ctccctgttt 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacagtg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
cagtctgccc tgactcagcc tgcctccgtg tctgggtctc ctggacattc gatcaccatc 480
tcctgcactg gaaccagaag tgacgtcggt ggttttgatt atgtctcctg gtaccagcat 540
aacccaggca aagcccccaa actcataatt tatgatgtca ctaagcggcc ctcaggggtc 600
tctaatcgct tctctggcgc caagtctggc atcacggcct ccctgaccat ctctgggctc 660
caggctgagg acgaggctga ttattactgc acctcatata gacccggtcc aacatttgtc 720
ttcggcaccg ggaccaagct caccgtccta                                  750
```

<210> 53
<211> 250
<212> PRT
<213> Homo sapiens

<400> 53

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe Asp Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ala Lys
        195                 200                 205
Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Arg Pro Gly Pro Thr Phe Val
225                 230                 235                 240
Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 54
<211> 741
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 227 scFv (nt)

<400> 54

```
gaagtgcagc tggtgcagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cataggctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacagtg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
gacatccagt tgacccagtc tccttccacc ctgtctgcat ctgtaggaga cagagtcacc 480
atcacttgcc gggccagtca gagtattagt aggtggttgg cctggtatca gcagaaacca 540
gggaaagccc ctaagctcct gatctacgat gcatccaatt tggaaacagg ggtcccatcc 600
aggttcagtg gaagtggatc tgggacagat tttactttca ccatcagcag cctgcagcct 660
gaagatattg caacatatta ctgtcaacag tatgataatc tccctctcac tttcggcgga 720
gggaccaagg tggagatcaa a                                           741
```

<210> 55
<211> 247
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 227 scFv (aa)

<400> 55

```
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Asp Ile Gln Leu
    130                 135                 140
Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160
Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Trp Leu Ala Trp Tyr
                165                 170                 175
Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser
            180                 185                 190
Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205
Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala
    210                 215                 220
Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Leu Thr Phe Gly Gly
225                 230                 235                 240
```

Gly Thr Lys Val Glu Ile Lys
245

<210> 56
<211> 744
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 1300 scFv (nt)

<400> 56

```
cagatgcagc tggtgcagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cataggctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacagtg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
gccatccgga tgacccagtc tccttccacc ctgtctgcat ctgtgggaga cagagtcacc 480
atcacttgcc gggccagtca gagcattagt cactacttgg cctggtatca acagaaacca 540
gggaaagccc ctaagctcct gatctttgat gcctcccgtt tggcaagtgg ggtcccatca 600
aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 660
gaagattttg cgacatacta ctgtcaacag agttacggtg cccctatgtt cactttcggc 720
cctgggacca gagtggatct caaa                                        744
```

<210> 57
<211> 248
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 1300 scFv (aa)

<400> 57

```
Gln Met Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
    130                 135                 140
Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160
Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser His Tyr Leu Ala Trp Tyr
                165                 170                 175
Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Phe Asp Ala Ser
            180                 185                 190
Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205
Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala


    210                 215                 220
Thr Tyr Tyr Cys Gln Gln Ser Tyr Gly Ala Pro Met Phe Thr Phe Gly
225                 230                 235                 240
Pro Gly Thr Arg Val Asp Leu Lys
                245
```

<210> 58
<211> 753
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 1 scFv (nt)

<400> 58

```
gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
gcggactctg taaagggccg attcaccatc tccagagaca acgccaagaa ctccctgttt 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacaatg 360
gtcacagtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
cagtctgccc tgactcagcc cgcctccgtg tctgggtctc ctggacagtc gatcaccatc 480
tcctgcactg ggaccagcag tgacgttggt gcttataact ttgtctcctg gtaccagcag 540
ctcccaggaa cagcccccaa attcctcatt tatgacaata ataaacgacc cccagggatt 600
cctgaccgat tctctggctc caagtctggc acgtcagcca ccctgggcat caccggactc 660
cagactgggg acgaggccga ttattactgc gcaacatggg atagcggcct gagtgctgtg 720
gtattcggcg gagggaccaa gctgaccgtc cta                              753
```

<210> 59
<211> 251
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 1 scFv (aa)

<400> 59

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Phe Val Ser
                165                 170                 175
Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Phe Leu Ile Tyr Asp
            180                 185                 190

Asn Asn Lys Arg Pro Pro Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Asp Ser Gly Leu Ser Ala Val
225                 230                 235                 240
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 60
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 192B (aa)

<400> 60

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120                 125
```

<210> 61
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 328 (aa)

<400> 61

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser


        115                 120                 125
```

<210> 62
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 1304 Clone 1300 (aa)

<400> 62

```
Gln Met Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 63
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clones 227, 488, 241 (aa)

<400> 63

```
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 64
<211> 111
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 192B (aa)

<400> 64

```
Gln Ala Val Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Val Thr Ile Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His
            20                  25                  30
Arg Tyr Val Ser Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Tyr Ala Ala Ile
                85                  90                  95
Ser Pro Asn Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 65
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 285 (aa)

<400> 65

```
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Ile Ile Tyr Asp Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser
                85                  90                  95
Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 66
<211> 110
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 328 (aa)

<400> 66

```
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe
            20                  25                  30
Asp Tyr Val Ser Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu
```

```
            35                  40                  45
        Ile Ile Tyr Asp Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
            50                  55                  60
        Ser Gly Ala Lys Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu
        65                  70                  75                  80
        Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Arg Pro Gly
                        85                  90                  95
        Pro Thr Phe Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
                    100                 105                 110
```

<210> 67
<211> 111
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 1 (aa)

<400> 67

```
        Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
         1               5                  10                  15
        Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr
                    20                  25                  30
        Asn Phe Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Phe
                35                  40                  45
        Leu Ile Tyr Asp Asn Asn Lys Arg Pro Pro Gly Ile Pro Asp Arg Phe
            50                  55                  60
        Ser Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu
        65                  70                  75                  80
        Gln Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Asp Ser Gly
                        85                  90                  95
        Leu Ser Ala Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                    100                 105                 110
```

<210> 68
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 1304 (aa)

<400> 68

```
Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                   10                  15
Asp Arg Val Thr Val Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln
                85                  90                  95
Ala Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 69
<211> 108
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 1300 (aa)

<400> 69

```
Ala Ile Arg Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1               5                   10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser His Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Phe Asp Ala Ser Arg Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Gly Ala Pro Met
                85                  90                  95
Phe Thr Phe Gly Pro Gly Thr Arg Val Asp Leu Lys
            100                 105
```

<210> 70
<211> 107
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 227 (aa)

<400> 70

```
Asp Ile Gln Leu Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1              5                   10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Arg Trp
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Leu Glu Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Tyr Asp Asn Leu Pro Leu
                85                  90                  95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> 71
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 488 (aa)

<400> 71

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly


 1              5                   10                  15
Glu Thr Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn His Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser His Pro Arg
                85                  90                  95
Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Asp Ile Lys
            100                 105
```

<210> 72
<211> 17
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-H2 Clone 1304 Clone 1300 Clone 227 Clone 488 Clone 241 (aa)

<400> 72

```
Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val Lys
 1              5                   10                  15
Gly
```

<210> 73

<211> 14
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 192B Clone 192 (aa)

<400> 73

```
Thr Gly Ile Ser Ser Gly Val Asp Ser His Arg Tyr Val Ser
1               5                   10
```

<210> 74
<211> 14
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 285 (aa)

<400> 74

```
Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
1               5                   10
```

<210> 75
<211> 14
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 328 (aa)

<400> 75

```
Thr Gly Thr Arg Ser Asp Val Gly Gly Phe Asp Tyr Val Ser
1               5                   10
```

<210> 76
<211> 14
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 1 (aa)

<400> 76

```
Thr Gly Thr Ser Ser Asp Val Gly Ala Tyr Asn Phe Val Ser
1               5                   10
```

<210> 77
<211> 11
<212> PRT

<213> Homo sapiens

<220>
<223> CDR-L1 Clone 1304 Clone 241 (aa)

<400> 77

Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 78
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 1300 (aa)

<400> 78

Arg Ala Ser Gln Ser Ile Ser His Tyr Leu Ala
1 5 10

<210> 79
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 227 (aa)

<400> 79

Arg Ala Ser Gln Ser Ile Ser Arg Trp Leu Ala

1 5 10

<210> 80
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 488 (aa)

<400> 80

Arg Ala Ser Gln Ser Ile Asn His Tyr Leu Ala
1 5 10

<210> 81
<211> 10
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-H2

<400> 81

Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly
1 5 10

<210> 82
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-H2

<400> 82

Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly
1 5 10

<210> 83
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-L1 Consensus

<220>
<221> VARIANT
<222> 1
<223> Xaa = Thr, Gln or Arg

<220>
<221> VARIANT
<222> 2
<223> Xaa = Gly or Ala

<220>
<221> VARIANT
<222> 3
<223> Xaa = Ile, Thr or Ser

<220>

<221> VARIANT
<222> 4
<223> Xaa = Ser, Arg or Gln

<220>
<221> VARIANT
<222> 5
<223> Xaa = null or Ser

<220>
<221> VARIANT
<222> 6
<223> Xaa = null, Asp or Gly

<220>
<221> VARIANT
<222> 7
<223> Xaa = null, Val or Leu

<220>
<221> VARIANT
<222> 8
<223> Xaa = Asp, Gly or Ser

<220>
<221> VARIANT
<222> 9
<223> Xaa = Ser, Gly, Ala or Ile

<220>
<221> VARIANT
<222> 10
<223> Xaa = His, Tyr, Phe, Ser or Asn

<220>
<221> VARIANT
<222> 11
<223> Xaa = Arg, Asn, Asp or His

<220>
<221> VARIANT
<222> 12
<223> Xaa = Tyr, Phe or Trp

<220>
<221> VARIANT
<222> 13
<223> Xaa = Val or Leu

<220>
<221> VARIANT
<222> 14
<223> Xaa = Ser, Asn or Ala

<400> 83

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 84
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-L2 Consensus

<220>
<221> VARIANT
<222> 2
<223> Xaa = Phe, Val, Asn or Ala

<220>
<221> VARIANT
<222> 3
<223> Xaa = Ser, Thr or Asn

<220>
<221> VARIANT
<222> 4
<223> Xaa = Lys, Val, Asn or Arg

<220>
<221> VARIANT
<222> 5
<223> Xaa = Arg, Val or Leu

<220>
<221> VARIANT
<222> 6
<223> Xaa = Pro, Lys, Ala or Glu

<220>
<221> VARIANT
<222> 7
<223> Xaa = Ser, Pro, Ala or Thr

<400> 84

Asp Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 85
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-L3 Consensus

<220>
<221> VARIANT
<222> 1
<223> Xaa = Ser, Gly, Thr, Ala or Gln

<220>
<221> VARIANT
<222> 2
<223> Xaa = Ser, Thr or Gln

<220>
<221> VARIANT
<222> 3
<223> Xaa = Tyr, Trp or Ser

<220>
<221> VARIANT
<222> 4
<223> Xaa = Ala, Thr, Arg, Asp or Tyr

<220>
<221> VARIANT
<222> 5
<223> Xaa = Ala, Ser, Pro, Gly or Asn

<220>
<221> VARIANT
<222> 6
<223> Xaa = Ile, Ser, Gly, Thr, Leu, Ala or His

<220>
<221> VARIANT
<222> 7
<223> Xaa = Ser, Pro or Leu

<220>
<221> VARIANT
<222> 8
<223> Xaa = Pro, Thr, Ser, Gln, Met, Arg or null

<220>
<221> VARIANT
<222> 9
<223> Xaa = Asn, Leu, Ala, Met or null

<220>
<221> VARIANT
<222> 10
<223> Xaa = Leu or null

<220>
<221> VARIANT
<222> 11
<223> Xaa = Tyr, Trp, Phe, Val or Leu

<220>
<221> VARIANT
<222> 12
<223> Xaa = Val or Thr

<400> 85
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

1 5 10

<210> 86
<211> 753
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 192 scFv (nt)

<400> 86

```
gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag gataggctat 180
gcggactctg taaagggccg attcaccatc tccagagaca acgccaagaa ctccctgttt 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacaatg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
caggctgtgc tgactcagcc tcgctcagtg tccgggtctc ctggacagtc agtcaccatc 480
tcctgcactg gaatcagcag tggtgttgat agtcataggt atgtctcctg gtaccaacac 540
cacccaggca aagcccccaa actcatgatt tatgatttca gtaagcggcc ctcaggggtc 600
cctgatcgtt tctctggctc caagtctggc aacacggcct ccctgaccat ctctgggctc 660
caggctgagg atgaggctga ttactattgc tgctcatatg cagccatctc ccctaattat 720
gtcttcggaa ctgggaccaa gctgaccgtc cta                              753
```

<210> 87
<211> 251
<212> PRT
<213> Homo sapiens

<220>
<223> Clone 192 scFv (aa)

<400> 87

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ala Val Leu
    130                 135                 140
Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His Arg Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr Asp
            180                 185                 190
Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Ala Ile Ser Pro Asn Tyr
225                 230                 235                 240
Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 88
<211> 747
<212> DNA
<213> Homo sapiens

<220>
<223> Clone 241 scFv (nt)

<400> 88

```
gaagtgcagc tggtgcagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt attagttgga atagtggtag cataggctat 180
gcggactctg tgaagggccg attcaccatc tccagagaca acgccaagaa ctccctgtat 240
ctgcaaatga acagtctgag agctgaggac acggccgtgt attactgtgc gagagatcag 300
gggtatcatt actatgatag tgccgaacat gcttttgata tctggggcca agggacagtg 360
gtcaccgtct cctcaggtgg aggcggttca ggcggaggtg gctctggcgg tggcggatcg 420
gccatccgga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 480
gtcacttgcc aggcgagtca ggacattagc aactatttaa attggtatca gcagaaacca 540
gggagagccc ctaagctcct gatctacgat gcatccaatg tgaaagcagg ggtcccatca 600
aggttcagtg gggtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct 660
gaagattttg caacttacta ctgtcaacag agttacagta cccctcaggc gtacactttt 720
ggccagggga ccaagctgga tatcaaa                                     747
```

<210> 89
<211> 249

<212> PRT
<213> Homo sapiens

<220>
<223> Clone 241 scFv (aa)

<400> 89

```
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
    130                 135                 140
Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160
Val Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn Trp Tyr
                165                 170                 175
Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser
            180                 185                 190
Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly
        195                 200                 205
Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220
Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr Phe
225                 230                 235                 240
Gly Gln Gly Thr Lys Leu Asp Ile Lys
                245
```

<210> 90
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 241 (aa)

<400> 90

Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15
Asp Arg Val Thr Val Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu Leu Ile
35 40 45
Tyr Asp Ala Ser Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln
85 90 95
Ala Tyr Thr Phe Gly Gln Gly Thr Lys Leu Asp Ile Lys
100 105

<210> 91
<211> 111
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 192

<400> 91

Gln Ala Val Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Val Thr Ile Ser Cys Thr Gly Ile Ser Ser Gly Val Asp Ser His
20 25 30
Arg Tyr Val Ser Trp Tyr Gln His His Pro Gly Lys Ala Pro Lys Leu
35 40 45
Met Ile Tyr Asp Phe Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Ala Ile
85 90 95
Ser Pro Asn Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 92
<211> 556
<212> PRT
<213> Homo sapiens

<220>
<223> CD19 Accession No. P15391

<400> 92

```
Met Pro Pro Pro Arg Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
 1               5                  10                  15
Glu Val Arg Pro Glu Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp
            20                  25                  30
Asn Ala Val Leu Gln Cys Leu Lys Gly Thr Ser Asp Gly Pro Thr Gln
        35                  40                  45
Gln Leu Thr Trp Ser Arg Glu Ser Pro Leu Lys Pro Phe Leu Lys Leu
    50                  55                  60
Ser Leu Gly Leu Pro Gly Leu Gly Ile His Met Arg Pro Leu Ala Ile
65                  70                  75                  80
Trp Leu Phe Ile Phe Asn Val Ser Gln Gln Met Gly Gly Phe Tyr Leu
                85                  90                  95
Cys Gln Pro Gly Pro Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr
            100                 105                 110
Val Asn Val Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp
        115                 120                 125
Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro
    130                 135                 140
Ser Ser Pro Ser Gly Lys Leu Met Ser Pro Lys Leu Tyr Val Trp Ala
145                 150                 155                 160
Lys Asp Arg Pro Glu Ile Trp Glu Gly Glu Pro Pro Cys Leu Pro Pro
                165                 170                 175
Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro
            180                 185                 190
Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser
        195                 200                 205
Arg Gly Pro Leu Ser Trp Thr His Val His Pro Lys Gly Pro Lys Ser
```

```
    210                 215                 220
Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Ala Arg Asp Met Trp
225                 230                 235                 240
Val Met Glu Thr Gly Leu Leu Leu Pro Arg Ala Thr Ala Gln Asp Ala
                245                 250                 255
Gly Lys Tyr Tyr Cys His Arg Gly Asn Leu Thr Met Ser Phe His Leu
            260                 265                 270
Glu Ile Thr Ala Arg Pro Val Leu Trp His Trp Leu Leu Arg Thr Gly
        275                 280                 285
Gly Trp Lys Val Ser Ala Val Thr Leu Ala Tyr Leu Ile Phe Cys Leu
    290                 295                 300
Cys Ser Leu Val Gly Ile Leu His Leu Gln Arg Ala Leu Val Leu Arg
305                 310                 315                 320
Arg Lys Arg Lys Arg Met Thr Asp Pro Thr Arg Arg Phe Phe Lys Val
                325                 330                 335
Thr Pro Pro Pro Gly Ser Gly Pro Gln Asn Gln Tyr Gly Asn Val Leu
            340                 345                 350
Ser Leu Pro Thr Pro Thr Ser Gly Leu Gly Arg Ala Gln Arg Trp Ala
        355                 360                 365
Ala Gly Leu Gly Gly Thr Ala Pro Ser Tyr Gly Asn Pro Ser Ser Asp
    370                 375                 380
Val Gln Ala Asp Gly Ala Leu Gly Ser Arg Ser Pro Pro Gly Val Gly
385                 390                 395                 400
Pro Glu Glu Glu Glu Gly Glu Gly Tyr Glu Glu Pro Asp Ser Glu Glu
                405                 410                 415
Asp Ser Glu Phe Tyr Glu Asn Asp Ser Asn Leu Gly Gln Asp Gln Leu
            420                 425                 430
Ser Gln Asp Gly Ser Gly Tyr Glu Asn Pro Glu Asp Glu Pro Leu Gly
        435                 440                 445
Pro Glu Asp Glu Asp Ser Phe Ser Asn Ala Glu Ser Tyr Glu Asn Glu
    450                 455                 460
Asp Glu Glu Leu Thr Gln Pro Val Ala Arg Thr Met Asp Phe Leu Ser
465                 470                 475                 480
Pro His Gly Ser Ala Trp Asp Pro Ser Arg Glu Ala Thr Ser Leu Gly
                485                 490                 495
Ser Gln Ser Tyr Glu Asp Met Arg Gly Ile Leu Tyr Ala Ala Pro Gln
            500                 505                 510
Leu Arg Ser Ile Arg Gly Gln Pro Gly Pro Asn His Glu Glu Asp Ala
        515                 520                 525
Asp Ser Tyr Glu Asn Met Asp Asn Pro Asp Gly Pro Asp Pro Ala Trp
    530                 535                 540
Gly Gly Gly Gly Arg Met Gly Thr Trp Ser Thr Arg
545                 550                 555
```

<210> 93
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 192B, Clone 192

<400> 93

```
Asp Phe Ser Lys Arg Pro Ser
1               5
```

<210> 94
<211> 7

<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 285

<400> 94

Asp Val Thr Val Arg Pro Ser
1 5

<210> 95
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 328

<400> 95

Asp Val Thr Lys Arg Pro Ser
1 5

<210> 96
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 1

<400> 96

Asp Asn Asn Lys Arg Pro Pro
1 5

<210> 97
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 1304 Clone 241

<400> 97

Asp Ala Ser Asn Val Lys Ala
1 5

<210> 98
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 1300

<400> 98

Asp Ala Ser Arg Leu Ala Ser
1 5

<210> 99
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 227

<400> 99

Asp Ala Ser Asn Leu Glu Thr
1 5

<210> 100
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 488

<400> 100

Asp Ala Ser Asn Arg Ala Thr
1 5

<210> 101
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 192B

<400> 101

Ser Ser Tyr Ala Ala Ile Ser Pro Asn Tyr Val
1 5 10

<210> 102
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 192

<400> 102

Cys Ser Tyr Ala Ala Ile Ser Pro Asn Tyr Val
1 5 10

<210> 103
<211> 12
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 285

<400> 103

Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu Trp Val
1 5 10

<210> 104
<211> 10
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 328

<400> 104

Thr Ser Tyr Arg Pro Gly Pro Thr Phe Val
1 5 10

<210> 105
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 1

<400> 105

Ala Thr Trp Asp Ser Gly Leu Ser Ala Val Val
1 5 10

<210> 106
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 1304 Clone 241

<400> 106

Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr
1 5 10

<210> 107
<211> 10
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 1300

<400> 107

Gln Gln Ser Tyr Gly Ala Pro Met Phe Thr

1 5 10

<210> 108
<211> 9
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 227

<400> 108

Gln Gln Tyr Asp Asn Leu Pro Leu Thr
1 5

<210> 109
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 488

<400> 109

Gln Gln Ser Tyr Ser His Pro Arg Met Tyr Thr
1 5 10

<210> 110
<211> 14
<212> PRT
<213> Artificial Sequence

<220>
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<220>
<223> CDR-L1 consensus

<220>
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<223> Xaa = Thr, Gln, Ser or Arg

<220>
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<223> Xaa = Gly or Ala

<220>
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<223> Xaa = Ile, Thr, Asp or Ser

<220>
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<223> Xaa = Ser, Arg, Thr or Gln

<220>
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<223> Xaa = null or Ser

<220>
<221> VARIANT
<222> 6
<223> Xaa = null, Asp, Asn or Gly

<220>
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<222> 7
<223> Xaa = null, Val or Leu

<220>
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<222> 8
<223> Xaa = any amino acid or null

<220>
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<222> 9
<223> Xaa = any amino acid or null

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<222> 12
<223> Xaa = Tyr, Phe, Asp or Trp

<220>
<221> VARIANT
<222> 13
<223> Xaa = Val, Ala or Leu

<220>
<221> VARIANT
<222> 14
<223> Xaa = Ser, Asn or Ala

<400> 110

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1               5                   10
```

<210> 111
<211> 14
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<220>
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<220>
<223> CDR-L1 consensus

<220>
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<220>
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<223> Xaa = Gly, Asp, Asn or null

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<223> Xaa = Asp, Gly, Ile, Leu, Ser or null

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<223> Xaa = Ser, Gly, Ala, Ile, Arg or null

<220>
<221> VARIANT
<222> 10
<223> Xaa = His, Tyr, Phe, Ser or Asn

<220>
<221> VARIANT
<222> 11
<223> Xaa = Arg, Asn, Asp, His or Tyr

<220>
<221> VARIANT
<222> 12
<223> Xaa = Tyr, Phe, Asp or Trp

<220>
<221> VARIANT
<222> 13
<223> Xaa = Val, Ala, Leu

<220>
<221> VARIANT
<222> 14
<223> Xaa = Ser, Asn or Ala

<400> 111

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1               5                   10
```

<210> 112
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-L2 Consensus

<220>
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<223> Xaa = Asp or Ser

<220>
<221> VARIANT
<222> 2
<223> Xaa = Phe, Val, Asn, Lys or Ala

<220>
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<223> Xaa = Ser, Thr, Asp or Asn

<220>
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<222> 4
<223> Xaa = Lys, Val, Asn, Gln or Arg

<220>
<221> VARIANT
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<223> Xaa = Arg, Val or Leu

<220>
<221> VARIANT
<222> 6
<223> Xaa = Pro, Lys, Ala or Glu

<220>
<221> VARIANT
<222> 7
<223> Xaa = Ser, Pro, Ala or Thr

<400> 112

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1               5
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<210> 113
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-L3

<220>
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<223> Xaa = Cys, Ser, Ala, Gly or Asn

<220>
<221> VARIANT
<222> 2
<223> Xaa = Ser, Ala or Thr

<220>
<221> VARIANT
<222> 3
<223> Xaa = Tyr, Trp or Arg

<220>
<221> VARIANT
<222> 4
<223> Xaa = Ala or Asp

<220>
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<222> 5
<223> Xaa = Gly, Asp or Ser

<220>
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<223> Xaa = Arg, Ser or Asn

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<223> Xaa = Tyr, Leu or Gly

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<220>
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<223> Xaa = Leu or Val

<400> 113

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 114
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<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-L3 consensus

<220>
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<223> Xaa = Ser, Gly, Thr, Ala, Gln, Cys or Asn

<220>
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<223> Xaa = Ser, Gln, Ala or Thr

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<223> Xaa = Tyr, Ser, Trp or Arg

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<223> Xaa = Ala, Asp, Arg, Thr or Tyr

<220>
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<223> Xaa = Ala, Ser, Pro, Gly, Asn or Asp

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<223> Xaa = Pro, Thr, Ser, Gln, Met, Arg, Asn or null

<220>
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<223> Xaa = Ser, Leu, Asn, Ala, Met or null

<220>
<221> VARIANT
<222> 10
<223> Xaa = Leu or null

<220>
<221> VARIANT
<222> 11
<223> Xaa = Tyr, Trp, Phe, Val, Ala or Leu

<220>
<221> VARIANT
<222> 12
<223> Xaa = Val, Thr or Leu

<400> 114

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1               5                   10
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<210> 115
<211> 12
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> CDR-L3 consensus

<220>
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<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 2
<223> Xaa = Ser, Gln, Ala or Thr

<220>
<221> VARIANT
<222> 3
<223> Xaa = Tyr, Ser, Trp or Arg

<220>
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<222> 4
<223> Xaa = Ala, Asp, Arg, Thr or Tyr

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<221> VARIANT
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<223> Xaa = any amino acid

<220>
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<223> Xaa = any amino acid

<220>
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<222> 7
<223> Xaa = Ser, Pro, Leu, Tyr or Gly

<220>
<221> VARIANT
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<223> Xaa = any amino acid or null

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<223> Xaa = any amino acid or null

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<221> VARIANT
<222> 10
<223> Xaa = Leu or null

<220>
<221> VARIANT
<222> 11
<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 12
<223> Xaa = Val, Thr or Leu

<400> 115

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1               5                   10
```

<210> 116
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 79

<400> 116

```
Gly Thr Trp Asp Ile Ser Leu Arg Phe Gly Val
1               5                   10
```

<210> 117
<211> 11
<212> PRT

<213> Homo sapiens

<220>
<223> CDR-L3 Clone 835

<400> 117

Cys Ser Tyr Glu Ala Pro Thr His Thr Tyr Val
1 5 10

<210> 118
<211> 10
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 184

<400> 118

Ala Ala Trp Asp Asp Ser Leu Asn Val Val
1 5 10

<210> 119
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 505

<400> 119

Cys Ser Tyr Ala Gly Ser Tyr Thr Phe Glu Val
1 5 10

<210> 120
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 506

<400> 120

Cys Ser Phe Ala Gly Tyr Tyr Thr Tyr Trp Leu
1 5 10

<210> 121
<211> 9
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 305

<220>
<221> VARIANT
<222> 3
<223> Xaa = any amino acid

<400> 121

Ser Ser Xaa Ala Gly Arg Lys Tyr Val
1 5

<210> 122
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> Linker

<400> 122

Gly Gly Gly Ser
1

<210> 123
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> Linker

<400> 123

Gly Gly Gly Gly Ser
1 5

<210> 124
<211> 12
<212> PRT
<213> Homo sapiens

<220>
<223> spacer (IgG4hinge) (aa)

<400> 124

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro
1 5 10

<210> 125
<211> 36
<212> PRT
<213> Homo sapiens

<220>
<223> spacer (IgG4hinge) (nt)

<400> 125

Gly Ala Ala Thr Cys Thr Ala Ala Gly Thr Ala Cys Gly Gly Ala Cys
1 5 10 15
Cys Gly Cys Cys Cys Thr Gly Cys Cys Cys Cys Cys Cys Thr Thr Gly
20 25 30
Cys Cys Cys Thr
35

<210> 126
<211> 119
<212> PRT
<213> Homo sapiens

<220>
<223> Hinge-CH3 spacer

<400> 126

Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Gly Gln Pro Arg
1 5 10 15
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
20 25 30
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
35 40 45
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
50 55 60
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
65 70 75 80
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
85 90 95
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
100 105 110
Leu Ser Leu Ser Leu Gly Lys
115

<210> 127
<211> 229
<212> PRT
<213> Homo sapiens

<220>
<223> Hinge-CH2-CH3 spacer

<400> 127

```
Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe
 1               5                  10                  15
Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
            20                  25                  30
Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
        35                  40                  45
Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val
    50                  55                  60
Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser
65                  70                  75                  80
Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
                85                  90                  95
Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser
            100                 105                 110
Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
        115                 120                 125
Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys Asn Gln
    130                 135                 140
Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
145                 150                 155                 160
Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
                165                 170                 175
Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu
            180                 185                 190
Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser Cys Ser
        195                 200                 205
Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
    210                 215                 220
Leu Ser Leu Gly Lys
225
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<210> 128
<211> 282
<212> PRT
<213> Homo sapiens

<220>
<223> IgD-hinge-Fc

<400> 128

Arg Trp Pro Glu Ser Pro Lys Ala Gln Ala Ser Ser Val Pro Thr Ala
1 5 10 15
Gln Pro Gln Ala Glu Gly Ser Leu Ala Lys Ala Thr Thr Ala Pro Ala
20 25 30
Thr Thr Arg Asn Thr Gly Arg Gly Gly Glu Glu Lys Lys Lys Glu Lys
35 40 45
Glu Lys Glu Glu Gln Glu Glu Arg Glu Thr Lys Thr Pro Glu Cys Pro
50 55 60
Ser His Thr Gln Pro Leu Gly Val Tyr Leu Leu Thr Pro Ala Val Gln
65 70 75 80
Asp Leu Trp Leu Arg Asp Lys Ala Thr Phe Thr Cys Phe Val Val Gly
85 90 95
Ser Asp Leu Lys Asp Ala His Leu Thr Trp Glu Val Ala Gly Lys Val
100 105 110
Pro Thr Gly Gly Val Glu Glu Gly Leu Leu Glu Arg His Ser Asn Gly
115 120 125
Ser Gln Ser Gln His Ser Arg Leu Thr Leu Pro Arg Ser Leu Trp Asn
130 135 140
Ala Gly Thr Ser Val Thr Cys Thr Leu Asn His Pro Ser Leu Pro Pro
145 150 155 160
Gln Arg Leu Met Ala Leu Arg Glu Pro Ala Ala Gln Ala Pro Val Lys
165 170 175
Leu Ser Leu Asn Leu Leu Ala Ser Ser Asp Pro Pro Glu Ala Ala Ser
180 185 190
Trp Leu Leu Cys Glu Val Ser Gly Phe Ser Pro Pro Asn Ile Leu Leu
195 200 205
Met Trp Leu Glu Asp Gln Arg Glu Val Asn Thr Ser Gly Phe Ala Pro
210 215 220
Ala Arg Pro Pro Pro Gln Pro Gly Ser Thr Thr Phe Trp Ala Trp Ser
225 230 235 240
Val Leu Arg Val Pro Ala Pro Pro Ser Pro Gln Pro Ala Thr Tyr Thr
245 250 255
Cys Val Val Ser His Glu Asp Ser Arg Thr Leu Leu Asn Ala Ser Arg
260 265 270
Ser Leu Glu Val Ser Tyr Val Thr Asp His
275 280

<210> 129
<211> 27
<212> PRT
<213> Homo sapiens

<220>
<223> CD28 (amino acids 153-179 of Accession No. P10747)

<400> 129

Phe Trp Val Leu Val Val Val Gly Gly Val Leu Ala Cys Tyr Ser Leu
1 5 10 15
Leu Val Thr Val Ala Phe Ile Ile Phe Trp Val
20 25

<210> 130
<211> 66
<212> PRT
<213> Homo sapiens

<220>
<223> CD28 (amino acids 114-179 of Accession No. P10747)

<400> 130

```
Ile Glu Val Met Tyr Pro Pro Pro Tyr Leu Asp Asn Glu Lys Ser Asn
 1              5                   10                  15
Gly Thr Ile Ile His Val Lys Gly Lys His Leu Cys Pro Ser Pro Leu
            20                  25                  30
Phe Pro Gly Pro Ser Lys Pro Phe Trp Val Leu Val Val Val Gly Gly
        35                  40                  45
Val Leu Ala Cys Tyr Ser Leu Leu Val Thr Val Ala Phe Ile Ile Phe
    50                  55                  60
Trp Val
65
```

<210> 131
<211> 41
<212> PRT
<213> Homo sapiens

<220>
<223> CD28 (amino acids 180-220 of P10747)

<400> 131

```
Arg Ser Lys Arg Ser Arg Leu Leu His Ser Asp Tyr Met Asn Met Thr
 1              5                   10                  15
Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
            20                  25                  30
Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        35                  40
```

<210> 132
<211> 41
<212> PRT
<213> Homo sapiens

<220>
<223> CD28 (LL to GG)

<400> 132

```
Arg Ser Lys Arg Ser Arg Gly Gly His Ser Asp Tyr Met Asn Met Thr
 1              5                   10                  15
Pro Arg Arg Pro Gly Pro Thr Arg Lys His Tyr Gln Pro Tyr Ala Pro
            20                  25                  30
Pro Arg Asp Phe Ala Ala Tyr Arg Ser
        35                  40
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<210> 133
<211> 42
<212> PRT
<213> Homo sapiens

<220>
<223> 4-1BB (amino acids 214-255 of Q07011.1)

<400> 133

```
Lys Arg Gly Arg Lys Lys Leu Leu Tyr Ile Phe Lys Gln Pro Phe Met
 1               5                  10                  15
Arg Pro Val Gln Thr Thr Gln Glu Glu Asp Gly Cys Ser Cys Arg Phe
            20                  25                  30
Pro Glu Glu Glu Glu Gly Gly Cys Glu Leu
        35                  40
```

<210> 134
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> CD3 zeta

<400> 134

```
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Gln Gln Gly
 1               5                  10                  15
Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
            20                  25                  30
Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
        35                  40                  45
Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
    50                  55                  60
Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65                  70                  75                  80
Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
                85                  90                  95
Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
            100                 105                 110
```

<210> 135
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> CD3 zeta

<400> 135

```
Arg Val Lys Phe Ser Arg Ser Ala Glu Pro Pro Ala Tyr Gln Gln Gly
 1               5                  10                  15
Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
            20                  25                  30
Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
        35                  40                  45
Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
    50                  55                  60
Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65                  70                  75                  80
Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
                85                  90                  95
Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
            100                 105                 110
```

<210> 136

<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> CD3 zeta

<400> 136

```
Arg Val Lys Phe Ser Arg Ser Ala Asp Ala Pro Ala Tyr Lys Gln Gly
 1               5                  10                  15
Gln Asn Gln Leu Tyr Asn Glu Leu Asn Leu Gly Arg Arg Glu Glu Tyr
            20                  25                  30
Asp Val Leu Asp Lys Arg Arg Gly Arg Asp Pro Glu Met Gly Gly Lys
        35                  40                  45
Pro Arg Arg Lys Asn Pro Gln Glu Gly Leu Tyr Asn Glu Leu Gln Lys
    50                  55                  60
Asp Lys Met Ala Glu Ala Tyr Ser Glu Ile Gly Met Lys Gly Glu Arg
65                  70                  75                  80
Arg Arg Gly Lys Gly His Asp Gly Leu Tyr Gln Gly Leu Ser Thr Ala
                85                  90                  95
Thr Lys Asp Thr Tyr Asp Ala Leu His Met Gln Ala Leu Pro Pro Arg
            100                 105                 110
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<210> 137
<211> 24
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> T2A

<400> 137

```
Leu Glu Gly Gly Gly Glu Gly Arg Gly Ser Leu Leu Thr Cys Gly Asp
 1               5                  10                  15
Val Glu Glu Asn Pro Gly Pro Arg
            20
```

<210> 138
<211> 357
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> tEGFR

<400> 138

```
Met Leu Leu Leu Val Thr Ser Leu Leu Leu Cys Glu Leu Pro His Pro
 1               5                  10                  15
Ala Phe Leu Leu Ile Pro Arg Lys Val Cys Asn Gly Ile Gly Ile Gly
            20                  25                  30
Glu Phe Lys Asp Ser Leu Ser Ile Asn Ala Thr Asn Ile Lys His Phe
        35                  40                  45
Lys Asn Cys Thr Ser Ile Ser Gly Asp Leu His Ile Leu Pro Val Ala
    50                  55                  60
Phe Arg Gly Asp Ser Phe Thr His Thr Pro Pro Leu Asp Pro Gln Glu
65                  70                  75                  80
Leu Asp Ile Leu Lys Thr Val Lys Glu Ile Thr Gly Phe Leu Leu Ile
                85                  90                  95


Gln Ala Trp Pro Glu Asn Arg Thr Asp Leu His Ala Phe Glu Asn Leu
            100                 105                 110
Glu Ile Ile Arg Gly Arg Thr Lys Gln His Gly Gln Phe Ser Leu Ala
        115                 120                 125
Val Val Ser Leu Asn Ile Thr Ser Leu Gly Leu Arg Ser Leu Lys Glu
    130                 135                 140
Ile Ser Asp Gly Asp Val Ile Ile Ser Gly Asn Lys Asn Leu Cys Tyr
145                 150                 155                 160
Ala Asn Thr Ile Asn Trp Lys Lys Leu Phe Gly Thr Ser Gly Gln Lys
                165                 170                 175
Thr Lys Ile Ile Ser Asn Arg Gly Glu Asn Ser Cys Lys Ala Thr Gly
            180                 185                 190
Gln Val Cys His Ala Leu Cys Ser Pro Glu Gly Cys Trp Gly Pro Glu
        195                 200                 205
Pro Arg Asp Cys Val Ser Cys Arg Asn Val Ser Arg Gly Arg Glu Cys
    210                 215                 220
Val Asp Lys Cys Asn Leu Leu Glu Gly Glu Pro Arg Glu Phe Val Glu
225                 230                 235                 240
Asn Ser Glu Cys Ile Gln Cys His Pro Glu Cys Leu Pro Gln Ala Met
                245                 250                 255
Asn Ile Thr Cys Thr Gly Arg Gly Pro Asp Asn Cys Ile Gln Cys Ala
            260                 265                 270
His Tyr Ile Asp Gly Pro His Cys Val Lys Thr Cys Pro Ala Gly Val
        275                 280                 285
Met Gly Glu Asn Asn Thr Leu Val Trp Lys Tyr Ala Asp Ala Gly His
    290                 295                 300
Val Cys His Leu Cys His Pro Asn Cys Thr Tyr Gly Cys Thr Gly Pro
305                 310                 315                 320
Gly Leu Glu Gly Cys Pro Thr Asn Gly Pro Lys Ile Pro Ser Ile Ala
                325                 330                 335
Thr Gly Met Val Gly Ala Leu Leu Leu Leu Leu Val Val Ala Leu Gly
            340                 345                 350
Ile Gly Leu Phe Met
        355
```

<210> 139
<211> 557
<212> PRT
<213> Macaca mulatta

<220>
<223> Accession No. F7F486

<400> 139

```
Met Pro Pro Pro Cys Leu Leu Phe Phe Leu Leu Phe Leu Thr Pro Met
 1               5                  10                  15
Glu Val Arg Pro Gln Glu Pro Leu Val Val Lys Val Glu Glu Gly Asp
            20                  25                  30
Asn Ala Val Leu Gln Cys Leu Glu Gly Thr Ser Asp Gly Pro Thr Gln
        35                  40                  45
Gln Leu Val Trp Cys Arg Asp Ser Pro Phe Glu Pro Phe Leu Asn Leu
    50                  55                  60
Ser Leu Gly Leu Pro Gly Met Gly Ile Arg Met Gly Pro Leu Gly Ile
65                  70                  75                  80
Trp Leu Leu Ile Phe Asn Val Ser Asn Gln Thr Gly Gly Phe Tyr Leu
                85                  90                  95
Cys Gln Pro Gly Leu Pro Ser Glu Lys Ala Trp Gln Pro Gly Trp Thr
            100                 105                 110
Val Ser Val Glu Gly Ser Gly Glu Leu Phe Arg Trp Asn Val Ser Asp
        115                 120                 125
Leu Gly Gly Leu Gly Cys Gly Leu Lys Asn Arg Ser Ser Glu Gly Pro
```

```
                130                 135                 140
Ser Ser Pro Ser Gly Lys Leu Asn Ser Ser Gln Leu Tyr Val Trp Ala
145                 150                 155                 160
Lys Asp Arg Pro Glu Met Trp Glu Gly Glu Pro Val Cys Gly Pro Pro
                165                 170                 175
Arg Asp Ser Leu Asn Gln Ser Leu Ser Gln Asp Leu Thr Met Ala Pro
            180                 185                 190
Gly Ser Thr Leu Trp Leu Ser Cys Gly Val Pro Pro Asp Ser Val Ser
        195                 200                 205
Arg Gly Pro Leu Ser Trp Thr His Val Arg Pro Lys Gly Pro Lys Ser
    210                 215                 220
Ser Leu Leu Ser Leu Glu Leu Lys Asp Asp Arg Pro Asp Arg Asp Met
225                 230                 235                 240
Trp Val Val Asp Thr Gly Leu Leu Leu Thr Arg Ala Thr Ala Gln Asp
                245                 250                 255
Ala Gly Lys Tyr Tyr Cys His Arg Gly Asn Trp Thr Lys Ser Phe Tyr
            260                 265                 270
Leu Glu Ile Thr Ala Arg Pro Ala Leu Trp His Trp Leu Leu Arg Ile
        275                 280                 285
Gly Gly Trp Lys Val Pro Ala Val Thr Leu Thr Tyr Leu Ile Phe Cys
    290                 295                 300
Leu Cys Ser Leu Val Gly Ile Leu Gln Leu Gln Arg Ala Leu Val Leu
305                 310                 315                 320
Arg Arg Lys Arg Lys Arg Met Thr Asp Pro Thr Arg Arg Phe Phe Lys
                325                 330                 335
Val Thr Pro Pro Pro Gly Ser Gly Pro Gln Asn Gln Tyr Gly Asn Val
            340                 345                 350
Leu Ser Leu Pro Thr Pro Thr Ser Gly Leu Gly Arg Ala Gln Arg Trp
        355                 360                 365
Ala Ala Gly Leu Gly Gly Thr Ala Pro Ser Tyr Gly Asn Pro Ser Ser
    370                 375                 380
Asp Val Gln Val Asp Gly Ala Val Gly Ser Arg Ser Pro Pro Gly Ala
385                 390                 395                 400
Gly Pro Glu Glu Glu Glu Gly Glu Gly Tyr Glu Glu Pro Asp Ser Glu
                405                 410                 415
Glu Gly Ser Glu Phe Tyr Glu Asn Asp Ser Asn Phe Gly Gln Asp Gln
            420                 425                 430
Leu Ser Gln Asp Gly Ser Gly Tyr Glu Asn Pro Glu Asp Glu Pro Leu
        435                 440                 445
Gly Pro Glu Asp Glu Asp Ser Phe Ser Asn Ala Glu Ser Tyr Glu Asn
    450                 455                 460
Glu Asp Glu Glu Leu Thr Gln Pro Val Ala Arg Thr Met Asp Phe Leu
465                 470                 475                 480
Ser Pro His Gly Ser Ala Trp Asp Pro Ser Arg Glu Ala Thr Ser Leu
                485                 490                 495
Gly Ser Gln Ser Tyr Glu Asp Met Arg Gly Leu Leu Tyr Ala Ala Pro
            500                 505                 510
Gln Leu Arg Thr Ile Arg Gly Gln Pro Gly Pro Asn His Glu Glu Asp
        515                 520                 525
Ala Asp Ser Tyr Glu Asn Met Asp Asn Pro Asp Gly Pro Asp Pro Ala
    530                 535                 540
Trp Gly Gly Gly Gly Arg Met Gly Thr Trp Ser Ala Arg
545                 550                 555
```

<210> 140
<211> 74
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> V1 chimeric rhesus/human

<400> 140

```
His Pro Lys Gly Pro Lys Ser Leu Leu Ser Leu Glu Leu Lys Asp Asp
 1               5                  10                  15
Arg Pro Ala Arg Asp Met Trp Val Met Glu Thr Gly Leu Leu Leu Pro
            20                  25                  30
Arg Ala Thr Ala Gln Asp Ala Gly Lys Tyr Tyr Cys His Arg Gly Asn
        35                  40                  45
Leu Thr Met Ser Phe His Leu Glu Ile Thr Ala Arg Pro Val Leu Trp
    50                  55                  60
His Trp Leu Leu Arg Thr Gly Gly Trp Lys
65                  70
```

<210> 141
<211> 75
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> V2 chimeric rhesus/human

<400> 141

```
Arg Pro Lys Gly Pro Lys Ser Ser Leu Leu Ser Leu Glu Leu Lys Asp
 1               5                  10                  15
Asp Arg Pro Asp Arg Asp Met Trp Val Val Asp Thr Gly Leu Leu Leu
            20                  25                  30
Thr Arg Ala Thr Ala Gln Asp Ala Gly Lys Tyr Tyr Cys His Arg Gly
        35                  40                  45
Asn Leu Thr Met Ser Phe His Leu Glu Ile Thr Ala Arg Pro Val Leu
    50                  55                  60
Trp His Trp Leu Leu Arg Thr Gly Gly Trp Lys
65                  70                  75
```

<210> 142
<211> 74
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<223> V3 chimeric rhesus/human

<400> 142

His Pro Lys Gly Pro Lys Ser Leu Leu Ser Leu Glu Leu Lys Asp Asp
1 5 10 15
Arg Pro Ala Arg Asp Met Trp Val Met Glu Thr Gly Leu Leu Leu Pro
20 25 30
Arg Ala Thr Ala Gln Asp Ala Gly Lys Tyr Tyr Cys His Arg Gly Asn
35 40 45
Trp Thr Lys Ser Phe Tyr Leu Glu Ile Thr Ala Arg Pro Ala Leu Trp
50 55 60
His Trp Leu Leu Arg Ile Gly Gly Trp Lys
65 70

<210> 143
<211> 32
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 143

His Pro Lys Gly Pro Lys Ser Leu Leu Ser Leu Glu Leu Lys Asp Asp
1 5 10 15
Arg Pro Ala Arg Asp Met Trp Val Met Glu Thr Gly Leu Leu Leu Pro
20 25 30

<210> 144
<211> 33
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 144

Arg Pro Lys Gly Pro Lys Ser Ser Leu Leu Ser Leu Glu Leu Lys Asp
1 5 10 15
Asp Arg Pro Asp Arg Asp Met Trp Val Val Asp Thr Gly Leu Leu Leu
20 25 30
Thr

<210> 145
<211> 16
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-H3 clone 305

<220>
<221> VARIANT
<222> 4
<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 6

<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 15
<223> Xaa = any amino acid

<400> 145

Asp Gln Gly Xaa His Xaa Tyr Asp Ser Ala Glu His Ala Phe Xaa Ile
1 5 10 15

<210> 146
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 255

<400> 146

Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn
1 5 10

<210> 147
<211> 14
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 305

<400> 147

Thr Gly Thr Gly Arg Asp Ile Gly Ala Tyr Asp Tyr Val Ser
1 5 10

<210> 148
<211> 14
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 327

<400> 148

Thr Glu Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 149
<211> 14
<212> PRT

<213> Homo sapiens

<220>
<223> CDR-L1 Clone 505

<400> 149

Thr Gly Ala Ser Thr Asp Val Gly Gly Tyr Asn Tyr Val Ser
1 5 10

<210> 150
<211> 14
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 506

<400> 150

Thr Gly Ala Ser Ser Asp Val Gly Gly Tyr Asp His Val Ser
1 5 10

<210> 151
<211> 13
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 184

<400> 151

Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Thr Val Asn
1 5 10

<210> 152
<211> 14
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 835

<400> 152

Thr Gly Pro Ile Ser Gly Val Gly Asp Tyr Thr Ser Val Ser
1 5 10

<210> 153
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 272

<400> 153

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> 154
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 305

<400> 154

Gly Val Asn Lys Arg Pro Ser
1 5

<210> 155
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 505

<400> 155

Asp Val Asn Lys Arg Pro Ser
1 5

<210> 156
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 79

<400> 156

Asp Asn Asn Lys Arg Pro Ser
1 5

<210> 157
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 835

<400> 157

Asp Val Thr Gln Arg Pro Ser
1 5

<210> 158
<211> 12
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 272

<400> 158

Gly Thr Trp Asp Ser Ser Leu Asn Arg Asp Trp Val
1 5 10

<210> 159
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 508

<400> 159

Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Pro
1 5 10

<210> 160
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-H1 Clone 1265

<400> 160

Thr Ser Gly Val Gly Val Gly
1 5

<210> 161
<211> 16
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-H2 Clone 1265

<400> 161

Leu Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser Leu Lys Ser
1 5 10 15

<210> 162
<211> 20
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-H3 Clone 1265

<400> 162

Ile Asp Tyr Gly Ser Gly Ser Tyr Ser Pro Arg Thr Ser Tyr Tyr Tyr
1 5 10 15
Tyr Met Ser Val
20

<210> 163
<211> 11
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L1 Clone 1265

<400> 163

Arg Ala Ser Gln Gly Ile Ser Ser Tyr Leu Asn
1 5 10

<210> 164
<211> 7
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L2 Clone 1265

<400> 164

Ala Ala Ser Asn Leu Gln Ser
1 5

<210> 165
<211> 9
<212> PRT
<213> Homo sapiens

<220>
<223> CDR-L3 Clone 1265

<400> 165

Gln Gln Gly Asp Ala Phe Pro Leu Thr
1 5

<210> 166
<211> 130
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 1265

<400> 166

Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
1 5 10 15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
20 25 30
Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45
Trp Leu Ala Leu Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser
50 55 60
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
85 90 95
Cys Ala His Ile Asp Tyr Gly Ser Gly Ser Tyr Ser Pro Arg Thr Ser
100 105 110
Tyr Tyr Tyr Tyr Met Ser Val Trp Gly Lys Gly Thr Thr Val Thr Val
115 120 125
Ser Ser
130

<210> 167
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 213

<400> 167

```
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 168
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 255

<400> 168

```
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 169
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 272

<400> 169

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 170
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 283

<400> 170

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 171
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 302

<400> 171

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val


    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 172
<211> 98
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 305

<220>
<221> VARIANT
<222> 64
<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 65
<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 68
<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 69
<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> 93
<223> Xaa = any amino acid

<220>
<221> VARIANT
<222> (98) ... (0)
<223> Xaa = any amino acid

<400> 172

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Xaa
    50                  55                  60
Xaa Gly Arg Xaa Xaa Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Xaa Tyr Tyr Cys
                85                  90                  95
Ala Xaa
```

<210> 173
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 314

<400> 173

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 174
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 379

<400> 174

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 175
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 324

<400> 175

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 176
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 327

<220>
<221> VARIANT
<222> 76
<223> Xaa = any amino acid

<400> 176

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Xaa Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 177
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 336

<400> 177

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 178
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 440

<400> 178

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 179
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 448

<400> 179

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 180
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 505

<400> 180

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120                 125
```

<210> 181
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 506

<400> 181

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val

    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120                 125
```

<210> 182
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 508

<400> 182

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20   25   30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100   105   110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115   120   125

<210> 183
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 184

<400> 183

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20   25   30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100   105   110

Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115   120   125

<210> 184
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 79

<400> 184

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser
        115                 120                 125
```

<210> 185
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<223> VH Clone 835

<400> 185

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Leu Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Lys Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120                 125
```

<210> 186
<211> 107
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 1265

<400> 186

```
Ala Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val Gly
 1               5                   10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Tyr
            20                  25                  30
Leu Asn Trp Tyr Gln Gln Arg Ala Gly Lys Ala Pro Glu Leu Leu Ile
        35                  40                  45
Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Val Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Ala Phe Pro Leu
                85                  90                  95
Thr Phe Gly Pro Gly Thr Lys Val Thr Ile Arg
            100                 105
```

<210> 187
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 213

<400> 187

```
Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
 1               5                   10                  15
Glu Thr Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn His Tyr
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser His Pro Arg
                85                  90                  95
Met Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
```

<210> 188
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 255

<400> 188

```
Ala Ile Arg Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1               5                   10                  15
Asp Arg Val Thr Val Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30
```

```
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Asp Ala Ser Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Gly Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln
                85                  90                  95
Ala Tyr Thr Phe Gly Gln Gly Thr Lys Leu Asp Ile Lys
            100                 105
```

<210> 189
<211> 111
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 272

<400> 189

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
 1               5                  10                  15
Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
            20                  25                  30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65                  70                  75                  80
Thr Gly Asp Glu Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu
                85                  90                  95
Asn Arg Asp Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 190
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 283

<400> 190

```
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Ile Ile Tyr Asp Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser
                85                  90                  95
Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 191
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 302

<400> 191

```
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Ile Ile Tyr Asp Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser
                85                  90                  95
Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 192
<211> 109
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 305

<220>
<221> VARIANT
<222> 5, 6, 8, 9, 93, 104
<223> Xaa = any amino acid

<400> 192

```
Gln Ser Val Leu Xaa Xaa Pro Xaa Xaa Ala Ser Gly Ser Pro Gly Gln
 1              5                   10                  15
Ser Val Thr Val Ser Cys Thr Gly Thr Gly Arg Asp Ile Gly Ala Tyr
            20                  25                  30
Asp Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Leu Ile Tyr Gly Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Asp Asn Thr Ala Ser Leu Thr Val Ser Gly Leu
65                  70                  75                  80
Gln Val Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ser Xaa Ala Gly Arg
                85                  90                  95
Lys Tyr Val Phe Gly Thr Gly Xaa Lys Val Thr Val Leu
            100                 105
```

<210> 193
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 314

<400> 193

```
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1              5                   10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Ile Ile Tyr Asp Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser
                85                  90                  95
Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 194
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 379

<400> 194

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
35 40 45
Ile Ile Tyr Asp Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser
85 90 95
Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 195
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 324

<400> 195

Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
1 5 10 15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr
20 25 30
Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
35 40 45

Ile Ile Tyr Asp Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe
50 55 60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65 70 75 80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser
85 90 95
Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 196
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 327

<400> 196

```
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Glu Thr Ser Ser Asp Leu Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Ile Ile Tyr Asp Val Thr Val Arg Pro Ser Gly Val Xaa Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser
                85                  90                  95
Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 197
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 336

<400> 197

```
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Ile Ile Tyr Asp Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser
                85                  90                  95
Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 198
<211> 110
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 440

<400> 198

```
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe
            20                  25                  30
Asp Tyr Val Ser Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Ile Ile Tyr Asp Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe
    50                  55                  60
Ser Gly Ala Lys Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Arg Pro Gly
                85                  90                  95
Pro Thr Phe Val Phe Gly Thr Gly Thr Lys Leu Asp Ile Lys
            100                 105                 110
```

<210> 199
<211> 112
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 448

<400> 199

```
Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Ile Ile Tyr Asp Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser
                85                  90                  95
Ser Thr Leu Leu Trp Val Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
            100                 105                 110
```

<210> 200
<211> 111
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 505

<400> 200

```
Gln Ser Val Leu Thr Gln Pro Arg Ser Leu Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
```

```
Ser Val Thr Ile Ala Cys Thr Gly Ala Ser Thr Asp Val Gly Gly Tyr
            20                  25                  30
Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu
        35                  40                  45
Met Ile Tyr Asp Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Phe Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser
                85                  90                  95
Tyr Thr Phe Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 201
<211> 111
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 506

<400> 201

```
Gln Leu Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Val Thr Phe Ser Cys Thr Gly Ala Ser Ser Asp Val Gly Gly Tyr
            20                  25                  30
Asp His Val Ser Trp Tyr Gln His His Pro Gly Lys Gly Pro Lys Leu
        35                  40                  45
Leu Ile Tyr Asp Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Phe Ala Gly Tyr
                85                  90                  95
Tyr Thr Tyr Trp Leu Phe Gly Gly Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 202
<211> 106
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 508

<400> 202

Gln Ser Ala Leu Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln
1 5 10 15
Ser Val Thr Ile Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp
20 25 30
Tyr Gln Gln His Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val
35 40 45
Ser Lys Arg Pro Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser
50 55 60
Gly Arg Ala Ala Ser Leu Ile Ile Ser Gly Leu Gln Thr Glu Asp Glu
65 70 75 80
Ala Asp Tyr Phe Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Pro
85 90 95
Phe Gly Gly Gly Thr Lys Leu Thr Val Leu

100 105

<210> 203
<211> 99
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 184

<400> 203

Ser Tyr Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15
Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30
Thr Val Asn Trp Tyr Gln Gln Phe Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45
Ile Tyr Ser Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60
Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
65 70 75 80
Ser Glu Asp Glu Ala Glu Tyr Tyr Cys Ala Ala Trp Asp Asp Ser Leu
85 90 95
Asn Val Val

<210> 204
<211> 110
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 79

<400> 204

```
Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln
 1               5                  10                  15
Lys Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn
            20                  25                  30
Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45
Ile Tyr Asp Asn Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser
    50                  55                  60
Gly Ser Lys Ser Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln
65                  70                  75                  80
Thr Gly Asp Glu Gly Asp Tyr Tyr Cys Gly Thr Trp Asp Ile Ser Leu
                85                  90                  95
Arg Phe Gly Val Phe Gly Gly Gly Thr Lys Val Thr Val Leu
            100                 105                 110
```

<210> 205
<211> 111
<212> PRT
<213> Homo sapiens

<220>
<223> VL Clone 835

<400> 205

```
Gln Ser Val Leu Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln
 1               5                  10                  15
Ser Val Thr Ile Ser Cys Thr Gly Pro Ile Ser Gly Val Gly Asp Tyr
            20                  25                  30
Thr Ser Val Ser Trp Tyr Gln His Tyr Pro Gly Lys Thr Pro Lys Leu
        35                  40                  45
Ile Ile Tyr Asp Val Thr Gln Arg Pro Ser Gly Val Pro Asn Arg Phe
    50                  55                  60
Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu
65                  70                  75                  80
Gln Ala Asp Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Glu Ala Pro
                85                  90                  95
Thr His Thr Tyr Val Phe Gly Thr Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
```

<210> 206
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 1265

<400> 206

```
Gln Ile Thr Leu Lys Glu Ser Gly Pro Thr Leu Val Lys Pro Thr Gln
 1               5                  10                  15
Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30
Gly Val Gly Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
        35                  40                  45
Trp Leu Ala Leu Ile Tyr Trp Asp Asp Asp Lys Arg Tyr Ser Pro Ser
    50                  55                  60
Leu Lys Ser Arg Leu Thr Ile Thr Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80
Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr
                85                  90                  95
Cys Ala His Ile Asp Tyr Gly Ser Gly Ser Tyr Ser Pro Arg Thr Ser
            100                 105                 110
Tyr Tyr Tyr Tyr Met Ser Val Trp Gly Lys Gly Thr Thr Val Thr Val
        115                 120                 125
Ser Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly
    130                 135                 140
Ser Ala Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Ala Ser Val
145                 150                 155                 160
Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser
                165                 170                 175
Tyr Leu Asn Trp Tyr Gln Gln Arg Ala Gly Lys Ala Pro Glu Leu Leu
            180                 185                 190
Ile Tyr Ala Ala Ser Asn Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
        195                 200                 205
Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Thr Ser Val Gln
    210                 215                 220
Pro Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Gly Asp Ala Phe Pro
225                 230                 235                 240
Leu Thr Phe Gly Pro Gly Thr Lys Val Thr Ile Arg
                245                 250
```

<210> 207
<211> 249
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 213

<400> 207

```
Gln Val Gln Leu Val Gln Ser Gly Gly Gly Val Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Glu Ile Val Leu
    130                 135                 140
Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly Glu Thr Ala Thr
145                 150                 155                 160
Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn His Tyr Leu Ala Trp Tyr
                165                 170                 175
Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile Tyr Asp Ala Ser
            180                 185                 190
Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly Ser Gly Ser Gly
        195                 200                 205
Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro Glu Asp Phe Ala
    210                 215                 220
Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser His Pro Arg Met Tyr Thr Phe
225                 230                 235                 240
Gly Gln Gly Thr Lys Leu Glu Ile Lys
                245
```

<210> 208
<211> 249
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 255

<400> 208

```
Glu Val Gln Leu Val Gln Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Ser Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80
```

```
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ala Ile Arg Met
    130                 135                 140
Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
145                 150                 155                 160
Val Thr Cys Gln Ala Ser Gln Asp Ile Ser Asn Tyr Leu Asn Trp Tyr
                165                 170                 175
Gln Gln Lys Pro Gly Arg Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser
            180                 185                 190
Asn Val Lys Ala Gly Val Pro Ser Arg Phe Ser Gly Gly Gly Ser Gly
        195                 200                 205
Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala
    210                 215                 220
Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Thr Pro Gln Ala Tyr Thr Phe
225                 230                 235                 240
Gly Gln Gly Thr Lys Leu Asp Ile Lys
                245
```

<210> 209
<211> 251
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 272

<400> 209

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu
    130                 135                 140
Thr Gln Pro Pro Ser Val Ser Ala Ala Pro Gly Gln Lys Val Thr Ile
145                 150                 155                 160
Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
                165                 170                 175
Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Asp Asn
            180                 185                 190
Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205
Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
    210                 215                 220
Ala Asp Tyr Tyr Cys Gly Thr Trp Asp Ser Ser Leu Asn Arg Asp Trp

225                 230                 235                 240
Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 210
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 283

<400> 210

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20   25   30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35   40   45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50   55   60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65   70   75   80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85   90   95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100   105   110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115   120   125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130   135   140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145   150   155   160
Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165   170   175
Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180   185   190
Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195   200   205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210   215   220
Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225   230   235   240
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245   250

<210> 211
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 302

<400> 211

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1   5   10   15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20   25   30

```
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 212
<211> 249
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 305

<220>
<221> VARIANT
<222> 64, 65, 68, 69, 93, 98, 102, 104, 113, 145, 146, 148, 149, 233, 244
<223> Xaa = any amino acid

<400> 212

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Xaa
    50                  55                  60
Xaa Gly Arg Xaa Xaa Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Xaa Tyr Tyr Cys
                85                  90                  95
Ala Xaa Asp Gln Gly Xaa His Xaa Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Xaa Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu


    130                 135                 140
Xaa Xaa Pro Xaa Xaa Ala Ser Gly Ser Pro Gly Gln Ser Val Thr Val
145                 150                 155                 160
Ser Cys Thr Gly Thr Gly Arg Asp Ile Gly Ala Tyr Asp Tyr Val Ser
                165                 170                 175
Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Gly
            180                 185                 190
Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Asp Asn Thr Ala Ser Leu Thr Val Ser Gly Leu Gln Val Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Ser Ser Xaa Ala Gly Arg Lys Tyr Val Phe
225                 230                 235                 240
Gly Thr Gly Xaa Lys Val Thr Val Leu
                245
```

<210> 213
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 314

<400> 213

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 214
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 379

<400> 214

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 215
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 324

<400> 215

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
```

```
                        85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 216
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 327

<220>
<221> VARIANT
<222> 76, 201
<223> Xaa = any amino acid

<400> 216

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Xaa Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Glu Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Val Arg Pro Ser Gly Val Xaa Asp Arg Phe Ser Gly Ser Lys

        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 217
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 336

<400> 217

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240
Trp Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
                245                 250
```

<210> 218
<211> 250
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 440

<400> 218

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly His Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Arg Ser Asp Val Gly Gly Phe Asp Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His Asn Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Lys Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ala Lys
        195                 200                 205
Ser Gly Ile Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Thr Ser Tyr Arg Pro Gly Pro Thr Phe Val
225                 230                 235                 240
Phe Gly Thr Gly Thr Lys Leu Asp Ile Lys
                245                 250
```

<210> 219
<211> 252
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 448

<400> 219

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Ser Ser Asp Leu Gly Gly Tyr Asn Tyr Val Ser
                165                 170                 175
Trp Tyr Gln His Arg Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Val Arg Pro Ser Gly Val Ser Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Gly Ser Tyr Thr Ser Ser Ser Thr Leu Leu
225                 230                 235                 240
Trp Val Phe Gly Gly Gly Thr Lys Leu Asp Ile Lys
                245                 250
```

<210> 220
<211> 236
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 505

<400> 220

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gln Ser Val
        115                 120                 125
Leu Thr Gln Pro Arg Ser Leu Ser Gly Ser Pro Gly Gln Ser Val Thr
    130                 135                 140
Ile Ala Cys Thr Gly Ala Ser Thr Asp Val Gly Gly Tyr Asn Tyr Val
145                 150                 155                 160
Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Met Ile Tyr
                165                 170                 175
Asp Val Asn Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser
            180                 185                 190
Lys Ser Gly Asn Thr Ala Phe Leu Thr Ile Ser Gly Leu Gln Ala Glu
        195                 200                 205
Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser Tyr Thr Phe
    210                 215                 220
Glu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
225                 230                 235
```

<210> 221
<211> 251
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 506

<400> 221

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Leu Val Leu
    130                 135                 140
Thr Gln Pro Pro Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr Phe
145                 150                 155                 160
Ser Cys Thr Gly Ala Ser Ser Asp Val Gly Gly Tyr Asp His Val Ser
                165                 170                 175
Trp Tyr Gln His His Pro Gly Lys Gly Pro Lys Leu Leu Ile Tyr Asp
            180                 185                 190
Val Ser Lys Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys
        195                 200                 205
Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Glu Asp
    210                 215                 220
Glu Ala Asp Tyr Tyr Cys Cys Ser Phe Ala Gly Tyr Tyr Thr Tyr Trp
225                 230                 235                 240
Leu Phe Gly Gly Gly Thr Lys Val Thr Val Leu
                245                 250
```

<210> 222
<211> 246
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 508

<400> 222

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
```

```
                115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Ala Leu
    130                 135                 140
Thr Gln Pro Arg Ser Val Ser Gly Phe Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Thr Thr Ser Asp Asp Val Ser Trp Tyr Gln Gln His
                165                 170                 175
Pro Gly Lys Ala Pro Gln Leu Met Leu Tyr Asp Val Ser Lys Arg Pro
            180                 185                 190
Ser Gly Val Pro His Arg Phe Ser Gly Ser Arg Ser Gly Arg Ala Ala
        195                 200                 205
Ser Leu Ile Ile Ser Gly Leu Gln Thr Glu Asp Glu Ala Asp Tyr Phe
    210                 215                 220
Cys Cys Ser Tyr Ala Gly Arg Tyr Asn Ser Val Pro Phe Gly Gly Gly
225                 230                 235                 240
Thr Lys Leu Thr Val Leu
                245
```

<210> 223
<211> 239
<212> PRT
<213> Homo sapiens

<220>
<223> scFv Clone 184

<400> 223

```
Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Ser Tyr Val Leu
    130                 135                 140
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145                 150                 155                 160
Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Thr Val Asn Trp
                165                 170                 175
Tyr Gln Gln Phe Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Ser Asn
            180                 185                 190
Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205
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        35                  40                  45
Ser Gly Ile Ser Trp Asn Ser Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
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Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Val Val Thr Val Ser Ser Gly Gly Gly
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Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Asn Asn Tyr Val Ser Trp
                165                 170                 175
Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu Ile Tyr Asp Asn
            180                 185                 190
Asn Lys Arg Pro Ser Gly Ile Pro Asp Arg Phe Ser Gly Ser Lys Ser
        195                 200                 205
Gly Thr Ser Ala Thr Leu Gly Ile Thr Gly Leu Gln Thr Gly Asp Glu
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        35                  40                  45
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    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Ala Lys Asp Thr Ala Val Tyr Tyr Cys


                85                  90                  95
Ala Arg Asp Gln Gly Tyr His Tyr Tyr Asp Ser Ala Glu His Ala Phe
            100                 105                 110
Asp Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Gly Gly Gly
        115                 120                 125
Gly Ser Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser Gln Ser Val Leu
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Thr Gln Pro Arg Ser Val Ser Gly Ser Pro Gly Gln Ser Val Thr Ile
145                 150                 155                 160
Ser Cys Thr Gly Pro Ile Ser Gly Val Gly Asp Tyr Thr Ser Val Ser
                165                 170                 175
Trp Tyr Gln His Tyr Pro Gly Lys Thr Pro Lys Leu Ile Ile Tyr Asp
            180                 185                 190
Val Thr Gln Arg Pro Ser Gly Val Pro Asn Arg Phe Ser Gly Ser Lys
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Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Ala Asp Asp
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```

Claims

1. A CD19 binding antibody or CD19 binding antigen binding fragment thereof comprising:

   a VH region comprising the amino acid sequence of SEQ ID NO: 11, and a VL region comprising the amino acid sequence of SEQ ID NO: 13; or
   a VH region comprising the amino acid sequence of SEQ ID NO: 11, and a VL region comprising the amino acid sequence of SEQ ID NO: 14; or
   a VH region comprising the amino acid sequence of SEQ ID NO: 11, and a VL region comprising the amino acid sequence of SEQ ID NO: 16; or
   a VH region comprising the amino acid sequence of SEQ ID NO: 12, and a VL region comprising the amino acid sequence of SEQ ID NO: 15; or
   a VH region comprising the amino acid sequence of SEQ ID NO: 12, and a VL region comprising the amino acid sequence of SEQ ID NO: 17.

2. The antibody or antigen binding fragment thereof of claim 1, wherein the antibody or antigen binding fragment thereof specifically binds to human CD19.

3. The antibody or antigen binding fragment thereof of claim 1 or claim 2, wherein the antibody or antigen binding fragment thereof is human.

4. The antibody or antigen binding fragment thereof of any of claims 1-3, wherein the antibody or antigen binding fragment thereof is monoclonal.

5. The antibody or antigen binding fragment thereof of any of claims 1-4, wherein the antibody or antigen binding fragment thereof is a single chain fragment that comprises a scFv.

6. The antibody or antigen binding fragment thereof of claim 5, wherein the scFv comprises the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10 or a sequence that exhibits at least 95% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, 4, 6, 8, 10.

7. A conjugate, comprising the antibody or antigen binding fragment thereof of any of claims 1-6 and a heterologous molecule or moiety.

8. A chimeric antigen receptor (CAR) comprising an extracellular portion comprising the antibody or antigen binding fragment thereof of any of claims 1-6 and an intracellular signaling domain, optionally wherein the antibody or fragment comprises an scFv and the intracellular signaling domain comprises an ITAM, optionally wherein the intracellular signaling domain comprises a signaling domain of a CD3-zeta (CD3ζ) chain.

9. The chimeric antigen receptor of claim 8, further comprising a transmembrane domain linking the extracellular domain and the intracellular signaling domain and/or further comprising an intracellular signaling domain of a T cell

costimulatory molecule, optionally wherein the T cell costimulatory molecule is selected from the group consisting of 4-1BB or CD28.

10. A nucleic acid encoding the antibody or antigen binding fragment thereof of any of claims 1-6, conjugate of claim 7 or the chimeric antigen receptor of claim 8 or claim 9.

11. Engineered cells expressing a receptor comprising the antibody or antigen binding fragment thereof of any of claims 1-6, conjugate of claim 7 or the chimeric antigen receptor of claim 8 or claim 9

12. The engineered cells of claim 11, wherein the engineered cells are T cells, optionally wherein the T cells are CD4+ and/ or CD8+ T cells.

13. A composition, comprising the antibody or fragment thereof of any of claims 1-6, conjugate of claim 7 or the chimeric antigen receptor of claim 8 or claim 9 or the cells of claim 11 or claim 12, and a pharmaceutically acceptable excipient.

14. A composition of claim 13 for use in a method of treating a disease or disorder associated with CD19, wherein the disease or disorder is a B cell malignancy.

15. The composition of claim 13 for use according to claim 14, wherein the B cell malignancy is selected from the group consisting of B cell chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), prolymphocytic leukemias, hairy cell leukemias, common acute lymphocytic leukemias, Null-acute lymphoblastic leukemias, non-Hodgkin lymphomas, diffuse large B cell lymphomas (DLBCLs), multiple myelomas, follicular lymphoma, splenic, marginal zone lymphoma, mantle cell lymphoma, indolent B cell lymphoma, and Hodgkin lymphoma.

Patentansprüche

1. CD19 bindender Antikörper oder CD19 bindendes Antigenbindungsfragment davon, umfassend:

eine VH-Region, die die Aminosäuresequenz unter SEQ ID NO: 11 umfasst, und eine VL-Region, die die Aminosäuresequenz unter SEQ ID NO: 13 umfasst; oder
eine VH-Region, die die Aminosäuresequenz unter SEQ ID NO: 11 umfasst, und eine VL-Region, die die Aminosäuresequenz unter SEQ ID NO: 14 umfasst; oder
eine VH-Region, die die Aminosäuresequenz unter SEQ ID NO: 11 umfasst, und eine VL-Region, die die Aminosäuresequenz unter SEQ ID NO: 16 umfasst; oder
eine VH-Region, die die Aminosäuresequenz unter SEQ ID NO: 12 umfasst, und eine VL-Region, die die Aminosäuresequenz unter SEQ ID NO: 15 umfasst; oder
eine VH-Region, die die Aminosäuresequenz unter SEQ ID NO: 12 umfasst, und eine VL-Region, die die Aminosäuresequenz unter SEQ ID NO: 17 umfasst.

2. Antikörper oder Antigenbindungsfragment davon nach Anspruch 1, wobei der Antikörper bzw. das Antigenbindungsfragment davon an menschliches CD19 spezifisch bindet.

3. Antikörper oder Antigenbindungsfragment davon nach Anspruch 1 oder Anspruch 2, wobei der Antikörper bzw. das Antigenbindungsfragment davon vom Menschen stammt.

4. Antikörper oder Antigenbindungsfragment davon nach einem der Ansprüche 1-3, wobei der Antikörper bzw. das Antigenbindungsfragment davon monoklonal ist.

5. Antikörper oder Antigenbindungsfragment davon nach einem der Ansprüche 1-4, wobei es sich bei dem Antikörper bzw. Antigenbindungsfragment davon um ein Einzelkettenfragment handelt, das ein scFv umfasst.

6. Antikörper oder Antigenbindungsfragment davon nach Anspruch 5, wobei das scFv die Aminosäuresequenz gemäß SEQ ID NO: 2, 4, 6, 8, 10 oder eine Sequenz, die eine Sequenzidentität von wenigstens 95% mit der Aminosäuresequenz gemäß SEQ ID NO: 2, 4, 6, 8, 10 zeigt, umfasst.

7. Konjugat, umfassend den Antikörper bzw. das Antigenbindungsfragment davon nach einem der Ansprüche 1-6 und ein heterologes Molekül bzw. eine heterologe Gruppierung.

8. Chimärer Antigenrezeptor (CAR), umfassend einen extrazellulären Teil, der den Antikörper bzw. das Antigenbindungsfragment davon nach einem der Ansprüche 1-6 umfasst, und eine intrazelluläre Signalgebungsdomäne, gegebenenfalls wobei der Antikörper bzw. das Fragment ein scFv und die intrazelluläre Signalgebungsdomäne ein ITAM umfasst, gegebenenfalls wobei die intrazelluläre Signalgebungsdomäne eine Signalgebungsdomäne einer CD3-zeta(CD3ζ)-Kette umfasst.

9. Chimärer Antigenrezeptor nach Anspruch 8, ferner umfassend eine Transmembrandomäne, die die extrazelluläre Domäne und die intrazelluläre Signalgebungsdomäne verknüpft, und/oder ferner umfassend eine intrazelluläre Signalgebungsdomäne eines T-Zell-Costimulatormoleküls, gegebenenfalls wobei das T-Zell-Costimulatormolekül ausgewählt ist aus der Gruppe bestehend aus 4-1BB oder CD28.

10. Nukleinsäure, codierend den Antikörper bzw. das Antigenbindungsfragment davon nach einem der Ansprüche 1-6, Konjugat nach Anspruch 7 oder den chimären Antigenrezeptor nach Anspruch 8 oder Anspruch 9.

11. Konstruierte Zellen, exprimierend einen Rezeptor, der den Antikörper bzw. das Antigenbindungsfragment davon nach einem der Ansprüche 1-6, Konjugat nach Anspruch 7 oder den chimären Antigenrezeptor nach Anspruch 8 oder Anspruch 9 umfasst.

12. Konstruierte Zellen nach Anspruch 11, wobei es sich bei den konstruierten Zellen um T-Zellen handelt, gegebenenfalls wobei es sich bei den T-Zellen um CD4+- und/oder CD8+-T-Zellen handelt.

13. Zusammensetzung, umfassend den Antikörper bzw. das Fragment davon nach einem der Ansprüche 1-6, Konjugat nach Anspruch 7 oder den chimären Antigenrezeptor nach Anspruch 8 oder Anspruch 9 oder die Zellen nach Anspruch 11 oder Anspruch 12 und einen pharmazeutisch unbedenklichen Exzipienten.

14. Zusammensetzung nach Anspruch 13 zur Verwendung bei einem Verfahren zur Behandlung einer Krankheit oder Störung in Zusammenhang mit CD19, wobei es sich bei der Krankheit oder Störung um ein B-Zell-Malignom handelt.

15. Zusammensetzung nach Anspruch 13 zur Verwendung gemäß Anspruch 14, wobei das B-Zell-Malignom ausgewählt ist aus der Gruppe bestehend aus chronischer lymphatischer B-Zell-Leukämie (CLL), akuter lymphatischer Leukämie (ALL), prolymphozytischen Leukämien, Haarzellleukämien, gemeinen akuten lymphatischen Leukämien, akuten lymphatischen Null-Zell-Leukämien, Non-Hodgkin-Lymphomen, diffusen großzelligen B-Zell-Lymphomen (DLBCL), multiplen Myelomen, follikulärem Lymphom, Randzonen-Lymphom der Milz, Mantelzelllymphom, indolentem B-Zell-Lymphom und Hodgkin-Lymphom.

Revendications

1. Anticorps de liaison au CD19 ou fragment de liaison à l'antigène de celui-ci comprenant :

une région VH comprenant la séquence d'acides aminés de SEQ ID n° : 11 et une région VL comprenant la séquence d'acides aminés de SEQ ID n° : 13 ; ou
une région VH comprenant la séquence d'acides aminés de SEQ ID n° : 11 et une région VL comprenant la séquence d'acides aminés de SEQ ID n° : 14 ; ou
une région VH comprenant la séquence d'acides aminés de SEQ ID n° : 11 et une région VL comprenant la séquence d'acides aminés de SEQ ID n° : 16 ; ou
une région VH comprenant la séquence d'acides aminés de SEQ ID n° : 12 et une région VL comprenant la séquence d'acides aminés de SEQ ID n° : 15 ; ou
une région VH comprenant la séquence d'acides aminés de SEQ ID n° : 12 et une région VL comprenant la séquence d'acides aminés de SEQ ID n° : 17.

2. Anticorps ou fragment de liaison à l'antigène de celui-ci de la revendication 1, l'anticorps ou le fragment de liaison à l'antigène de celui-ci se liant spécifiquement au CD19 humain.

3. Anticorps ou fragment de liaison à l'antigène de celui-ci de la revendication 1 ou la revendication 2, l'anticorps ou le fragment de liaison à l'antigène de celui-ci étant humain.

4. Anticorps ou fragment de liaison à l'antigène de celui-ci de l'une quelconque des revendications 1 à 3, l'anticorps ou le fragment de liaison à l'antigène de celui-ci étant monoclonal.

5. Anticorps ou fragment de liaison à l'antigène de celui-ci de l'une quelconque des revendications 1 à 4, l'anticorps ou le fragment de liaison à l'antigène de celui-ci étant un fragment en simple chaîne qui comprend un scFv.

6. Anticorps ou fragment de liaison à l'antigène de celui-ci de la revendication 5, dans lequel le scFv comprend la séquence d'acides aminés indiquée dans les SEQ ID n° : 2, 4, 6, 8, 10 ou une séquence qui présente une identité de séquence d'au moins 95% avec la séquence d'acides aminés indiquée dans les SEQ ID n° : 2, 4, 6, 8, 10.

7. Conjugué comprenant l'anticorps ou le fragment de liaison à l'antigène de celui-ci de l'une quelconque des revendications 1 à 6 ainsi qu'une molécule ou fraction hétérologue.

8. Récepteur antigénique chimérique (CAR) comprenant une partie extracellulaire, comprenant l'anticorps ou le fragment de liaison à l'antigène de celui-ci de l'une quelconque des revendications 1 à 6, et un domaine de signalisation intracellulaire, en option dans lequel l'anticorps ou le fragment comprend un scFv et le domaine de signalisation intracellulaire comprend un ITAM, en option dans lequel le domaine de signalisation intracellulaire comprend un domaine de signalisation d'une chaîne CD3-zêta (OPB3ζ).

9. Récepteur antigénique chimérique de la revendication 8, comprenant en outre un domaine transmembranaire reliant le domaine extracellulaire et le domaine de signalisation intracellulaire et/ou comprenant en outre un domaine de signalisation intracellulaire d'une molécule de co-stimulation de lymphocytes T, en option dans lequel la molécule de co-stimulation de lymphocytes T est choisie dans le groupe constitué par le 4-1BB ou le CD28.

10. Acide nucléique codant pour l'anticorps ou le fragment de liaison à l'antigène de celui-ci de l'une quelconque des revendications 1 à 6, le conjugué de la revendication 7 ou le récepteur antigénique chimérique de la revendication 8 ou la revendication 9.

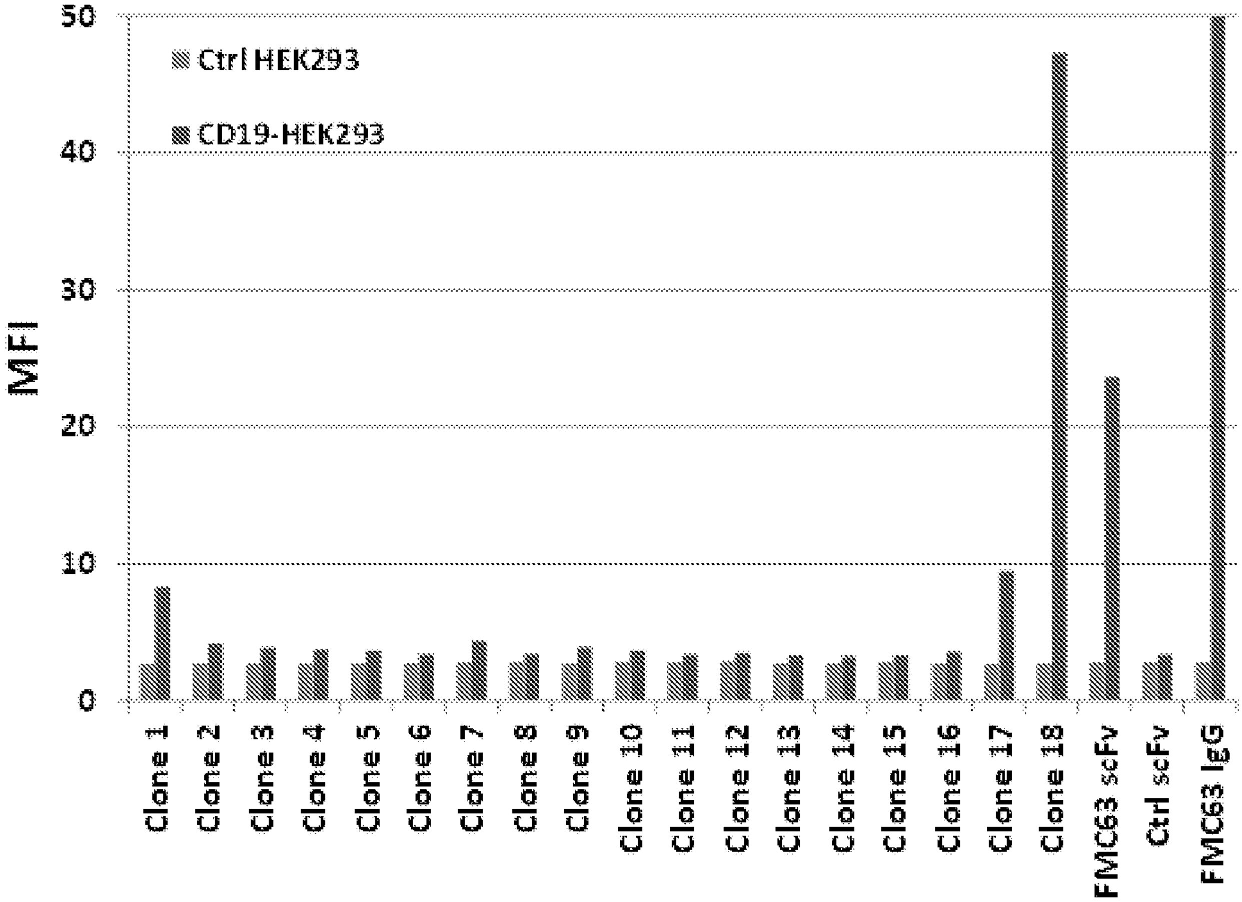
11. Cellules génétiquement manipulées exprimant un récepteur comprenant l'anticorps ou le fragment de liaison à l'antigène de celui-ci de l'une quelconque des revendications 1 à 6, le conjugué de la revendication 7 ou le récepteur antigénique chimérique de la revendication 8 ou la revendication 9.

12. Cellules génétiquement manipulées de la revendication 11, les cellules génétiquement manipulées étant des lymphocytes T, en option les lymphocytes T étant des lymphocytes T CD4+ et/ou CD8+.

13. Composition comprenant l'anticorps ou le fragment de celui-ci de l'une quelconque des revendications 1 à 6, le conjugué de la revendication 7 ou le récepteur antigénique chimérique de la revendication 8 ou la revendication 9 ou bien les cellules de la revendication 11 ou la revendication 12, ainsi qu'un excipient acceptable d'un point de vue pharmaceutique.

14. Composition de la revendication 13 destinée à être utilisée dans un procédé de traitement d'une maladie ou d'un trouble associé au CD19, dans laquelle la maladie ou le trouble est une affection maligne à lymphocytes B.

15. Composition de la revendication 13 destinée à être utilisée selon la revendication 14, dans laquelle l'affection maligne à lymphocytes B est choisie dans le groupe constitué par une leucémie lymphoïde chronique (LLC) à lymphocytes B, une leucémie lymphoïde aiguë (LLA), des leucémies pro-lymphocytaires, des leucémies à tricholeucocytes, des leucémies lymphoïdes aiguës communes, des leucémies aiguës lymphoblastiques à cellules Null, des lymphomes non-Hodgkiniens, des lymphomes diffus à grands lymphocytes B (DLBCL), des myélomes multiples, un lymphome folliculaire, un lymphome à cellules de la zone marginale splénique, un lymphome à cellules du manteau, un lymphome indolent à lymphocytes B et un lymphome Hodgkinien.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40
30
20
10
0
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Ctrl HEK293
CD19-HEK293
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Clone 2
Clone 3
Clone 4
Clone 5
Clone 6
Clone 7
Clone 8
Clone 9
Clone 10
Clone 11
Clone 12
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Clone 17
Clone 18
FMC63 scFv
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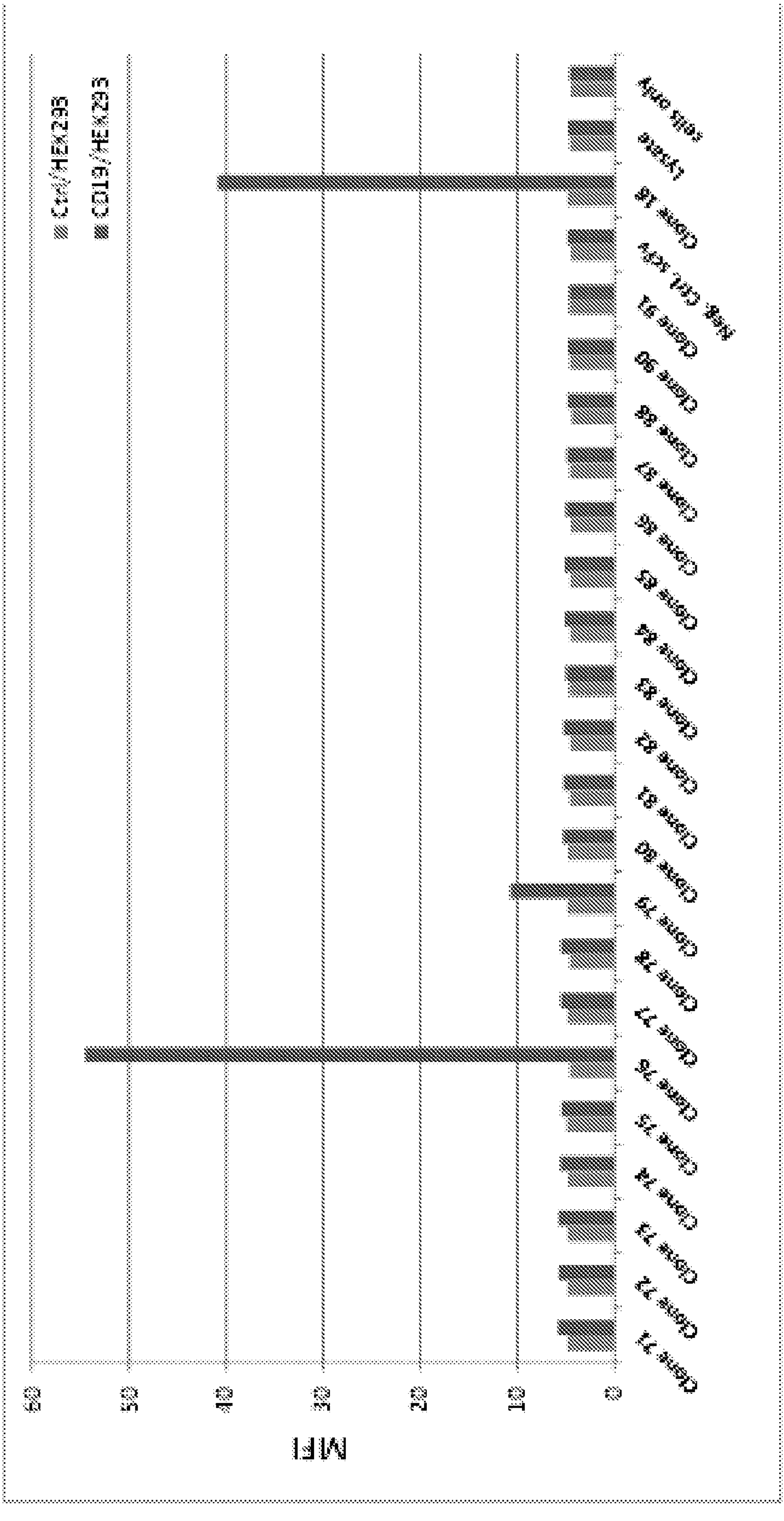
FMC63 IgG

FIGURE 1A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10
20
30
40
50
60
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CD19/HEK293
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Clone 72
Clone 73
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Clone 75
Clone 76
Clone 77
Clone 78
Clone 79
Clone 80
Clone 81
Clone 82
Clone 83
Clone 84
Clone 85
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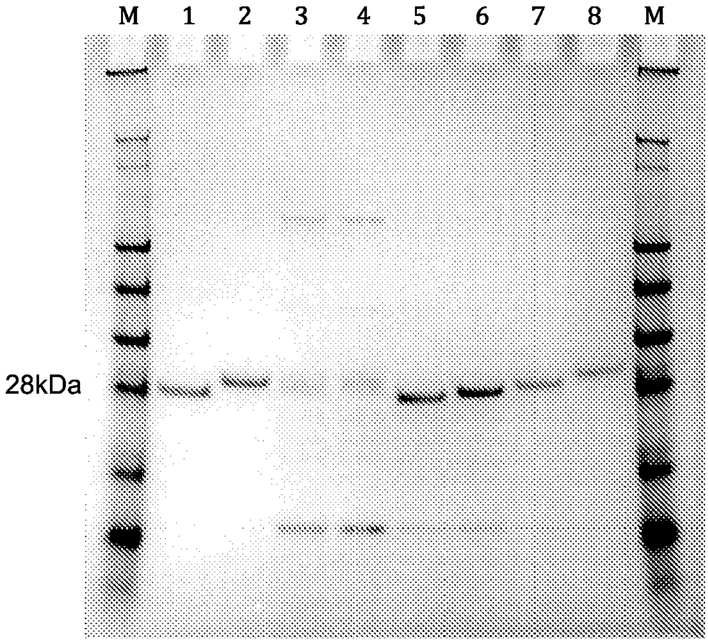
Clone 88
Clone 90
Clone 91
Neg. Ctrl. scFv
Clone 16
Lysate
cells only

FIGURE 1B



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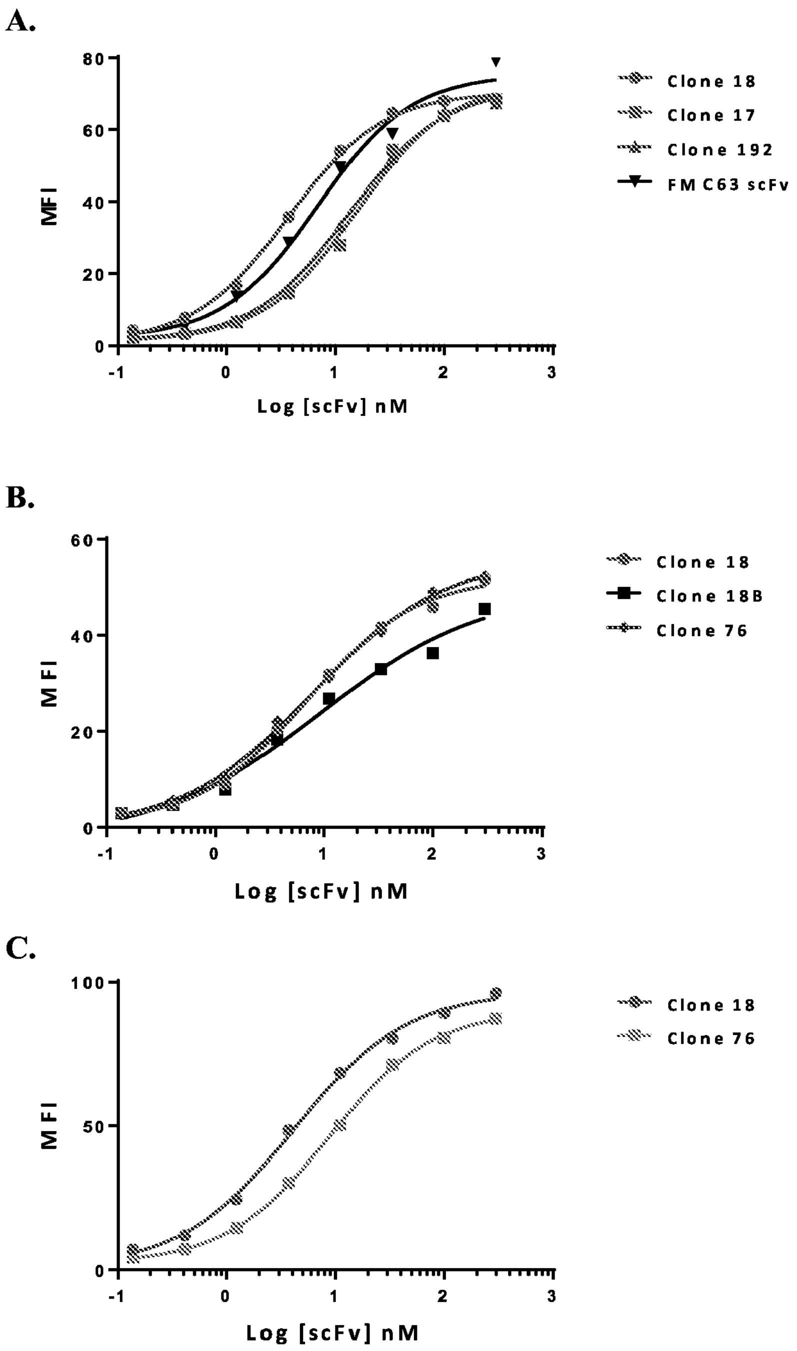
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60
40
20
0
MFI
-1
0
1
2
3
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Clone 18
Clone 17
Clone 192
FMC63 scFv
B.
60
40
20
0
MFI
-1
0
1
2
3
Log [scFv] nM
Clone 18
Clone 18B
Clone 76
C.
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50
0
MFI
-1
0
1
2
3
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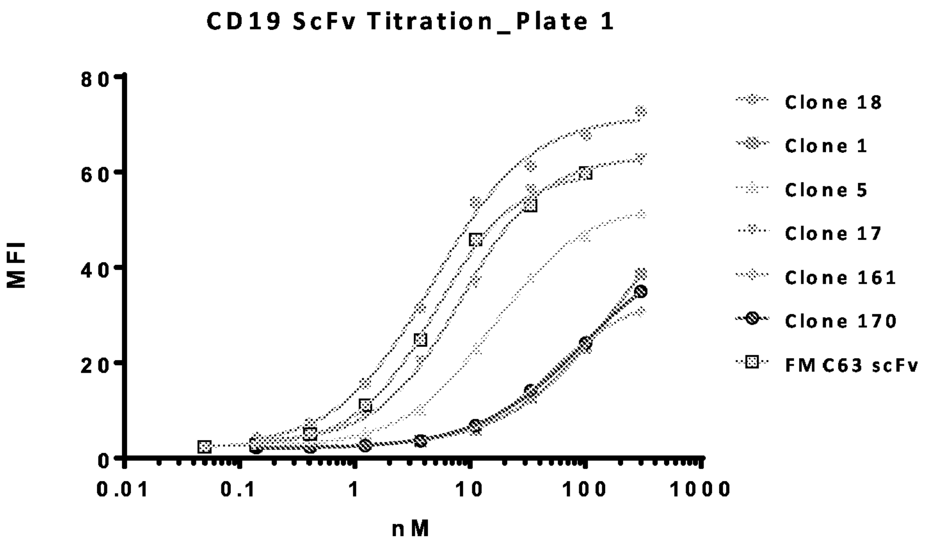
Clone 18
Clone 76

FIGURE 3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60
40
20
0
0.01
0.1
1
10
100
1000
nM
Clone 18
Clone 1
Clone 5
Clone 17
Clone 161
Clone 170
FMC63 scFv

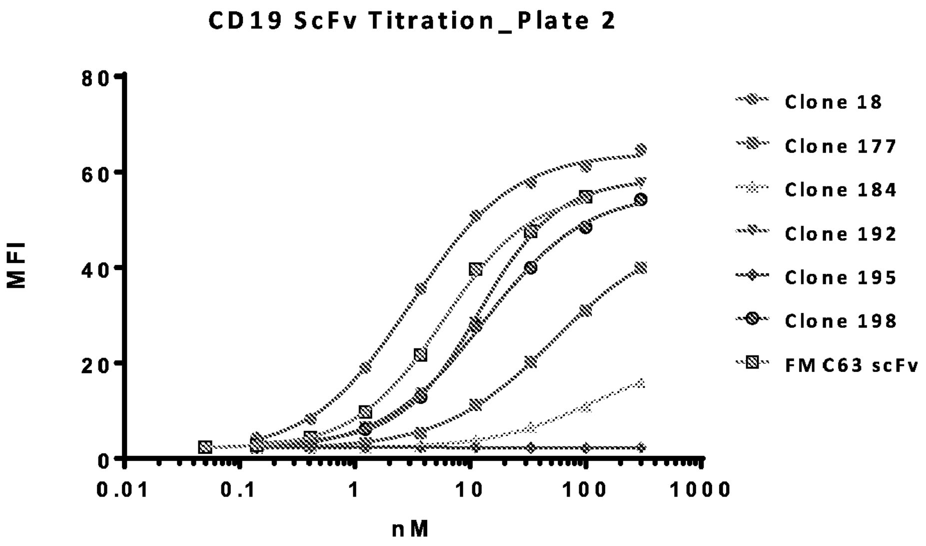
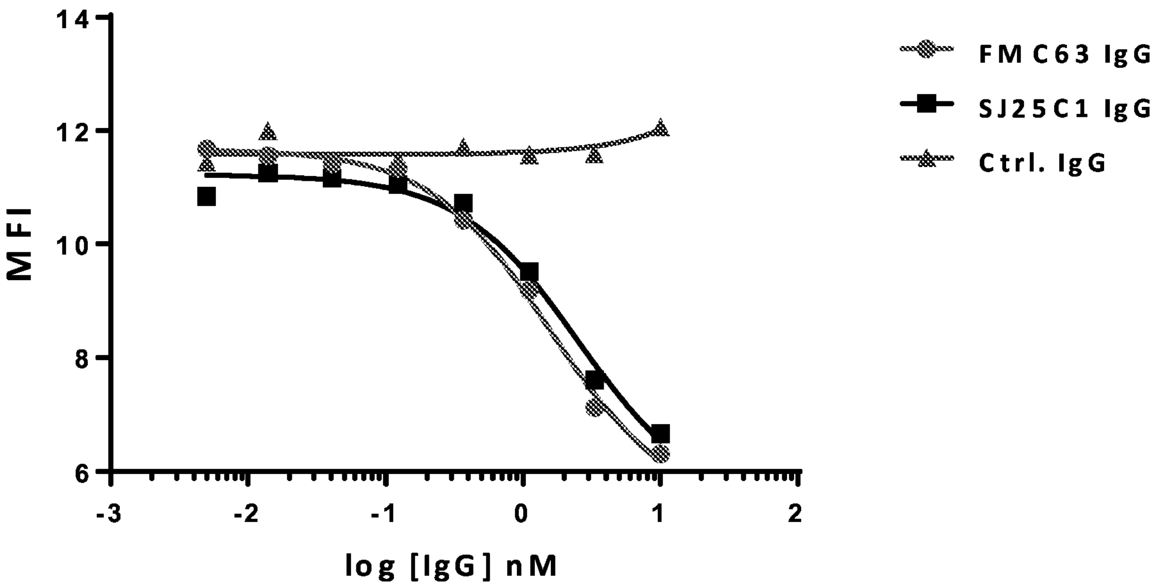

CD19 ScFv Titration_Plate 2
MFI
80
60
40
20
0
0.01
0.1
1
10
100
1000
nM
Clone 18
Clone 177
Clone 184
Clone 192
Clone 195
Clone 198
FMC63 scFv

FIGURE 4

A.


14
12
10
8
6
MFI
-3
-2
-1
0
1
2
log [IgG] nM
FMC63 IgG
SJ25C1 IgG
Ctrl. IgG

B

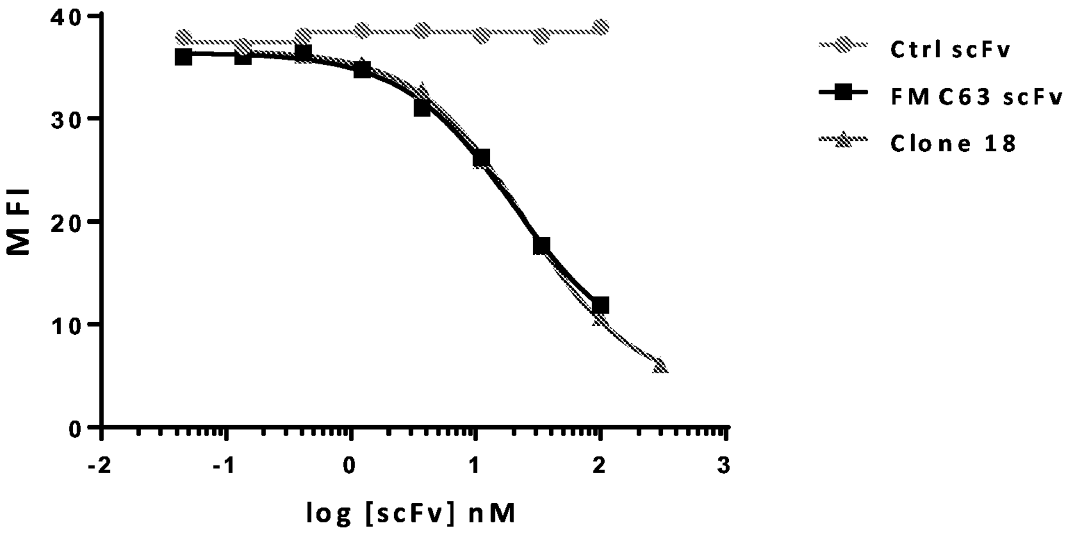

40
30
20
10
0
MFI
-2
-1
0
1
2
3
log [scFv] nM
Ctrl scFv
FMC63 scFv
Clone 18

FIGURE 5

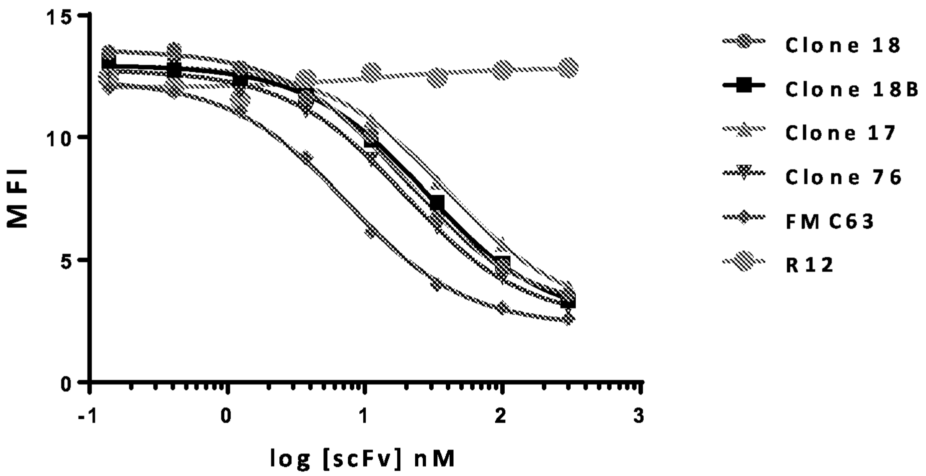

15
10
5
0
MFI
-1
0
1
2
3
log [scFv] nM
Clone 18
Clone 18B
Clone 17
Clone 76
FMC63
R12

FIGURE 6

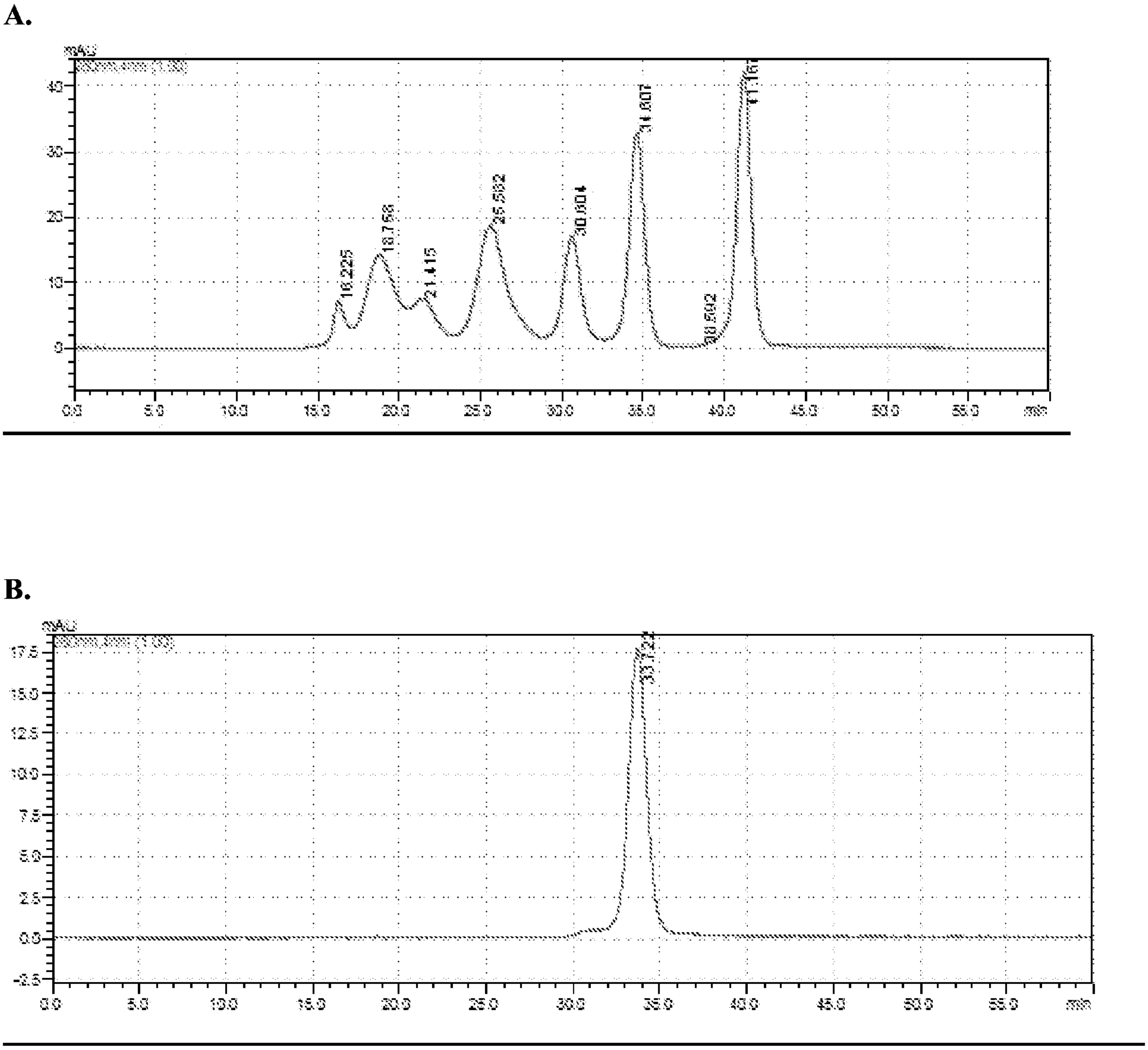

A.
mAU
40
30
20
10
0
16.225
18.758
21.415
25.582
30.604
34.607
38.592
0.0
5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0
45.0
50.0
55.0
min
B.
mAU
17.5
15.0
12.5
10.0
7.5
5.0
2.5
0.0
-2.5
0.0
5.0
10.0
15.0
20.0
25.0
30.0
35.0
40.0
45.0
50.0
55.0
min

FIGURE 7

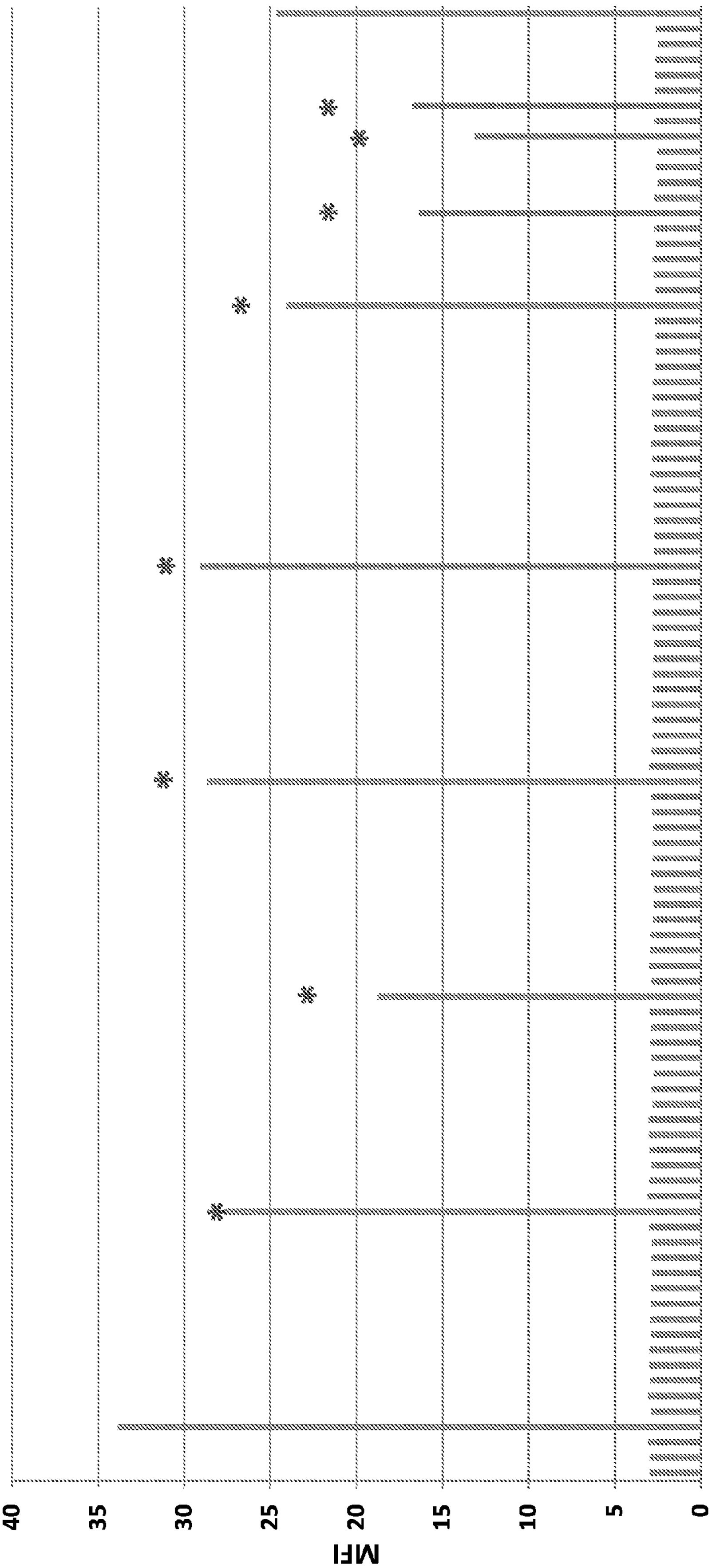


Figure 8A

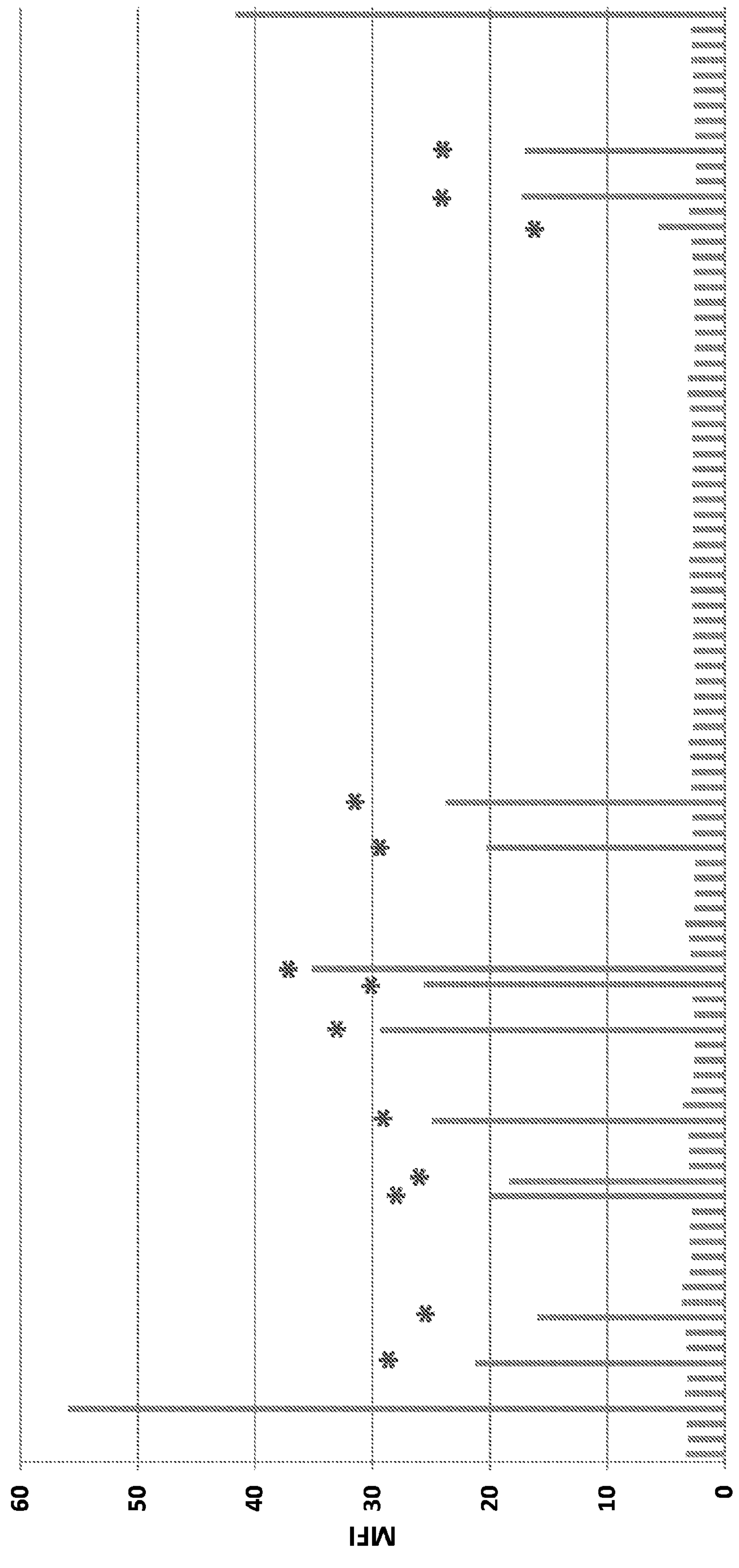


Figure 8B

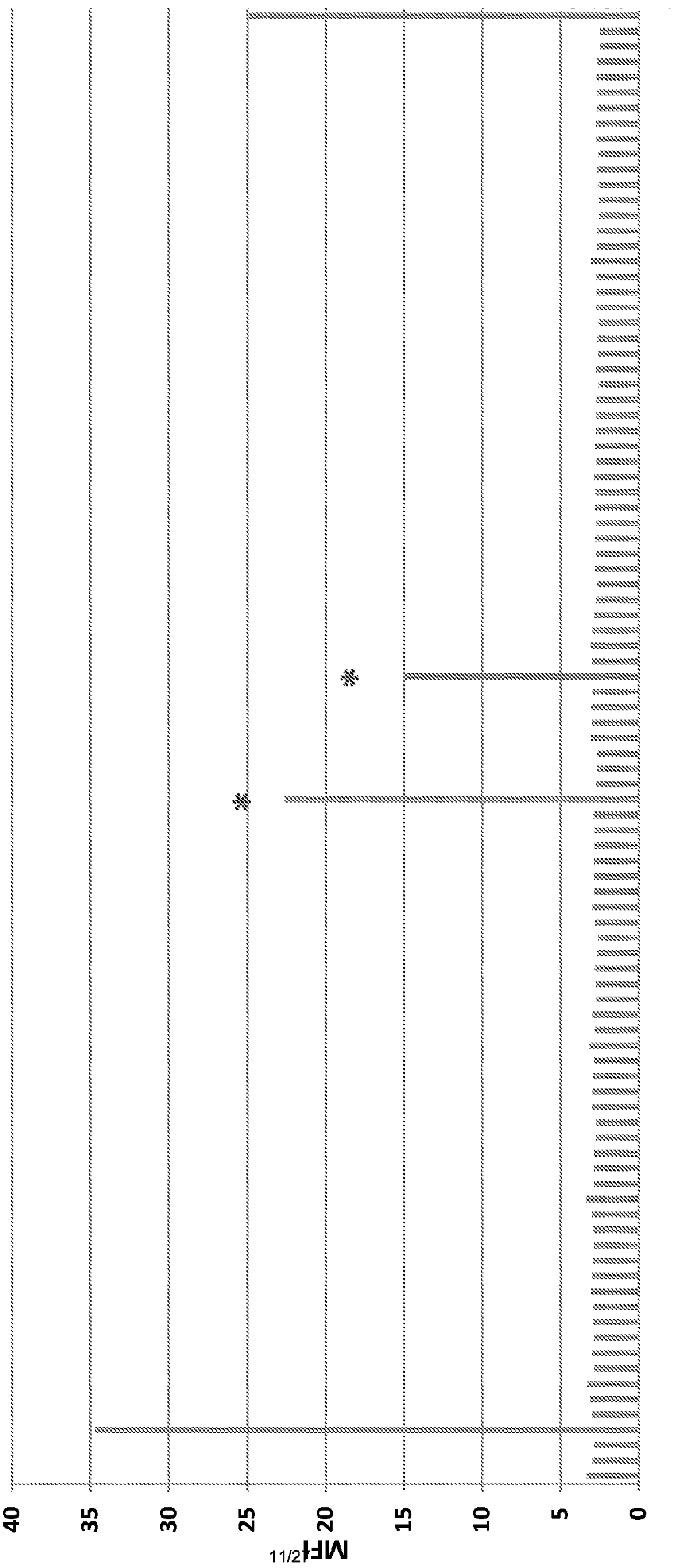


Figure 8C

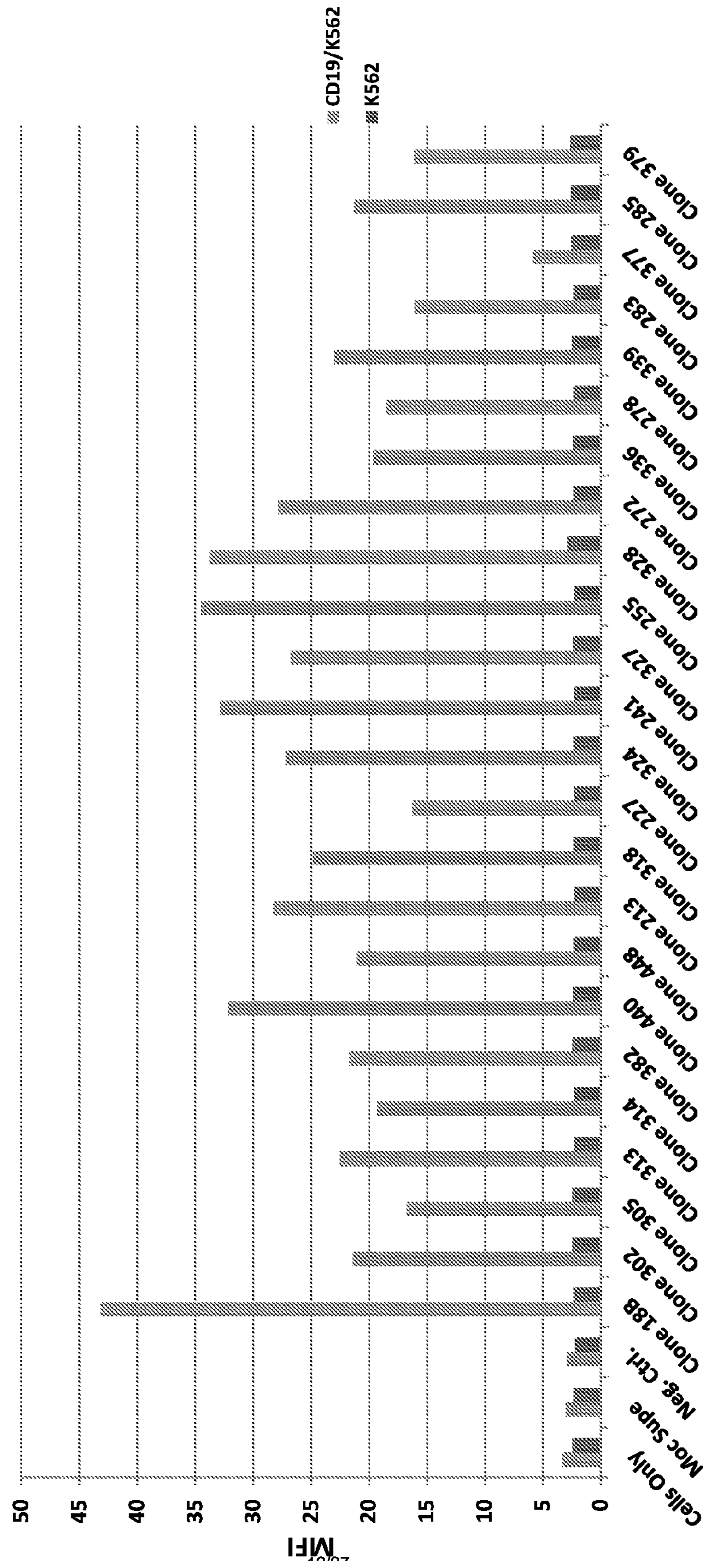

CD19/K562
K562
MFI
0
5
10
15
20
25
30
35
40
45
50
Cells Only
Moc Supe
Neg. Ctrl.
Clone 188
Clone 302
Clone 305
Clone 313
Clone 314
Clone 382
Clone 440
Clone 448
Clone 213
Clone 318
Clone 227
Clone 324
Clone 241
Clone 327
Clone 255
Clone 328
Clone 272
Clone 336
Clone 278
Clone 339
Clone 283
Clone 377
Clone 285
Clone 379

Figure 8D

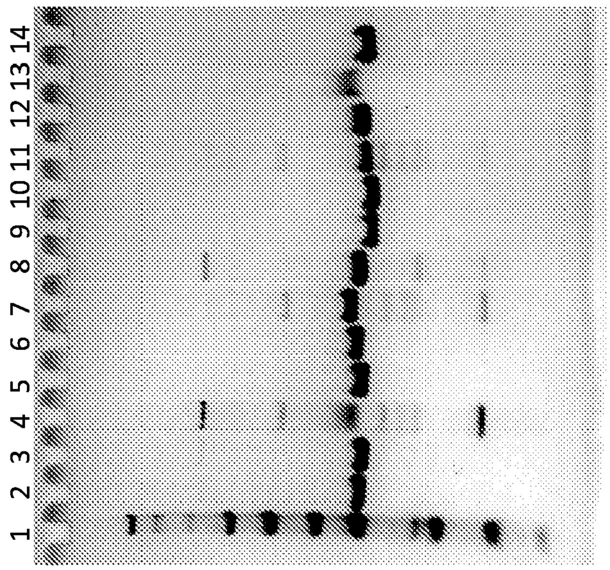


Figure 9

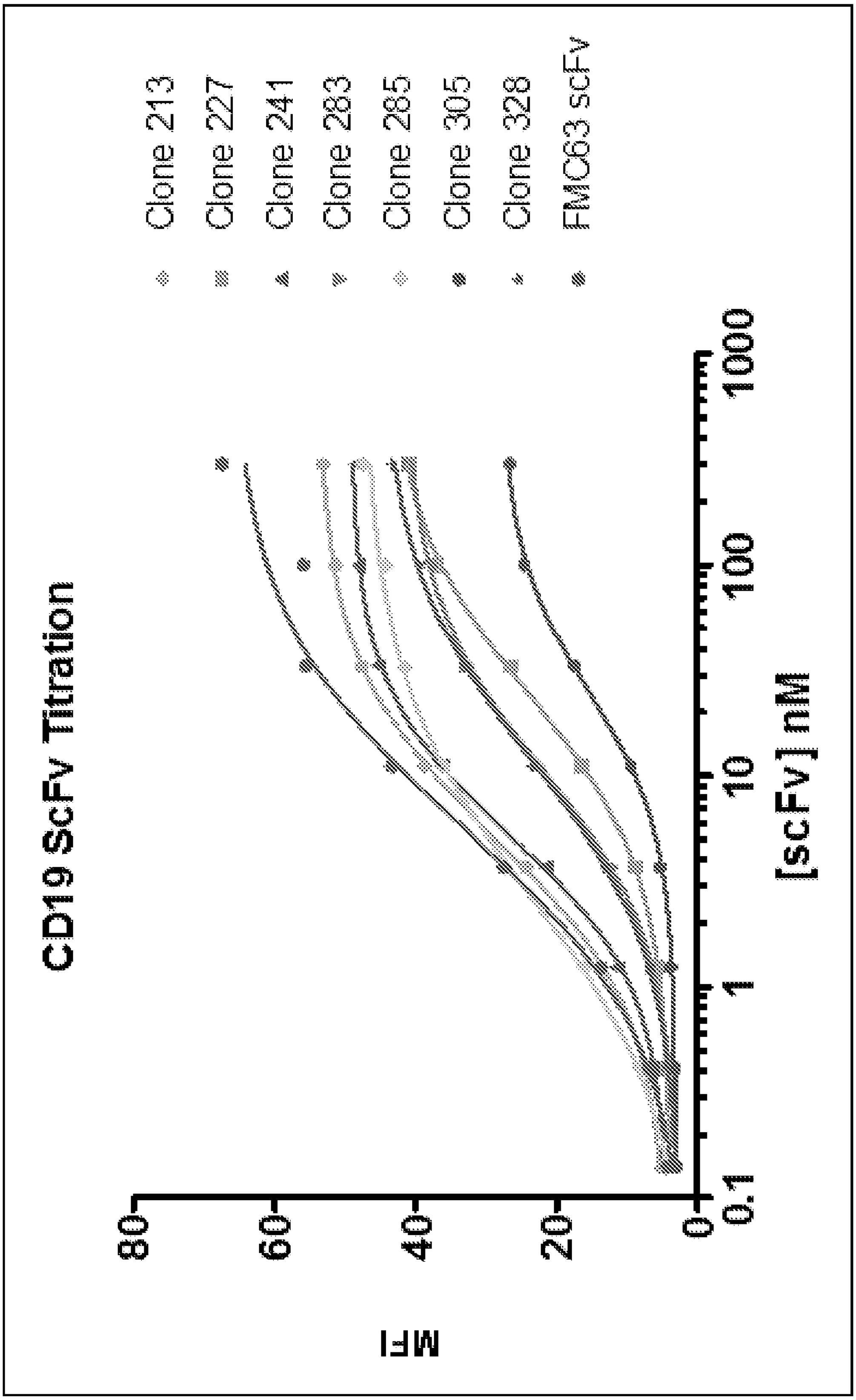

CD19 ScFv Titration
MFI
80
60
40
20
0
0.1
1
10
100
1000
[scFv] nM
Clone 213
Clone 227
Clone 241
Clone 283
Clone 285
Clone 305
Clone 328
FMC63 scFv

Figure 10A

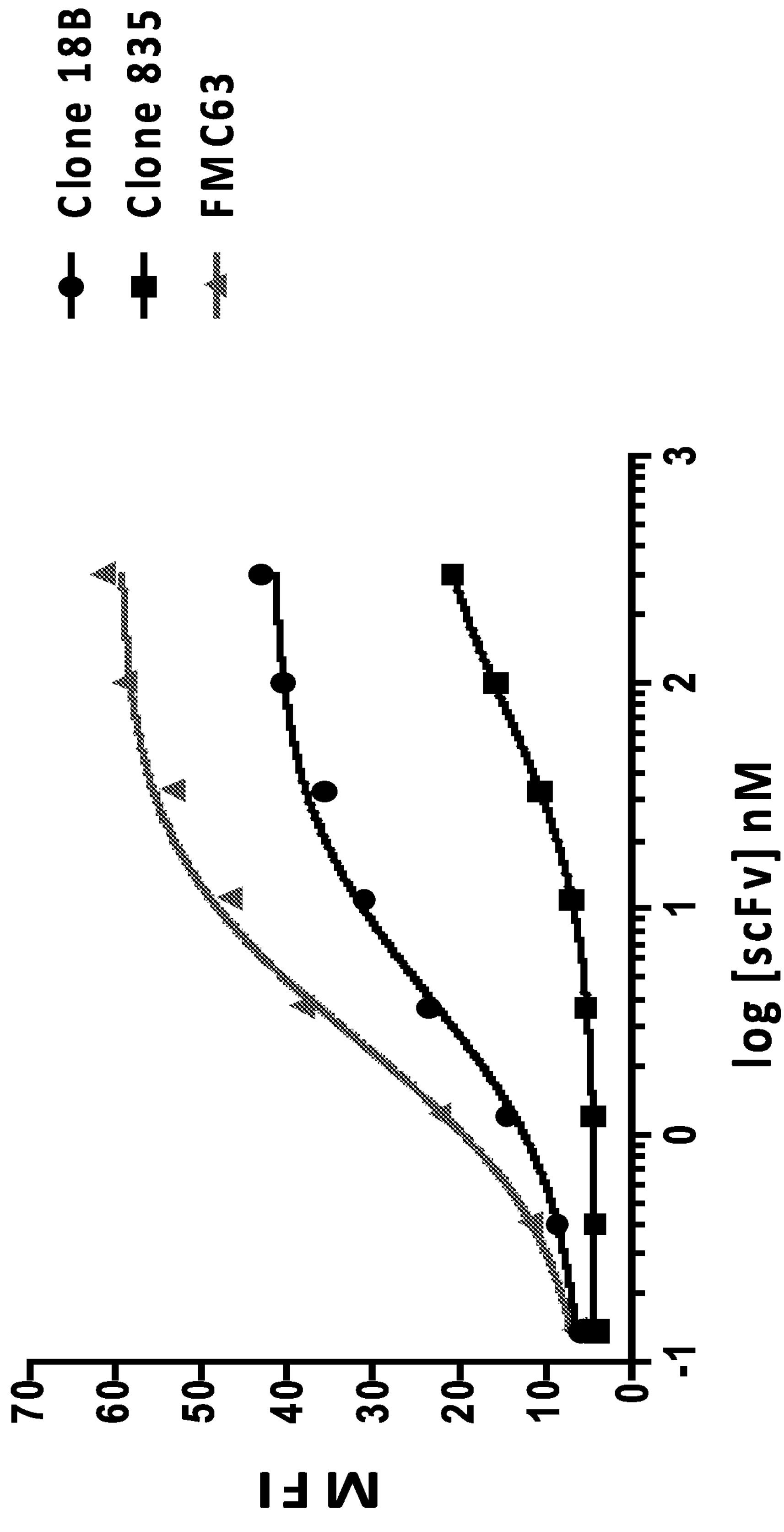

Clone 18B
Clone 835
FMC63
M F I
0
10
20
30
40
50
60
70
-1
0
1
2
3
log [scFv] nM

Figure 10B

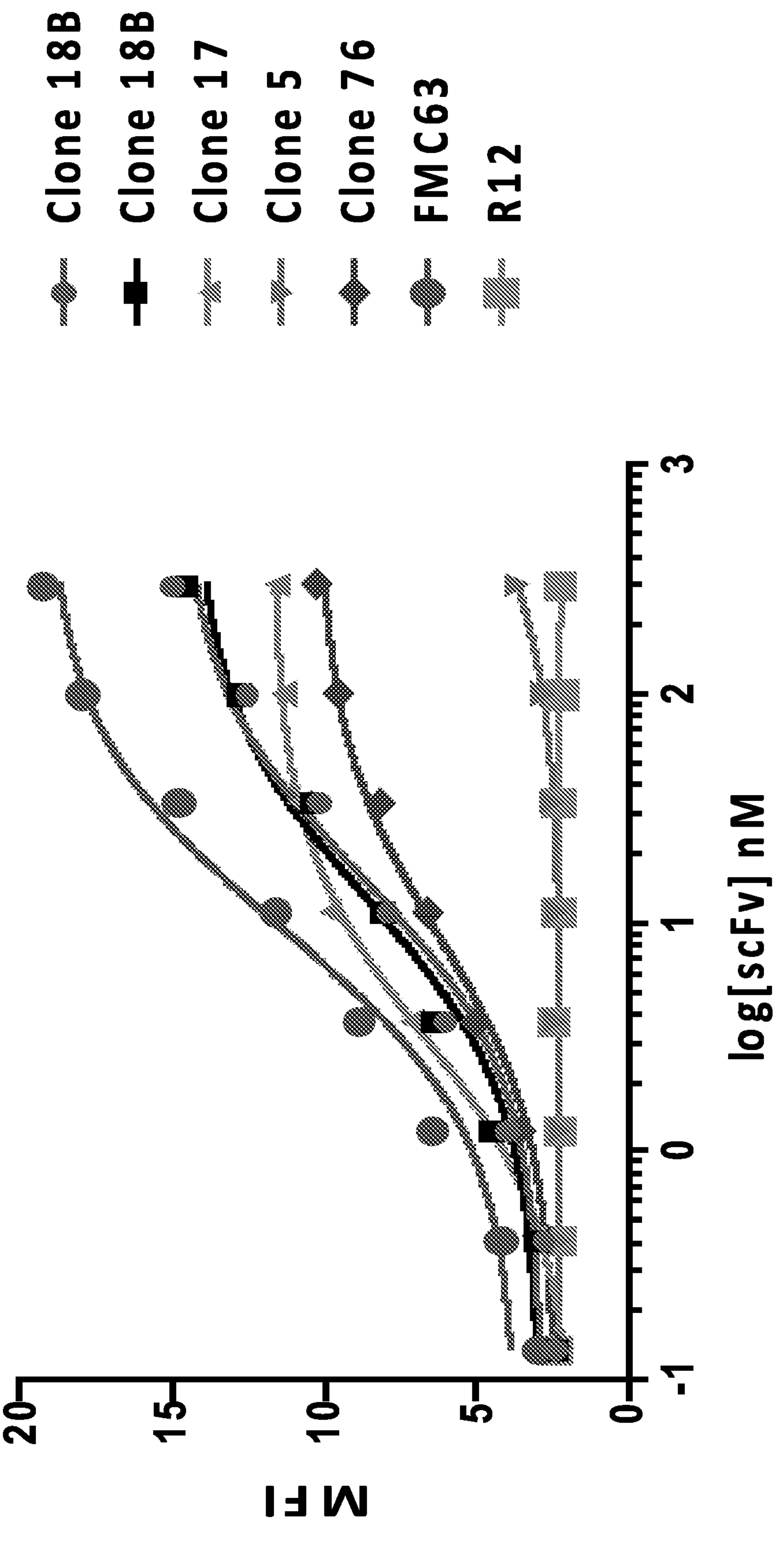

Clone 18B
Clone 18B
Clone 17
Clone 5
Clone 76
FMC63
R12
MFI
log[scFv] nM
0
5
10
15
20
-1
0
1
2
3

Figure 10C

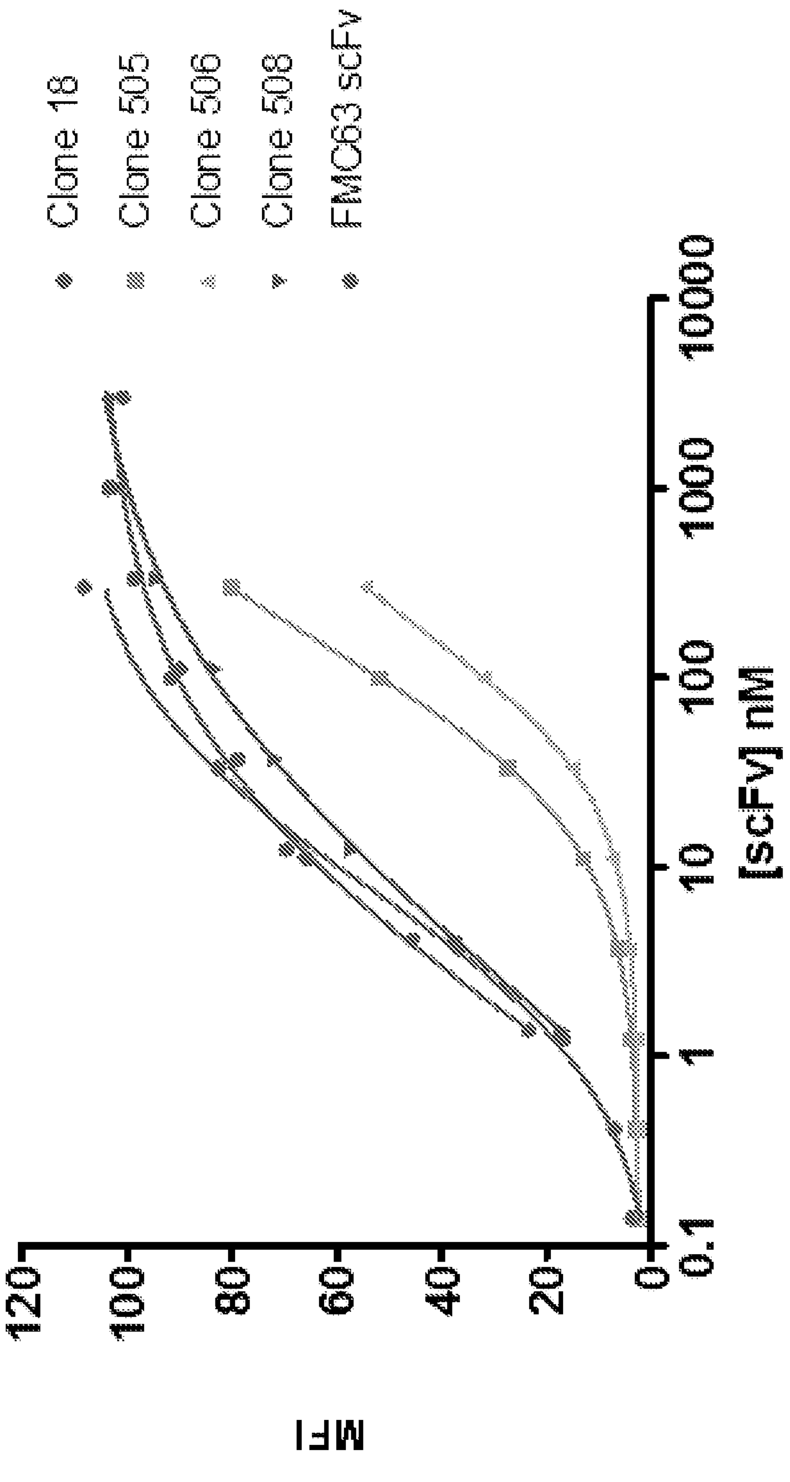

MFI
0
20
40
60
80
100
120
0.1
1
10
100
1000
10000
[scFv] nM
Clone 18
Clone 505
Clone 506
Clone 508
FMC63 scFv

Figure 10D

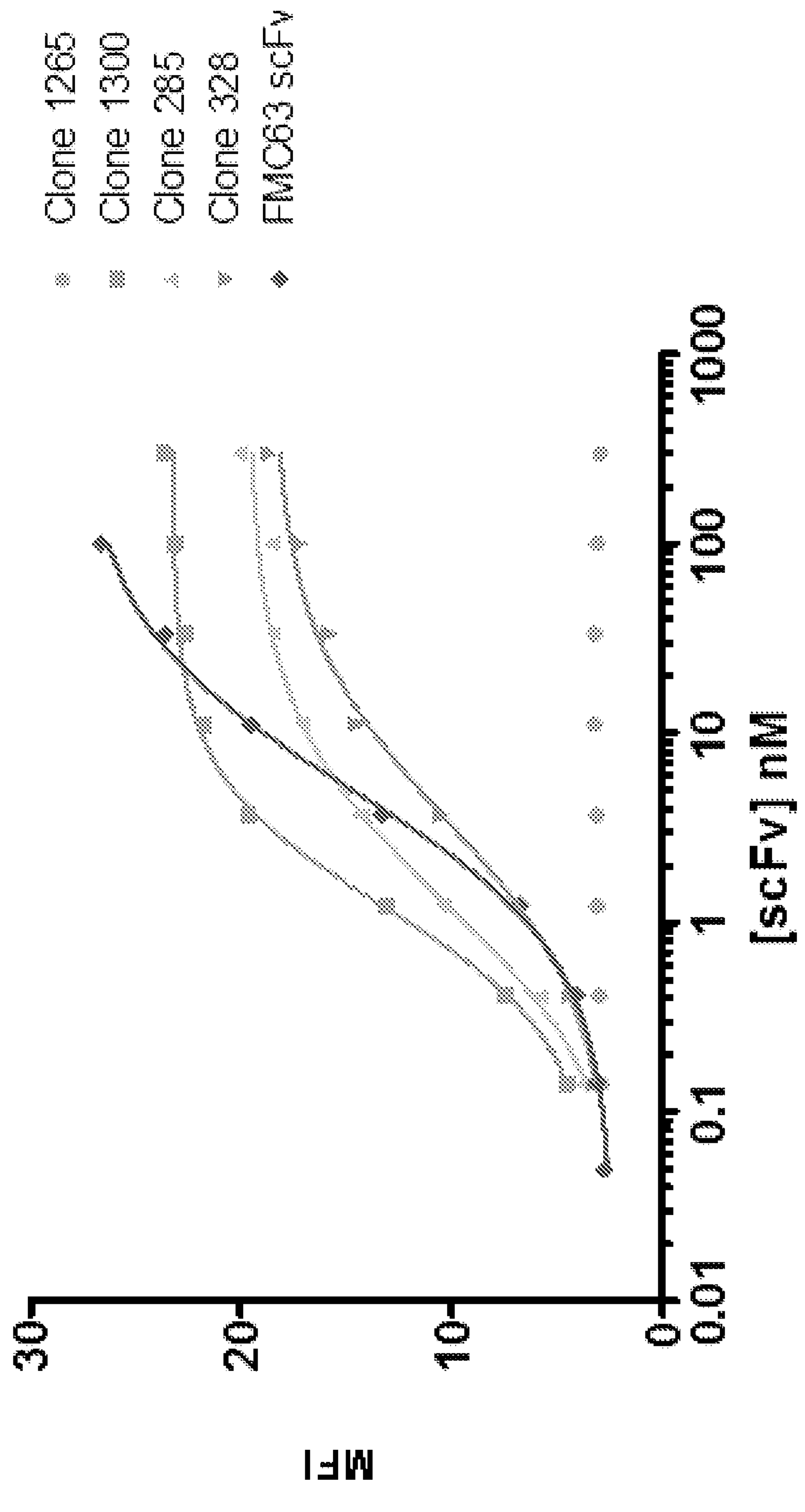

MFI
30
20
10
0
0.01
0.1
1
10
100
1000
[scFv] nM
Clone 1265
Clone 1300
Clone 285
Clone 328
FMC63 scFv

Figure 10E

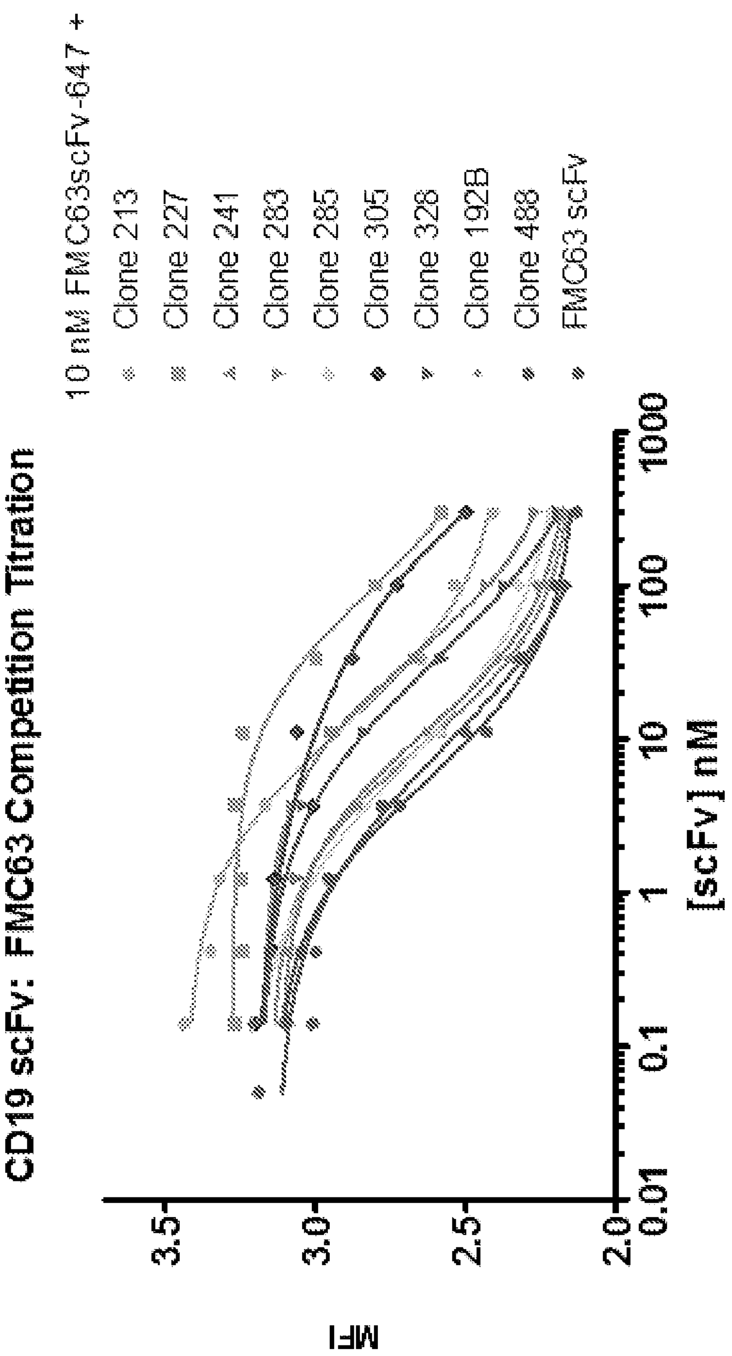

CD19 scFv: FMC63 Competition Titration
MFI
3.5
3.0
2.5
2.0
0.01
0.1
1
10
100
1000
[scFv] nM
10 nM FMC63scFv-647 +
Clone 213
Clone 227
Clone 241
Clone 283
Clone 285
Clone 305
Clone 328
Clone 192B
Clone 488
FMC63 scFv

Figure 11

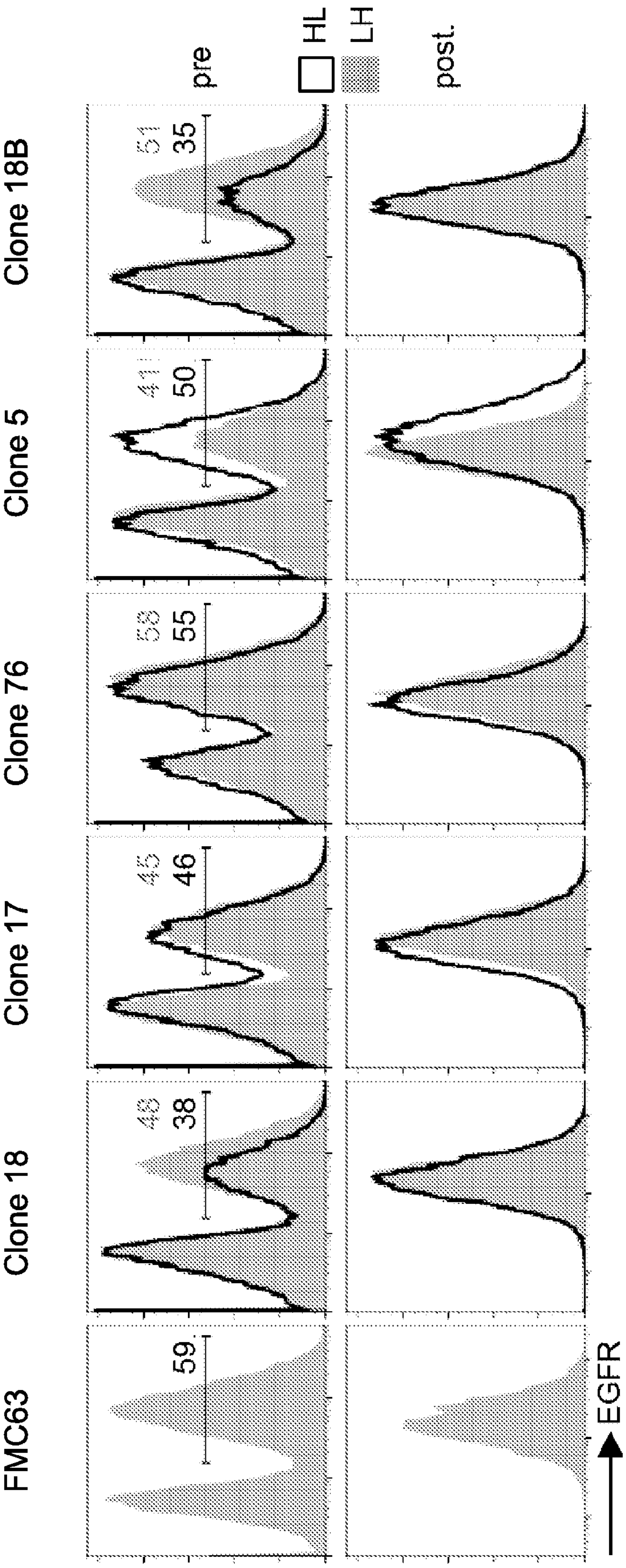

FMC63
Clone 18
Clone 17
Clone 76
Clone 5
Clone 18B
pre
HL
LH
post.
59
48
38
45
46
58
55
41
50
51
35
EGFR

FIGURE 12A

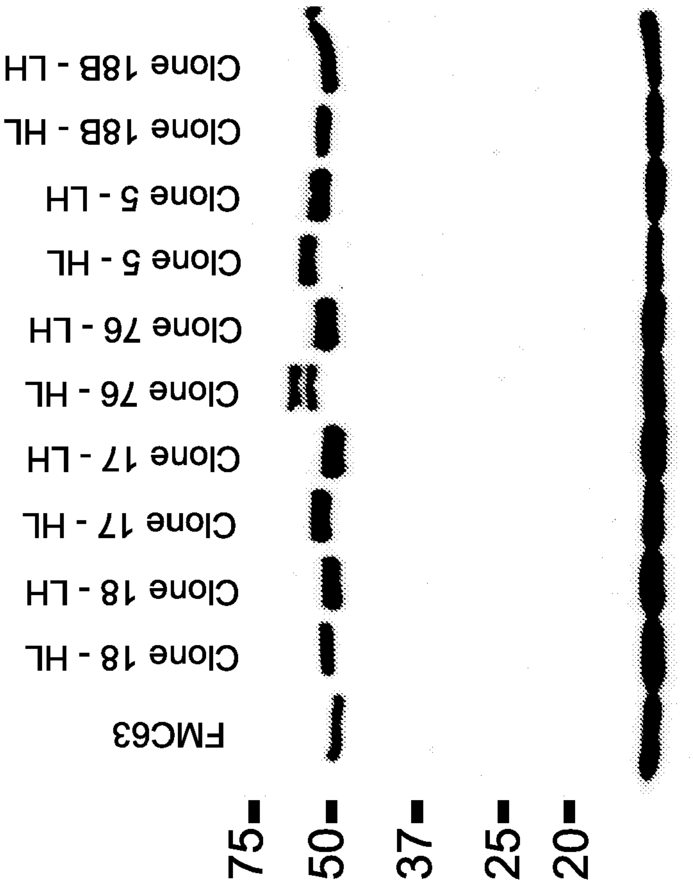

Clone 18B - LH
Clone 18B - HL
Clone 5 - LH
Clone 5 - HL
Clone 76 - LH
Clone 76 - HL
Clone 17 - LH
Clone 17 - HL
Clone 18 - LH
Clone 18 - HL
FMC63
75
50
37
25
20

FIGURE 12B

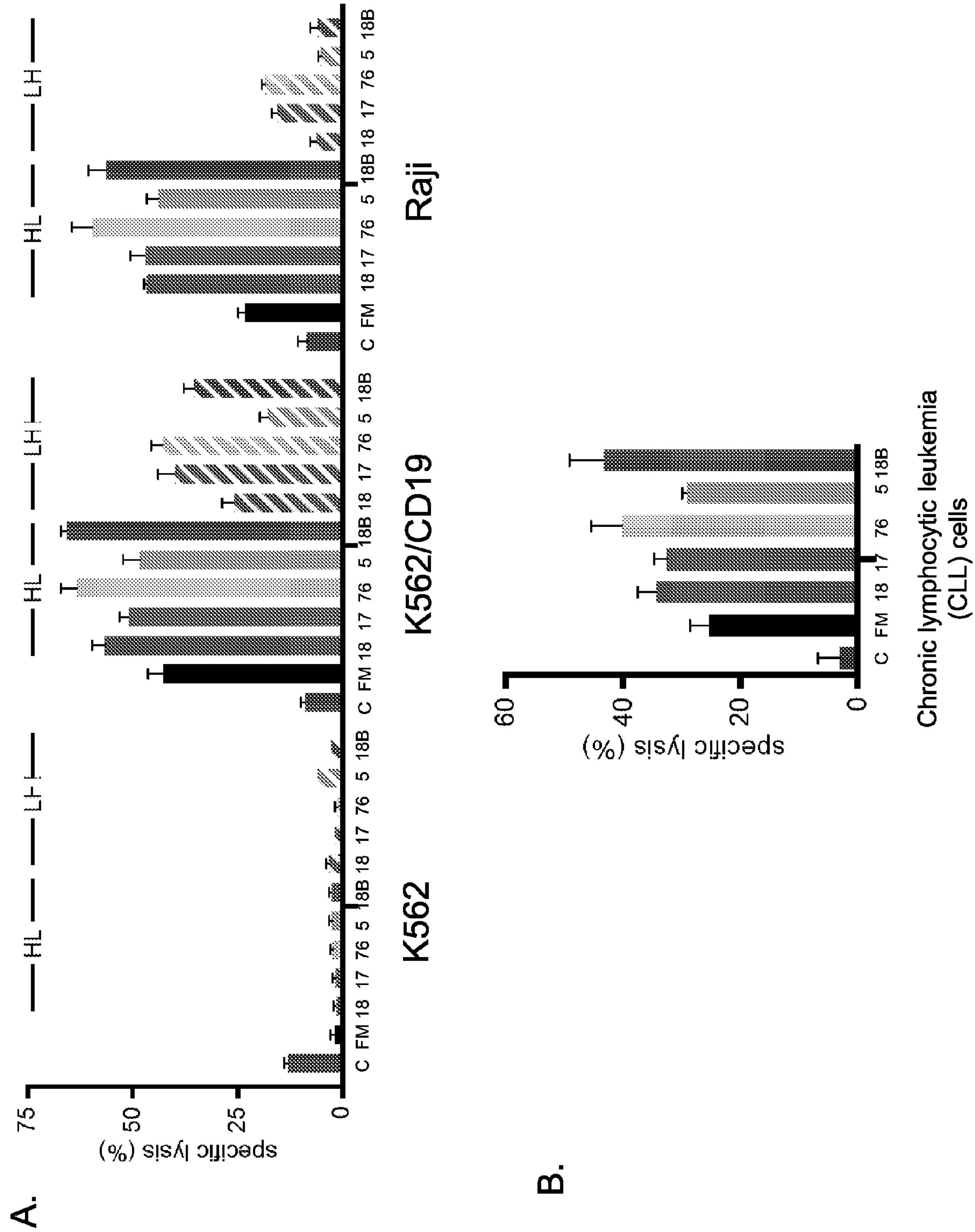

A.
specific lysis (%)
75
50
25
0
HL
LH
C FM 18 17 76 5 18B 18 17 76 5 18B
K562
K562/CD19
Raji
B.
specific lysis (%)
60
40
20
0
C FM 18 17 76 5 18B
Chronic lymphocytic leukemia
(CLL) cells

FIGURE 13

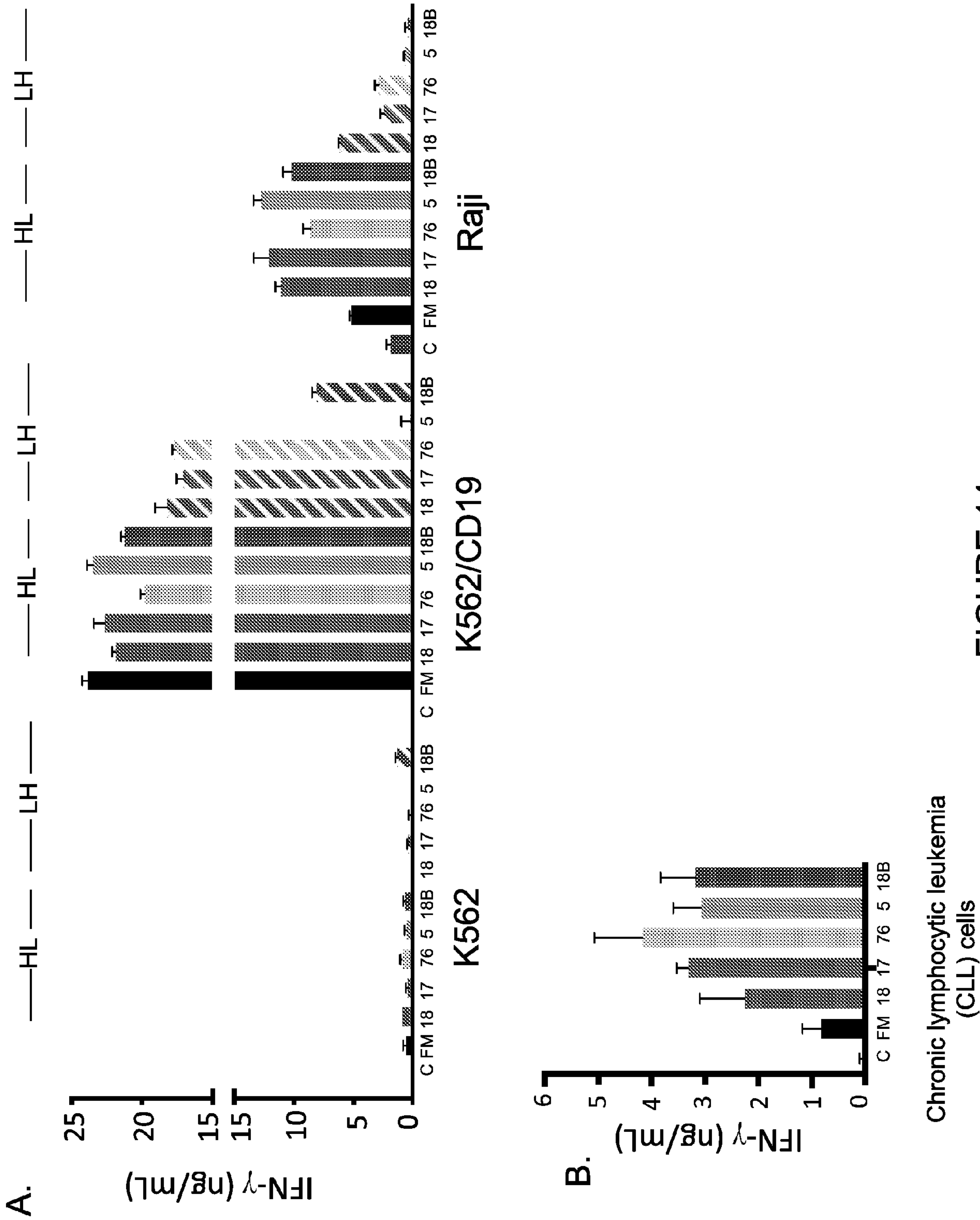

A.
IFN-γ (ng/mL)
25
20
15
15
10
5
0
HL
LH
C FM 18 17 76 5 18B 18 17 76 5 18B
K562
K562/CD19
Raji
B.
IFN-γ (ng/mL)
6
5
4
3
2
1
0
C FM 18 17 76 5 18B
Chronic lymphocytic leukemia
(CLL) cells

FIGURE 14

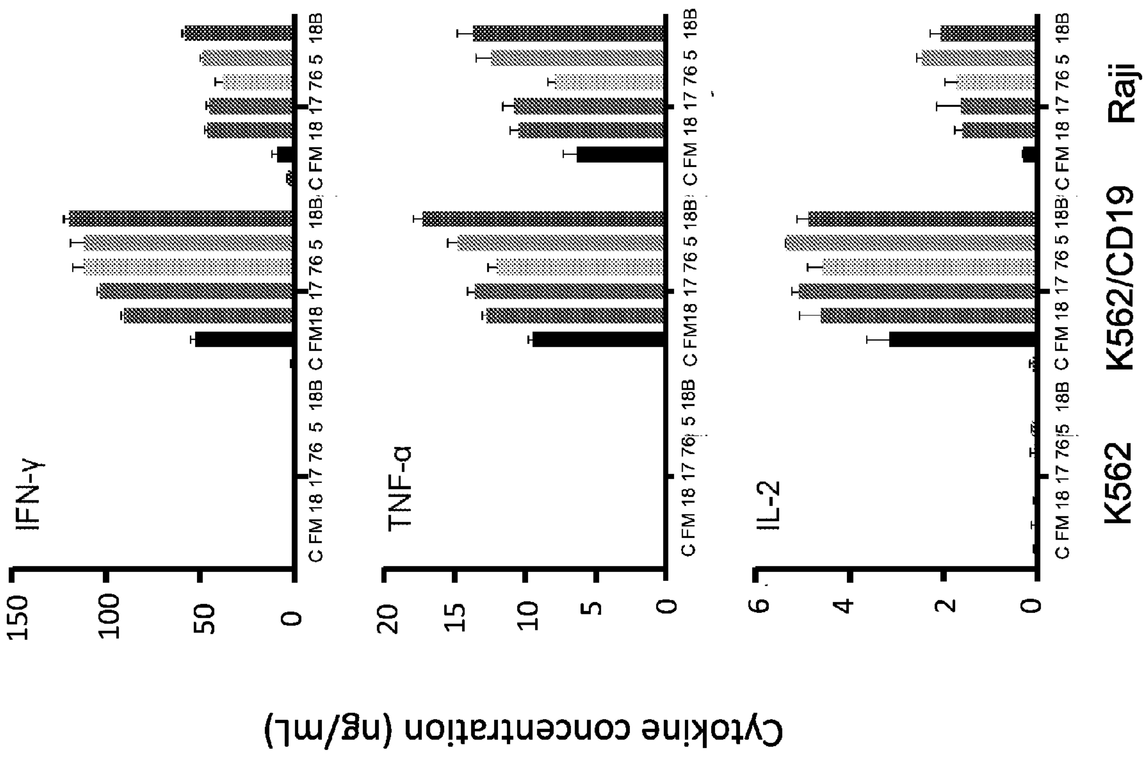

IFN-γ
TNF-α
IL-2
Cytokine concentration (ng/mL)
150
100
50
0
20
15
10
5
6
4
2
C FM 18 17 76 5 18B
K562
K562/CD19
Raji

FIGURE 15

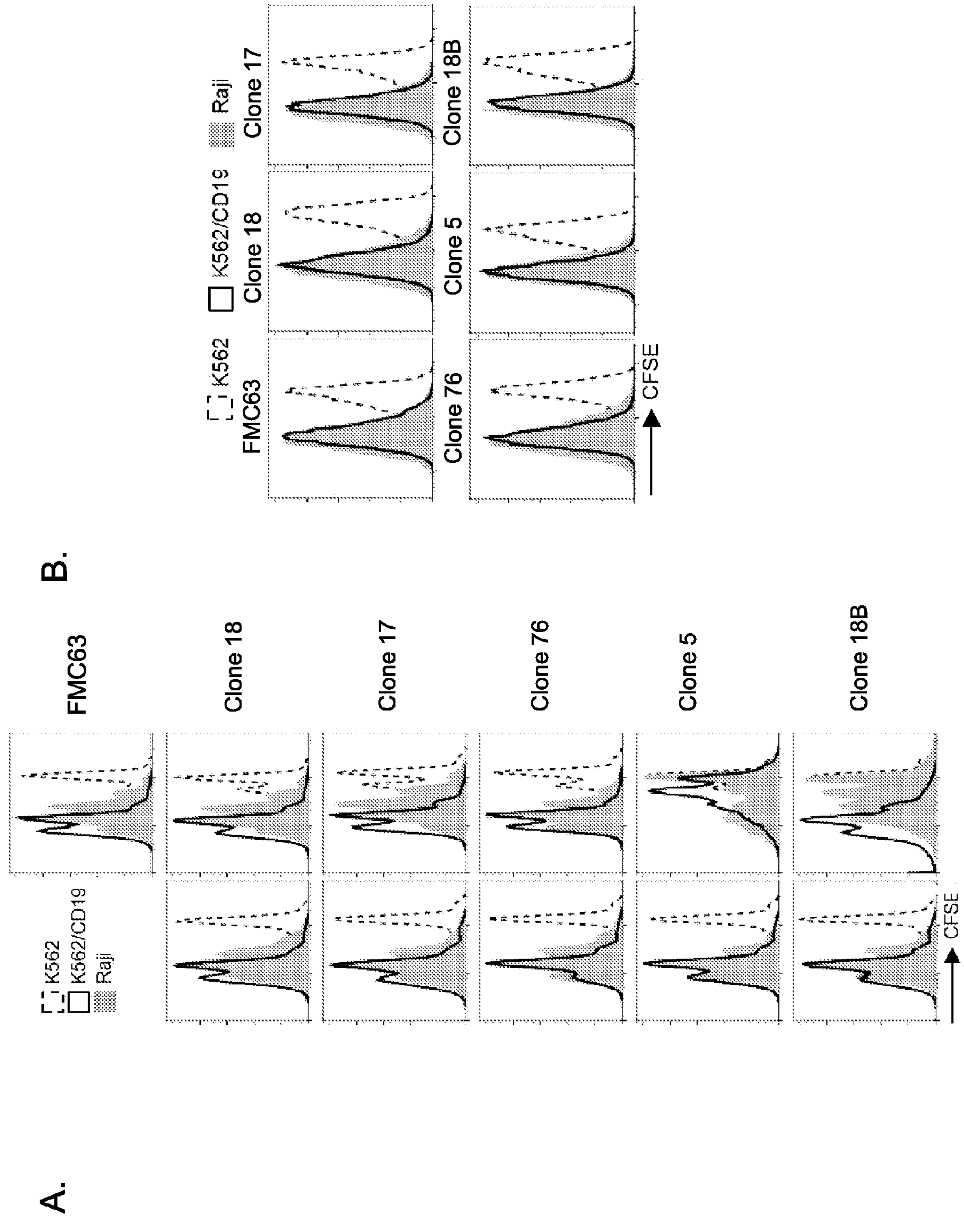

A.
HL
LH
K562
K562/CD19
Raji
FMC63
Clone 18
Clone 17
Clone 76
Clone 5
Clone 18B
CFSE
B.
K562
K562/CD19
Raji
FMC63
Clone 18
Clone 17
Clone 76
Clone 5
Clone 18B
CFSE

FIGURE 16

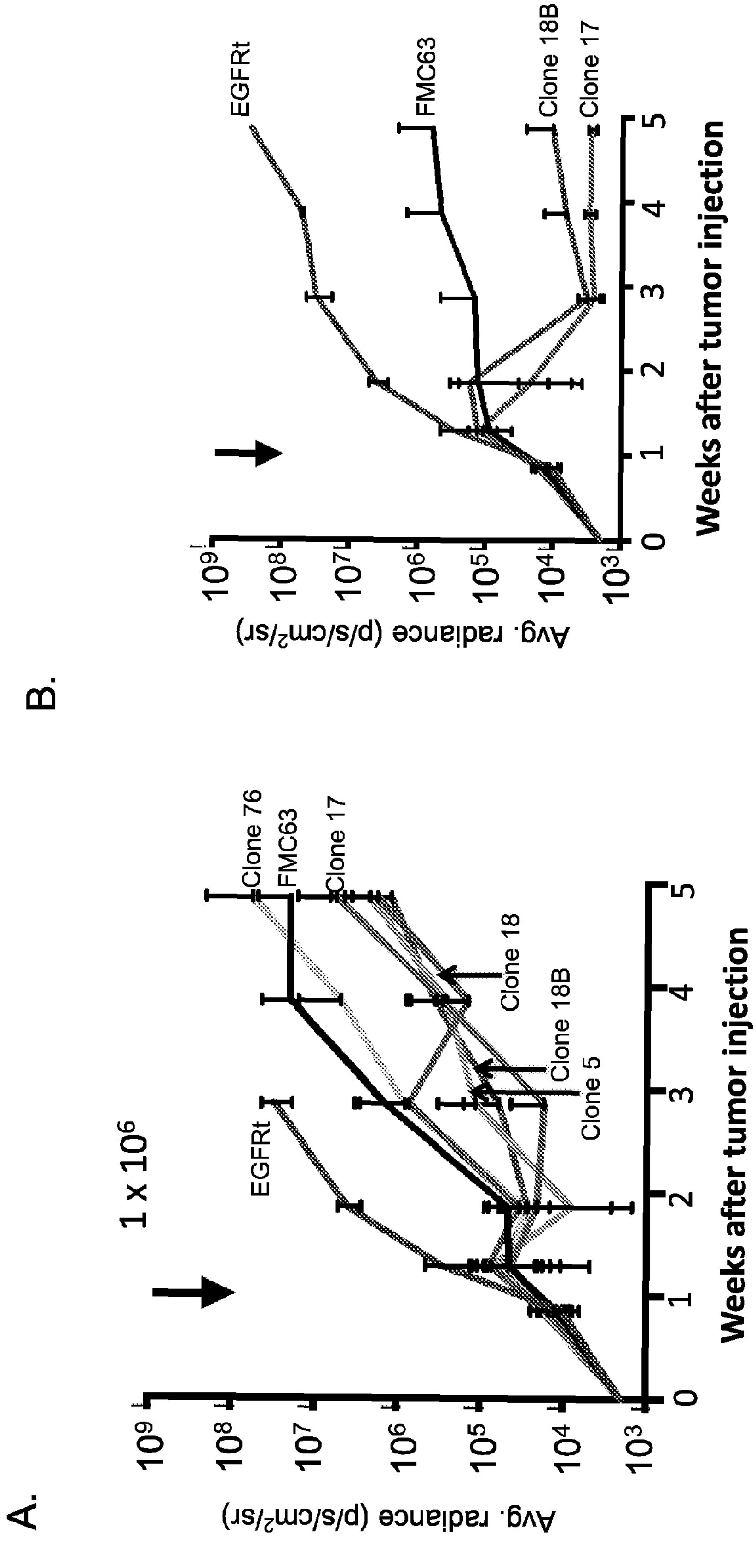

A.
1 x 10^6
Avg. radiance (p/s/cm²/sr)
10⁹
10⁸
10⁷
10⁶
10⁵
10⁴
10³
EGFRt
Clone 76
FMC63
Clone 17
Clone 18
Clone 18B
Clone 5
0
1
2
3
4
5
Weeks after tumor injection
B.
Avg. radiance (p/s/cm²/sr)
EGFRt
FMC63
Clone 18B
Clone 17
Weeks after tumor injection

FIGURE 17

A.

```
V1: HPKGPKS-LLSLELKDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWLLRTGGWK
V2: RPKGPKSSLLSLELKDDRPDRDMWVVDTGLLLTRATAQDAGKYYCHRGNLTMSFHLEITARPVLWHWLLRTGGWK
V3: HPKGPKS-LLSLELKDDRPARDMWVMETGLLLPRATAQDAGKYYCHRGNWTKSFYLEITARPALWHWLLRIGGWK
    :****** *********** *****::*****.*************** * **:*******.******* ****
```

B.

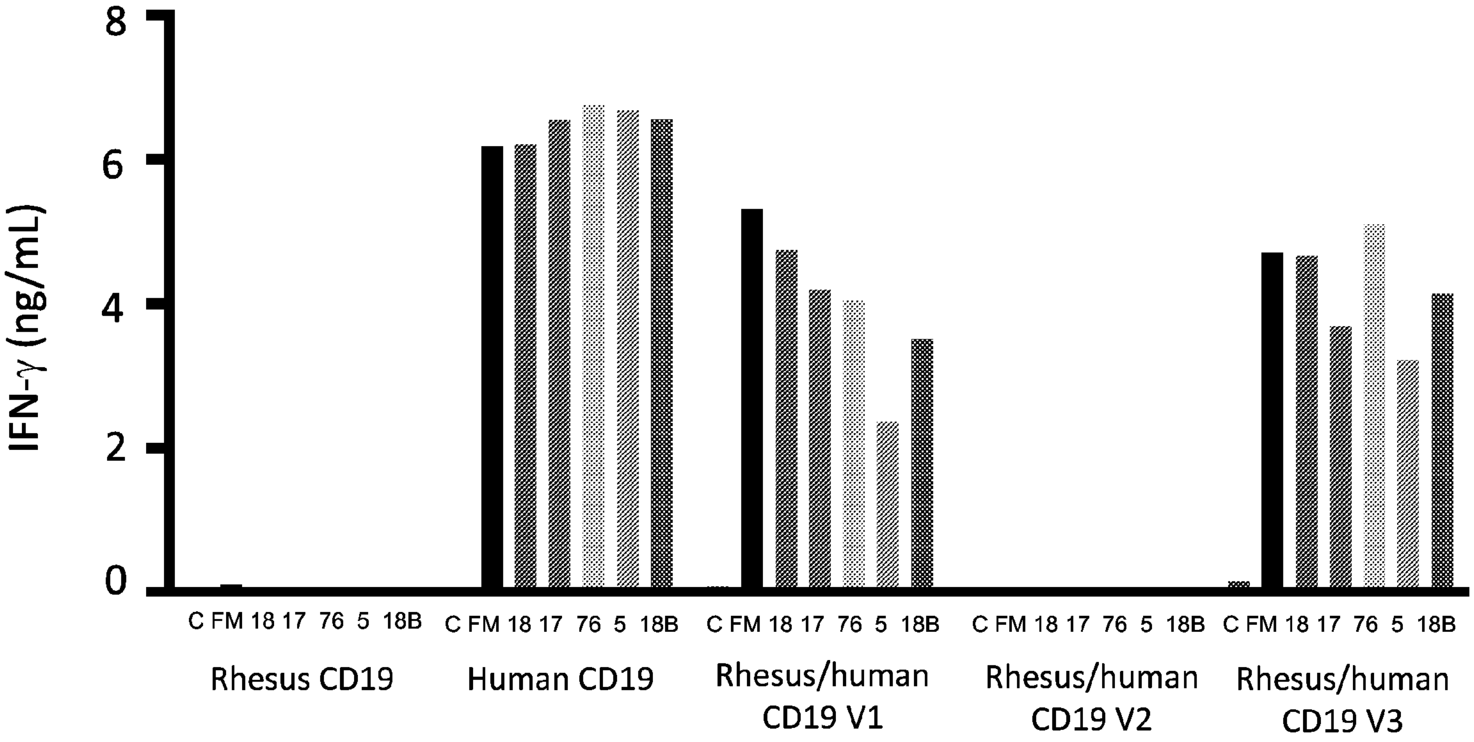


FIGURE 18

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 62043273 **[0001]**
- US 62078942 **[0001]**
- WO 2012170807 A **[0005]**
- WO 2009054863 A **[0006]**
- WO 2009091826 A **[0007]**
- US 2005070693 A **[0008]**
- US 20060270045 A1 **[0155]**
- US 7446190 B **[0172] [0209] [0211] [0235] [0252]**
- US 5208020 A **[0189] [0192]**
- US 5416064 A **[0189]**
- EP 0425235 B1 **[0189]**
- US 5635483 A **[0189]**
- US 5780588 A **[0189]**
- US 7498298 B **[0189]**
- US 5712374 A **[0189]**
- US 5714586 A **[0189]**
- US 5739116 A **[0189]**
- US 5767285 A **[0189]**
- US 5770701 A **[0189]**
- US 5770710 A **[0189]**
- US 5773001 A **[0189]**
- US 5877296 A **[0189]**
- US 6630579 B **[0189]**
- WO 9411026 A **[0192]**
- US 20030157108 A **[0203]**
- US 20040093621 A **[0203]**
- WO 200061739 A **[0203]**
- WO 200129246 A **[0203]**
- US 20030115614 A **[0203]**
- US 20020164328 A **[0203]**
- US 20040132140 A **[0203]**
- US 20040110704 A **[0203]**
- US 20040110282 A **[0203]**
- US 20040109865 A **[0203]**
- WO 2003085119 A **[0203]**
- WO 2003084570 A **[0203]**
- WO 2005035586 A **[0203]**
- WO 2005035778 A **[0203]**
- WO 2005053742 A **[0203]**
- WO 2002031140 A **[0203]**
- US 20030157108 A1, Presta, L **[0203]**
- WO 2004056312 A1 **[0203]**
- WO 2003085107 A **[0203]**
- WO 2003011878 A, Jean-Mairet **[0203]**
- US 6602684 B, Umana **[0203]**
- US 20050123546 A, Umana **[0203]**
- WO 199730087 A, Patel **[0203]**
- WO 199858964 A, Raju, S. **[0203]**
- WO 199922764 A, Raju, S. **[0203]**
- US 7855275 B **[0206]**
- US 7521541 B **[0206]**
- WO 200014257 A **[0209]**
- WO 2013126726 A **[0209]**
- WO 2012129514 A **[0209]**
- WO 2014031687 A **[0209] [0211] [0212] [0226]**
- WO 2013166321 A **[0209]**
- WO 2013071154 A **[0209]**
- WO 2013123061 A **[0209]**
- US 2002131960 A **[0209]**
- US 2013287748 A **[0209]**
- US 20130149337 A **[0209] [0211]**
- US 6451995 B **[0209]**
- US 8252592 B **[0209]**
- US 8339645 B **[0209] [0211]**
- US 8398282 B **[0209]**
- US 7446179 B **[0209] [0211]**
- US 6410319 B **[0209]**
- US 7070995 B **[0209]**
- US 7265209 B **[0209]**
- US 7354762 B **[0209]**
- US 7446191 B **[0209]**
- US 8324353 B **[0209]**
- US 8479118 B **[0209]**
- EP 2537416 A **[0209]**
- WO 2014055668 A1 **[0209]**
- US 8389282 B **[0209] [0211]**
- US 8822647 B **[0212]**
- US 20140271635 A **[0212]**
- WO 2014055668 A **[0223] [0252]**
- US 8911993 B **[0235]**
- US 5219740 A **[0249]**
- US 6207453 B **[0249]**
- US 9108442 W **[0253]**
- US 9405601 W, Lupton **[0253]**
- US 6040177 A, Riddell **[0253] [0296]**
- US 4452773 A, Molday **[0277]**
- EP 452342 B **[0277]**
- US 4795698 A, Owen **[0277]**
- US 5200084 A, Liberti **[0277]**
- WO 2009072003 A **[0283]**
- US 20110003380 A1 **[0283]**
- WO 2010033140 A **[0288]**
- US 4235871 A **[0308]**
- US 4501728 A **[0308]**
- US 4837028 A **[0308]**
- US 5019369 A **[0308]**
- US 20030170238, Gruenberg **[0332]**
- US 4690915 A, Rosenberg **[0332]**

- US 5087616 A **[0343]**
- WO 2015095895 A **[0407] [0409] [0421]**
- US 62043273 B **[0430]**
- US 62078942 B **[0430]**

Non-patent literature cited in the description

- **KOCHENDERFER et al.** describe B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-tarnsduced T cells. *Blood,* 2012, vol. 119 (12), 2709-2720 **[0009]**
- **TURTLE et al.** describe CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. *The Journal of Clinical Investigation,* 2016, vol. 126 (6), 2123-2138 **[0010]**
- **KABAT et al.** Sequences of Proteins of Immunological Interest. Public Health Service, National Institutes of Health, 1991 **[0090] [0092] [0356]**
- **AL-LAZIKANI et al.** *JMB,* 1997, vol. 273, 927-948 **[0090] [0092]**
- **MACCALLUM et al.** *J. Mol. Biol.,* 1996, vol. 262, 732-745 **[0090]**
- Antibody-antigen interactions: Contact analysis and binding site topography. *J. Mol. Biol.,* vol. 262, 732-745 **[0090]**
- **LEFRANC MP et al.** IMGT unique numbering for immunoglobulin and T cell receptor variable domains and Ig superfamily V-like domains. *Dev Comp Immunol,* January 2003, vol. 27 (1), 55-77 **[0090]**
- **HONEGGER A ; PLÜCKTHUN A.** Yet another numbering scheme for immunoglobulin variable domains: an automatic modeling and analysis tool. *J Mol Biol,* 08 June 2001, vol. 309 (3), 657-70 **[0090]**
- **KINDT et al.** Kuby Immunology. W.H. Freeman and Co, 2007, 91 **[0095]**
- **PORTOLANO et al.** *J. Immunol.,* 1993, vol. 150, 880-887 **[0095]**
- **CLARKSON et al.** *Nature,* 1991, vol. 352, 624-628 **[0095]**
- **GERNGROSS.** *Nat. Biotech.,* 2004, vol. 22, 1409-1414 **[0154]**
- **LI et al.** *Nat. Biotech.,* 2006, vol. 24, 210-215 **[0154]**
- **SITARAMAN et al.** *Methods Mol. Biol.,* 2009, vol. 498, 229-44 **[0156]**
- **SPIRIN.** *Trends Biotechnol.,* 2004, vol. 22, 538-45 **[0156]**
- **ENDO et al.** *Biotechnol. Adv.,* 2003, vol. 21, 695-713 **[0156]**
- **ZOLA H et al.** *Immunol Cell Biol.,* December 1991, vol. 69, 411-22 **[0172]**
- **JUNGHANS et al.** *Cancer Res.,* 1990, vol. 50, 1495-1502 **[0179]**
- **HINMAN et al.** *Cancer Res.,* 1993, vol. 53, 3336-3342 **[0189]**
- **LODE et al.** *Cancer Res.,* 1998, vol. 58, 2925-2928 **[0189]**
- **KRATZ et al.** *Current Med. Chem.,* 2006, vol. 13, 477-523 **[0189]**
- **JEFFREY et al.** *Bioorganic & Med. Chem. Letters,* 2006, vol. 16, 358-362 **[0189]**
- **TORGOV et al.** *Bioconj. Chem.,* 2005, vol. 16, 717-721 **[0189]**
- **NAGY et al.** *Proc. Natl. Acad. Sci. USA,* 2000, vol. 97, 829-834 **[0189]**
- **DUBOWCHIK et al.** *Bioorg. & Med. Chem. Letters,* 2002, vol. 12, 1529-1532 **[0189]**
- **KING et al.** *J. Med. Chem.,* 2002, vol. 45, 4336-4343 **[0189]**
- **VITETTA et al.** *Science,* 1987, vol. 238, 1098 **[0192]**
- **CHARI et al.** *Cancer Res.,* 1992, vol. 52, 127-131 **[0192]**
- **CHOWDHURY.** *Methods Mol. Biol.,* 2008, vol. 207, 179-196 **[0199]**
- **HOOGENBOOM et al.** Methods in Molecular Biology. Human Press, 2001, vol. 178, 1-37 **[0199]**
- **OKAZAKI et al.** *J. Mol. Biol.,* 2004, vol. 336, 1239-1249 **[0203]**
- **YAMANE-OHNUKI et al.** *Biotech. Bioeng.,* 2004, vol. 87, 614 **[0203]**
- **RIPKA et al.** *Arch. Biochem. Biophys.,* 1986, vol. 249, 533-545 **[0203]**
- **KANDA, Y. et al.** *Biotechnol. Bioeng.,* 2006, vol. 94 (4), 680-688 **[0203]**
- **SADELAIN et al.** *Cancer Discov.,* April 2013, vol. 3 (4), 388-398 **[0209]**
- **DAVILA et al.** *PLoS ONE,* 2013, vol. 8 (4), e61338 **[0209] [0332]**
- **TURTLE et al.** *Curr. Opin. Immunol,* October 2012, vol. 24 (5), 633-39 **[0209]**
- **WU et al.** *Cancer,* 18 March 2012, vol. 2, 160-75 **[0209]**
- **KOCHENDERFER et al.** *Nature Reviews Clinical Oncology,* 2013, vol. 10, 267-276 **[0211]**
- **WANG et al.** *J. Immunother.,* 2012, vol. 35 (9), 689-701 **[0211] [0250]**
- **BRENTJENS et al.** *Sci Transl Med.,* 2013, vol. 5 (177 **[0211]**
- **HUDECEK et al.** *Clin. Cancer Res.,* 2013, vol. 19, 3153 **[0212]**
- **FEDOROV et al.** *Sci. Transl. Medicine,* December 2013, vol. 5 (215 **[0223]**
- **MULLEN et al.** *Proc. Natl. Acad. Sci. USA.,* 1992, vol. 89, 33 **[0246]**
- **KOSTE et al.** *Gene Therapy,* 03 April 2014 **[0248]**
- **CARLENS et al.** *Exp Hematol,* 2000, vol. 28 (10), 1137-46 **[0248]**
- **ALONSO-CAMINO et al.** *Mol Ther Nucl Acids,* 2013, vol. 2, e93 **[0248]**
- **PARK et al.** *Trends Biotechnol.,* November 2011, vol. 29 (11), 550-557 **[0248]**

- **MILLER ; ROSMAN.** *BioTechniques,* 1989, vol. 7, 980-990 **[0249]**
- **MILLER, A. D.** *Human Gene Therapy,* 1990, vol. 1, 5-14 **[0249]**
- **SCARPA et al.** *Virology,* 1991, vol. 180, 849-852 **[0249]**
- **BURNS et al.** *Proc. Natl. Acad. Sci. USA,* 1993, vol. 90, 8033-8037 **[0249]**
- **BORIS-LAWRIE ; TEMIN.** *Cur. Opin. Genet. Develop.,* 1993, vol. 3, 102-109 **[0249]**
- **COOPER et al.** *Blood,* 2003, vol. 101, 1637-1644 **[0250]**
- **VERHOEYEN et al.** *Methods Mol Biol.,* 2009, vol. 506, 97-114 **[0250]**
- **CAVALIERI et al.** *Blood,* 2003, vol. 102 (2), 497-505 **[0250]**
- **CHICAYBAM et al.** *PLoS ONE,* 2013, vol. 8 (3), e60298 **[0251]**
- **VAN TEDELOO et al.** *Gene Therapy,* 2000, vol. 7 (16), 1431-1437 **[0251]**
- **MANURI et al.** *Hum Gene Ther,* 2010, vol. 21 (4), 427-437 **[0251]**
- **SHARMA et al.** *Molec Ther Nucl Acids,* 2013, vol. 2, e74 **[0251]**
- **HUANG et al.** *Methods Mol Biol,* 2009, vol. 506, 115-126 **[0251]**
- Current Protocols in Molecular Biology. John Wiley & Sons **[0251]**
- **JOHNSTON.** *Nature,* 1990, vol. 346, 776-777 **[0251]**
- **BRASH et al.** *Mol. Cell Biol.,* 1987, vol. 7, 2031-2034 **[0251]**
- **LUPTON S. D. et al.** *Mol. and Cell Biol.,* 1991, vol. 11, 6 **[0253]**
- **RIDDELL et al.** *Human Gene Therapy,* 1992, vol. 3, 319-338 **[0253]**
- **TERAKURAET.** *Blood.,* 2012, vol. 1, 72-82 **[0270]**
- **WANG et al.** *J Immunother.,* 2012, vol. 35 (9), 689-701 **[0270] [0287] [0296]**
- Methods in Molecular Medicine. *Metastasis Research Protocols,* vol. 58 **[0275]**
- Cell Behavior In Vitro and In Vivo. U. Schumacher © Humana Press Inc, vol. 2, 17-25 **[0275]**
- **KLEBANOFF et al.** *J Immunother.,* 2012, vol. 35 (9), 651-660 **[0287] [0296]**
- **TERAKURA et al.** *Blood,* 2012, vol. 1, 72-82 **[0287] [0296]**
- **CHO et al.** *Lab Chip,* 2010, vol. 10, 1567-1573 **[0288]**
- **GODIN et al.** *J Biophoton.,* 2008, vol. 1 (5), 355-376 **[0288]**
- Remington's Pharmaceutical Sciences. 1980 **[0304]**
- Remington: The Science and Practice of Pharmacy. Lippincott Williams & Wilkins, 01 May 2005 **[0305]**
- **SZOKA et al.** *Ann. Rev. Biophys. Bioeng,* 1980, vol. 9, 467 **[0308]**
- **ROSENBERG.** *Nat Rev Clin Oncol.,* vol. 8 (10), 577-85 **[0332]**
- **THEMELI et al.** *Nat Biotechnol.,* 2013, vol. 31 (10), 928-933 **[0332]**
- **TSUKAHARA et al.** *Biochem Biophys Res Commun,* 2013, vol. 438 (1), 84-9 **[0332]**
- **KOCHENDERFER et al.** *J. Immunotherapy,* 2009, vol. 32 (7), 689-702 **[0342]**
- **HERMAN et al.** *J. Immunological Methods,* 2004, vol. 285 (1), 25-40 **[0342]**
- **WADWA et al.** *J. Drug Targeting,* 1995, vol. 3, 1-1 1 **[0343]**
- **ZOLA.** Monoclonal Antibodies: A Manual of Techniques. CRC Press, Inc, 1987, 147-158 **[0349]**
- Computational Molecular Biology. Oxford University Press, 1988 **[0354]**
- Biocomputing: Informatics and Genome Projects. Academic Press, 1993 **[0354]**
- Computer Analysis of Sequence Data. Humana Press, 1994 **[0354]**
- **VON HEINJE, G.** Sequence Analysis in Molecular Biology. Academic Press, 1987 **[0354]**
- Sequence Analysis Primer. M Stockton Press, 1991 **[0354]**
- **CARRILLO et al.** *SIAM J Applied Math,* 1988, vol. 48, 1073 **[0354]**
- **FLATMAN et al.** *J. Chromatogr. B,* 2007, vol. 848, 79-87 **[0358]**
- **YAM et al.** *Mol. Ther.,* 2002, vol. 5, 479 **[0407] [0409]**