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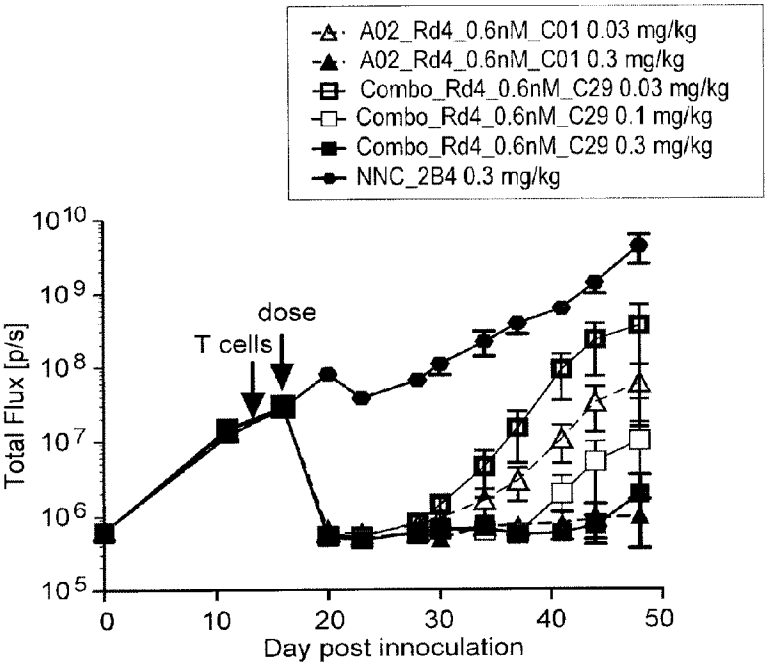

(57) Abrégé/Abstract:
The present invention relates to antibodies, e.g., full length antibodies or antigen binding fragments thereof, that specifically bind to BCMA (B-Cell Maturation Antigen) and CD3 (Cluster of Differentiation 3). The invention also relates to antibody conjugates (e g., antibody-drug-conjugates) comprising the BCMA antibodies, compositions comprising the BCMA antibodies. The invention further relates to heteromultimeric antibodies that specifically bind to CD3 and a tumor cell antigen, (e.g., bispecific antibodies that specifically bind to CD3 and BCMA). Compositions comprising such heteromultimeric antibodies and methods for producing and purifying such heterodimeric antibodies are also provided.

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ABSTRACT

The present invention relates to antibodies, e.g., full length antibodies or antigen binding fragments thereof, that specifically bind to BCMA (B-Cell Maturation Antigen) and CD3 (Cluster of Differentiation 3). The invention also relates to antibody conjugates (e.g., antibody-drug-conjugates) comprising the BCMA antibodies, compositions comprising the BCMA antibodies. The invention further relates to heteromultimeric antibodies that specifically bind to CD3 and a tumor cell antigen, (e.g., bispecific antibodies that specifically bind to CD3 and BCMA). Compositions comprising such heteromultimeric antibodies and methods for producing and purifying such heterodimeric antibodies are also provided.

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ANTI-BCMA ANTIBODIES, ANTI-CD3 ANTIBODIES AND BI-SPECIFIC ANTIBODIES BINDING TO BCMA AND CD3

Field

The present invention relates to antibodies, e.g., full length antibodies or antigen binding fragments thereof, that specifically bind to BCMA (B-Cell Maturation Antigen) and/or CD3 (Cluster of Differentiation 3). The invention also relates to antibody conjugates (e.g., antibody-drug-conjugates) comprising the BCMA antibodies and compositions comprising the BCMA antibodies. The invention further relates to heteromultimeric antibodies that specifically bind to CD3 and a tumor cell antigen, (e.g., bispecific antibodies that specifically bind to CD3 and BCMA). Compositions comprising such heteromultimeric antibodies and methods for producing and purifying such heterodimeric antibodies are also provided.

Background

B-cell maturation antigen (BCMA, CD269, or TNFRSF17) is a member of the tumor necrosis factor receptor (TNFR) superfamily. BCMA was identified in a malignant human T cell lymphoma containing a t(4;16) translocation. The gene is selectively expressed in the B-cell lineage with the highest expression in plasma blasts and plasma cells, antibody secreting cells. BCMA binds two ligands, B-cell activation factor (BAFF) (also called B-lymphoctye stimulator (BLyS) and APOL-related leukocyte expressed ligand (TALL-1)) and a proliferation-inducing ligand (APRIL) with affinity of 1uM and 16nM, respectively. Binding of APRIL or BAFF to BCMA promotes a signaling cascade involving NF-kappa B, Elk-1, c-Jun N-terminal kinase and the p38 mitogen-activated protein kinase, which produce signals for cell survival and proliferation.

BCMA is also expressed on malignant B cells and several cancers that involve B lymphocytes including multiple myeloma, plasmacytoma, Hodgkin's Lymphoma, and chronic lymphocytic leukemia. In autoimmune diseases where plasmablasts are involved such as systemic lupus erythematosus (SLE) and rheumatoid arthritis, BCMA expressing antibody-producing cells secrete autoantibodies that attack self.

In the case of multiple myeloma, about 24,000 new cases are newly diagnosed in the United States each year, and this number represents about 15% of the newly

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diagnosed hematological cancers in the United States. An average of 11,000 deaths result from multiple myeloma each year, and the average 5-year survival rate is about 44%, with median survival of 50-55 months. Current treatment for multiple myeloma is focused on plasma cells apoptosis and/or decreasing osteoclast activity (e.g., chemotherapy, thalidomide, lenalidomide, bisphosphonates, and/or proteasome inhibitors such as bortezomib (VELCADE®) or carfilzomib). However, multiple myeloma remains an incurable disease, and almost all patients have developed resistance to these agents and eventually relapse. Accordingly, there remains a need for potential alternative treatments of multiple myeloma, such as using an anti-BCMA antagonist including antibodies and other immunotherapeutic agents (e.g. bispecific antibodies or antibody-drug conjugates).

Summary

The invention disclosed herein is directed to antibodies that bind to BCMA and/or CD3. Antibody conjugates (e.g., antibody-drug conjugates) comprising BCMA are also provided. Further, the heteromultimeric antibodies (e.g., bispecific antibodies) that specifically bind to CD3 and a tumor cell antigen (e.g., bispecific antibodies that specifically bind to CD3 and BCMA) are also provided.

In one aspect, the invention provides an isolated antibody, or an antigen binding fragment thereof, which specifically binds to B-Cell Maturation Antigen (BCMA), wherein the antibody comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementary determining region one (CDR1) comprising the sequence SYX_1MX_2, wherein X_1 is A or P; and X_2 is T, N, or S (SEQ ID NO: 301), $GFTFX_1SY$, wherein X_1 is G or S (SEQ ID NO: 302), or $GFTFX_1SYX_2MX_3$, wherein X_1 is G or S, X_2 is A or P; and X_3 is T, N, or S (SEQ ID NO: 303); (ii) a VH CDR2 comprising the sequence $AX_1X_2X_3X_4GX_5X_6X_7X_8YADX_9X_{10}KG$, wherein X_1 is I, V, T, H, L, A, or C; X_2 is S, D, G, T, I, L, F, M, or V; X_3 is G, Y, L, H, D, A, S, or M; X_4 is S, Q, T, A, F, or W; X_5 is G or T;X_6 is N, S, P, Y, W, or F; X_7 is S, T, I, L, T, A, R, V, K, G, or C; X_8 is F, Y, P, W, H, or G; X_9 is V, R, or L; and X_{10} is G or T (SEQ ID NO: 305), or $X_1X_2X_3X_4X_5X_6$, wherein X_1 is S, V, I, D, G, T, L, F, or M; X_2 is G, Y, L, H, D, A, S, or M; X_3 is S, G, F, or W; X_4 is G or S; X_5 is G or T; and X_6 is N, S, P, Y, or W (SEQ ID NO: 306); and iii) a VH CDR3 comprising the sequence $VSPIX_1X_2X_3X_4$, wherein X_1 is A or Y; X_2 is A or S; and X_3 is G, Q, L, P, or E (SEQ ID NO:

307), or YWPMX_1X_2, wherein X_1 is D, S, T, or A; and X_2 is I, S, L, P, or D (SEQ ID NO: 308); and/or (b) a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$, wherein X_1 is R, G, W, A, or C; X_2 is A, P, G, L, C, or S; X_3 is S, G, or R; X_4 is Q, C, E, V, or I; X_5 is S, P, G, A, R, or D; X_6 is V, G, I, or L; X_7 is S, E, D, P, or G; X_8 is S, P, F, A, M, E, V, N, D, or Y; X_9 is I, T, V, E, S, A, M, Q, Y, H, R, or F; X_{10} is Y or F; X_{11} is L, W, or P; and X_{12} is A, S, or G (SEQ ID NO: 309); (ii) a VL CDR2 comprising the sequence $X_1ASX_2RAX_3$, wherein X_1 is G or D; X_2 is S or I; and X_3 is T or P (SEQ ID NO: 310); and (iii) a VL CDR3 comprising the sequence QQY$X_1X_2X_3PX_4$T, wherein X_1 is G, Q, E, L, F, A, S, M, K, R, or Y; X_2 is S, R, T, G, V, F, Y, D, A, H, V, E, K, or C; X_3 is W, F, or S; and X_4 is L or I (SEQ ID NO: 311), or QQY$X_1X_2X_3PX_4$, wherein X_1 is G, Q, E, L, F, A, S, M, R, K, or Y; X_2 is S, R, T, G, R, V, D, A, H, E, K, C, F, or Y; X_3 is W, S, or F; and X_4 is L or I (SEQ ID NO: 312).

In another aspect, the invention provides an isolated antibody, or an antigen binding fragment thereof, which specifically binds to BCMA, wherein the antibody comprises: a VH region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 2, 3, 7, 8, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 37, 39, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 83, 87, 92, 95, 97, 99, 101, 104, 106, 110, 112, 114, 118, 120, 122, 125, 127, 313, 314, 363, or 365; and/or a VL region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 1, 4, 5, 6, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 34, 36, 38, 40, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 317, 81, 82, 84, 85, 86, 88, 89, 90, 91, 93, 94, 96, 98, 100, 102, 103, 105, 107, 108, 109, 111, 113, 115, 116, 117, 119, 121, 123, 124, 126, 128, 315, 316, or 364. In some embodiments, the VH region comprises (i) a VH CDR1 comprising SEQ ID NO:150, 151, 152, 156, or 157; (ii) a VH CDR2 comprising SEQ ID NO: 169, 154, 194, 159, 195, 196, 162, 158, 198, 177, 178, 199, 200, 201, 202, 203, 204, 206, 207, 208, 172, 203, or 204 ; and (iii) a VH CDR3 comprising SEQ ID NO: 155, 161, 197, 205, or 164; and/or wherein the VL region comprises (i) a VL CDR1 comprising SEQ ID NO: 209, 271, 273, 275, 251, 277, 260, 279, 245, 283, 285, 287, 290, 292, 235, 297, or 299; (ii) a VL CDR2 comprising SEQ ID NO: 221; and (iii) a VL CDR3 comprising SEQ ID NO: 225, 272, 274, 276, 278, 280, 281, 282, 284, 286, 288, 289, 291, 293, 294, 229, 296, 298, or 300. In some embodiments, the VH region comprises the

sequence shown in SEQ ID NO: 112 or a variant with one or several conservative amino acid substitutions in residues that are not within a CDR and/or the VL region comprises the amino acid sequence shown in SEQ ID NO: 38 or a variant thereof with one or several amino acid substitutions in amino acids that are not within a CDR. In some embodiments, the antibody comprises a light chain comprising the sequence shown in SEQ ID NO: 357 and a heavy chain comprising the sequence shown in SEQ ID NO: 358. In some embodiments, the antibody comprises a VH region produced by the expression vector with ATCC Accession No. PTA-122094. In some embodiments, the antibody comprises a VL region produced by the expression vector with ATCC Accession No. PTA-122093.

In another aspect, the invention provides an isolated antibody comprising an acyl donor glutamine-containing tag engineered at a specific site of the BCMA antibody of the present invention. In some embodiments, the tag comprises an amino acid sequence selected from the group consisting of Q, LQG, LLQGG (SEQ ID NO:318), LLQG (SEQ ID NO:454), LSLSQG (SEQ ID NO: 455), GGGLLQGG (SEQ ID NO: 456), GLLQG (SEQ ID NO: 457), LLQ, GSPLAQSHGG (SEQ ID NO: 458), GLLQGGG (SEQ ID NO: 459), GLLQGG (SEQ ID NO: 460), GLLQ (SEQ ID NO: 461), LLQLLQGA (SEQ ID NO: 462), LLQGA (SEQ ID NO: 463), LLQYQGA (SEQ ID NO: 464), LLQGSG (SEQ ID NO: 465), LLQYQG (SEQ ID NO: 466), LLQLLQG (SEQ ID NO: 467), SLLQG (SEQ ID NO: 468), LLQLQ (SEQ ID NO: 469), LLQLLQ (SEQ ID NO: 470), LLQGR (SEQ ID NO: 471), LLQGPP (SEQ ID NO: 472), LLQGPA (SEQ ID NO: 473), GGLLQGPP (SEQ ID NO: 474), GGLLQGA (SEQ ID NO: 475), LLQGPGK (SEQ ID NO: 476), LLQGPG (SEQ ID NO: 477), LLQGP (SEQ ID NO: 478), LLQP (SEQ ID NO: 479), LLQPGK (SEQ ID NO: 480), LLQAPGK (SEQ ID NO: 481), LLQGAPG (SEQ ID NO: 482), LLQGAP (SEQ ID NO: 483), and LLQLQG (SEQ ID NO: 484).

In one variation, the invention provides an isolated antibody comprising an acyl donor glutamine-containing tag and an amino acid modification at position 222, 340, or 370 of the BCMA antibody of the present invention. In some embodiments, the amino acid modification is a substitution from lysine to arginine.

In some embodiments, the BCMA antibody of the present invention further comprises a linker. In some embodiments, the linker is selected from the group consisting of Ac-Lys-Gly (acetyl-lysine-glycine), aminocaproic acid, Ac-Lys-β-Ala (acetyl-lysine-β-

alanine), amino-PEG2 (polyethylene glycol)-C2, amino-PEG3-C2, amino-PEG6-C2, Ac-Lys-Val-Cit-PABC (acetyl-lysine-valine-citrulline-*p*-aminobenzyloxycarbonyl), amino-PEG6-C2-Val-Cit-PABC, aminocaproyl-Val-Cit-PABC, [(3R,5R)-1-{3-[2-(2-aminoethoxy)ethoxy]propanoyl}piperidine-3,5-diyl]bis-Val-Cit-PABC, [(3S,5S)-1-{3-[2-(2-aminoethoxy)ethoxy]propanoyl}piperidine-3,5-diyl]bis-Val-Cit-PABC, putrescine, and Ac-Lys-putrescine.

In another aspect, the invention provides a conjugate of the BCMA antibody or the antigen binding fragment as described herein, wherein the antibody or the antigen binding fragment is conjugated to an agent, wherein the agent is selected from the group consisting of a cytotoxic agent, an immunomodulating agent, an imaging agent, a therapeutic protein, a biopolymer, and an oligonucleotide. In some embodiments, the agent is a cytotoxic agent including, but not limited to, an anthracycline, an auristatin, a camptothecin, a combretastatin, a dolastatin, a duocarmycin, an enediyne, a geldanamycin, an indolino-benzodiazepine dimer, a maytansine, a puromycin, a pyrrolobenzodiazepine dimer, a taxane, a vinca alkaloid, a tubulysin, a hemiasterlin, a spliceostatin, a pladienolide, and stereoisomers, isosteres, analogs, or derivatives thereof. For example, the cytotoxic agent is MMAD (Monomethyl Auristatin D), 0101 (2-methylalanyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-{[(1*S*)-2-phenyl-1-(1,3-thiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide), 3377 (N,2-dimethylalanyl-N-{(1S,2R)-4-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxyl-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxobutyl}-N-methyl-L-valinamide), 0131 (2-methyl-L-proly-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide), or 0121(2-methyl-L-proly-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide).

In some embodiments, the present invention provides a conjugate comprising the formula: antibody-(acyl donor glutamine-containing tag)-(linker)-(cytotoxic agent). In some embodiments, the acyl donor glutamine-containing tag comprises an amino acid sequence

LLQG (SEQ ID NO: 319) and/or GGLLQGPP (SEQ ID NO: 339) and wherein the linker comprises acetyl-lysine-valine-citrulline-*p*-aminobenzyloxycarbonyl or amino-PEG6-C2. In some embodiments, the conjugate is selected from the group consisting of 1) antibody-GGLLQGPP (SEQ ID NO: 339)-(acetyl-lysine-valine-citrulline-*p*-aminobenzyloxycarbonyl (AcLys-VC-PABC))-0101; 2) antibody-LLQG (SEQ ID NO: 319)-amino-PEG6-C2-0131; and 3) antibody-LLQG (SEQ ID NO: 319)-amino-PEG6-C2-3377. In some embodiments, the conjugate further comprises an amino acid substitution from lysine to arginine at antibody position 222. In some embodiments, the conjugate further comprises amino acid substitutions at antibody position N297Q or N297A.

In another aspect, provided is a method of producing the BCMA antibody as described herein, comprising culturing the host cell under conditions that result in production of the BCMA antibody, and isolating the BCMA antibody from the host cell or culture.

In another aspect, the invention provides an isolated antibody, or an antigen binding fragment thereof, which specifically binds to CD3, wherein the antibody comprises a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 320, 322, 324, 326, 328, 330, 345, 347, 349, 351, 444, 354, 356, 378, 442, 380, 382, 384 386, 388, 390, 392, 394, 396, 398, or 400; and/or a light chain variable (VL) region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 319, 321, 323, 325, 327, 329, 344, 346, 348, 350, 352, 355, 377, 443, 445, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, or 399. In some embodiments, the antibody comprises a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 324 or 388; and/or a light chain variable (VL) region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 323 or 387. In some embodiments, the VH region comprises (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 331, 332, 333, 401, 402, 403, 407, 408, 415, 416, 418, 419, 420, 424, 425, 426, 446, 447, or 448 (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 334, 336, 337, 338, 339, 404, 405, 409, 410, 411, 412, 413, 414, 417, 418, 421, 422, 427, 428, 449, or 450; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 335, 406, 423, 429, or 451; and/or a light chain variable (VL) region

comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 340, 343, 430, 431, 435, or 440, 441; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 341, 433, 452, or 436; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 342, 432, 434, 437, 438, 439, 446, or 453. In some embodiments, the VH region comprises (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 331, 332, 333, 401, 407, or 408 (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 336, 404, 405, or 417; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 335 or 406; and/or a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 343 or 441; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 341 or 436; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 342 or 439. In some embodiments, the antibody comprises a VH region produced by the expression vector with ATCC Accession No. PTA-122513. In some embodiments, the antibody comprises a VL region produced by the expression vector with ATCC Accession No. PTA-122512.

In another aspect, provided is an isolated antibody which specifically binds to CD3 and competes with the anti-CD3 antibody of the present invention as described herein.

In another aspect, the invention provides a bispecific antibody wherein the bispecific antibody is a full-length human antibody, comprising a first antibody variable domain of the bispecific antibody capable of recruiting the activity of a human immune effector cell by specifically binding to an effector antigen located on the human immune effector cell, and comprising a second antibody variable domain of the bispecific antibody capable of specifically binding to a target antigen, wherein the first antibody variable domain comprises a heavy chain variable (VH) region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 320, 322, 324, 326, 328, 330, 345, 347, 349, 351, 444, 354, 356, 378, 442, 380, 382, 384 386, 388, 390, 392, 394, 396, 398, or 400; and/or a light chain variable (VL) region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 319, 321, 323, 325, 327, 329, 344, 346, 348, 350, 352, 355, 377, 443, 445, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, or 399. In some embodiments, the first antibody variable domain comprises a heavy chain variable (VH) region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH

sequence shown in SEQ ID NO: SEQ ID NO: 331, 332, 333, 401, 402, 403, 407, 408, 415, 416, 418, 419, 420, 424, 425, 426, 446, 447, or 448 (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 334, 336, 337, 338, 339, 404, 405, 409, 410, 411, 412, 413, 414, 417, 418, 421, 422, 427, 428, 449, or 450; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 335, 406, 423, 429, or 451; and/or a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 340, 343, 430, 431, 435, or 440, 441; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 341, 433, 452, or 436; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 342, 432, 434, 437, 438, 439, 446, or 453. In some embodiments, the first antibody variable domain comprises a heavy chain variable (VH) region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 324 or 388; and/or a light chain variable (VL) region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 323 or 387; and the second antibody variable domain comprises a heavy chain variable (VH) region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 112; and/or a light chain variable (VL) region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 38.

In some embodiments, the second antibody variable domain comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence SYX_1MX_2, wherein X_1 is A or P; and X_2 is T, N, or S (SEQ ID NO: 301), $GFTFX_1SY$, wherein X_1 is G or S (SEQ ID NO: 302), or $GFTFX_1SYX_2MX_3$, wherein X_1 is G or S, X_2 is A or P; and X_3 is T, N, or S (SEQ ID NO: 303); (ii) a VH CDR2 comprising the sequence $AX_1X_2X_3X_4GX_5X_6X_7X_8YADX_9X_{10}KG$, wherein X_1 is I, V, T, H, L, A, or C; X_2 is S, D, G, T, I, L, F, M, or V; X_3 is G, Y, L, H, D, A, S, or M; X_4 is S, Q, T, A, F, or W; X_5 is G or T;X_6 is N, S, P, Y, W, or F; X_7 is S, T, I, L, T, A, R, V, K, G, or C; X_8 is F, Y, P, W, H, or G; X_9 is V, R, or L; and X_{10} is G or T (SEQ ID NO: 305), or $X_1X_2X_3X_4X_5X_6$, wherein X_1 is S, V, I, D, G, T, L, F, or M; X_2 is G, Y, L, H, D, A, S, or M; X_3 is S, G, F, or W; X_4 is G or S; X_5 is G or T; and X_6 is N, S, P, Y, or W (SEQ ID NO: 306); and iii) a VH CDR3 comprising the sequence $VSPIX_1X_2X_3X_4$ wherein X_1 is A or Y; X_2 is A or S; and X_3 is G, Q, L, P, or E (SEQ ID NO: 307), or $YWPMX_1X_2$, wherein X_1 is D, S, T, or A; and X_2 is I, S, L, P, or D (SEQ ID NO: 308); and/or (b) a light chain variable (VL)

region comprising (i) a VL CDR1 comprising the sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$, wherein X_1 is R, G, W, A, or C; X_2 is A, P, G, L, C, or S; X_3 is S, G, or R; X_4 is Q, C, E, V, or I; X_5 is S, L, P, G, A, R, or D; X_6 is V, G, or I; X_7 is S, E, D, or P; X_8 is S, P, F, A, M, E, V, N, D, or Y; X_9 is I, T, V, E, S, A, M, Q, Y, H, or R; X_{10} is Y or F; X_{11} is L, W, or P; and X_{12} is A, S, or G (SEQ ID NO: 309); (ii) a VL CDR2 comprising the sequence $X_1ASX_2RAX_3$, wherein X_1 is G or D; X_2 is S or I; and X_3 is T or P (SEQ ID NO: 310); and (iii) a VL CDR3 comprising the sequence $QQYX_1X_2X_3PX_4T$, wherein X_1 is G, Q, E, L, F, A, S, M, K, R, or Y; X_2 is S, R, T, G, V, F, Y, D, A, H, V, E, K, or C; X_3 is W, F, or S; and X_4 is L or I (SEQ ID NO: 311), or $QQYX_1X_2X_3PX_4$, wherein X_1 is G, Q, E, L, F, A, S, M, R, K, or Y; X_2 is S, R, T, G, R, V, D, A, H, E, K, C, F, or Y; X_3 is W, S, or F; and X_4 is L or I (SEQ ID NO: 312). In some embodiments, the second antibody variable domain comprises a heavy chain variable (VH) region comprising (i) a VH CDR1 comprising the sequence shown in SEQ ID NO:150, 151, 152, 156, 157, 348, 349, 353, 354, or 355; (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 169, 154, 194, 159, 195, 196, 162, 158, 198, 177, 178, 199, 200, 201, 202, 203, 204, 206, 207, 208, 172, 203, 204, 350, 351, 356 or 357; and (iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 155, 161, 197, 205,164, or 352, or 358; and/or wherein the light chain variable (VL) region comprises (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 209, 271, 273, 275, 251, 277, 260, 279, 245, 283, 285, 287, 290, 292, 235, 297, 299, or 361; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221, 359 or 362; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 211, 225, 272, 274, 276, 278, 280, 281, 282, 284, 286, 288, 289, 291, 293, 294, 229, 296, 298, 300 or 360.

In some embodiments, (a) the first antibody variable domain comprises a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 331, 332, 333, 401, 407, or 408 (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 336, 417, 404, or 405; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 335 or 406; and/or a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 343 or 441; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 341 or 436; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 342 or 439; and (b) the second antibody variable domain comprises a heavy chain VH region

comprising a heavy chain variable (VH) region comprising (i) a VH CDR1 comprising the sequence shown in SEQ ID NO: 151, 156, or 157; (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 158 OR 159; and (iii) a VH CDR3 comprising SEQ ID NO: 155; and/or wherein the light chain variable (VL) region comprises (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 225.

In some embodiments, both the first and the second antibody variable domains of the bispecific antibody comprise amino acid modifications at positions 223, 225, and 228 in the hinge region and at position 409 or 368 (EU numbering scheme) in the CH3 region of a human IgG2 (SEQ ID NO: 493). In some embodiments, the bispecific antibody as described herein further comprises an amino acid modification at position 265 of the human IgG2.

In another aspect, the invention provides pharmaceutical compositions comprising any of the antibodies (e.g., BCMA, CD3, or bispecific) or the conjugates thereof (e.g., BCMA antibody-drug conjugate) described herein.

In another aspect, the invention also provides cell lines that recombinantly produce any of the antibodies (e.g., BCMA, CD3, or bispecific) or the conjugates thereof (e.g., BCMA antibody-drug conjugate) described herein.

In another aspect, the invention also provides nucleic acids encoding any of the antibodies (e.g., BCMA, CD3, or bispecific) or the conjugates thereof (e.g., BCMA antibody-drug conjugate) described herein. The invention also provides nucleic acids encoding a heavy chain variable region and/or a light chain variable region of any of these antibodies described herein.

In some embodiments, the antibodies described herein comprise a constant region. In some embodiments, the antibodies described herein are of the human IgG1, IgG2 or IgG2Δa, IgG3, or IgG4 subclass. In some embodiments, the antibodies described herein comprise a glycosylated constant region. In some embodiments, the antibodies described herein comprise a constant region having increased binding affinity to one or more human Fc gamma receptor(s).

The invention as claimed relates to:

- a bispecific antibody comprising a first antibody variable domain and a second antibody variable domain, wherein the first antibody variable domain specifically binds to Cluster of Differentiation 3 (CD3), the second antibody variable domain specifically binds to B-Cell Maturation Antigen (BCMA), and wherein (a) the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 333; a VH CDR2 comprising the sequence shown in SEQ ID NO: 417; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 157; a VH CDR2 comprising the sequence shown in SEQ ID NO: 159; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225; (b) the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 331; a VH CDR2 comprising the sequence shown in SEQ ID NO: 336; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL_CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 156; a VH CDR2 comprising the sequence shown in SEQ ID NO: 158; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225; (c) the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 332; a VH CDR2 comprising the sequence shown in SEQ ID NO: 417; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in

SEQ ID NO: 341; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 151; a VH CDR2 comprising the sequence shown in SEQ ID NO:159; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225; or (d) the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 333; a VH CDR2 comprising the sequence shown in SEQ ID NO: 336; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 157; a VH CDR2 comprising the sequence shown in SEQ ID NO:158; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225;

- a bispecific antibody comprising a first antibody variable domain and a second antibody variable domain, wherein the first antibody variable domain comprises a heavy chain variable region comprising the sequence shown in SEQ ID NO: 324, and a light chain variable region comprising the sequence shown in SEQ ID NO: 323; and the second antibody variable domain comprises a heavy chain variable region comprising the sequence shown in SEQ ID NO: 112, and a light chain variable region comprising the sequence shown in SEQ ID NO: 38; and

- a bispecific antibody comprising a first antibody variable domain and a second antibody variable domain, wherein the first antibody variable domain comprises a heavy chain variable region comprising the sequence shown in SEQ ID NO: 324, and a light chain variable region comprising the sequence shown in SEQ ID NO: 323; and the second antibody variable domain comprises a heavy chain variable region encoded by the polynucleotide sequence shown in SEQ ID NO: 486, and a light chain variable region encoded by the polynucleotide sequence shown in SEQ ID NO: 485.

Brief Description of the Figures/Drawings

Figure 1A – Figure 1D depict the double-referenced sensorgrams with fit curves for interactions between selected anti-BCMA antibodies of the present invention and human BCMA.

Figure 2 depicts *in vivo* efficacy studies of various anti-BCMA ADCs in the MM1S orthotopic multiple myeloma model, including P6E01_VHVL-AcLys-Val-Cit-PABC-Aur0101; P5A2_VHVL-AcLys-Val-Cit-PABC-Aur0101; P5C1_VHVL-AcLys-Val-Cit-PABC-Aur0101; P4G4-AcLys-Val-Cit-PABC-Aur0101; and P1A11-AcLys-Val-Cit-PABC-Aur0101. NNC is a negative control non-BCMA antibody. "LCQ05" and "LCQ04" correspond to glutamine-containing transglutaminase tag SEQ ID NOs: 474 and 475, respectively.

Figure 3 depicts *in vivo* efficacy of the anti-BCMA ADCs in the MM1S orthotopic multiple myeloma model, including L3.PY/P6E01 antibody conjugated with 1) H7c/N297A/K222R-amino-PEG6-C2-3377, 2) N297Q/K222R-AcLys-Val-Cit-PABC-0101, 3) LCQ05/K222R-AcLys-Val-Cit-PABC-0101, 4) H7c/N297A/K222R-amino-PEG6-C2-0131, and 5) N297Q/K222R/LCQ05-AcLys-Val-Cit-PABC-Aur0101. NNC is a control non-BCMA antibody. "LCQ05" and H7c correspond to glutamine-containing transglutaminase tag SEQ ID NO: 474 and SEQ ID NO: 454, respectively

Figure 4 also depicts *in vivo* efficacy of the anti-BCMA ADCs in the MM1S orthotopic multiple myeloma model, including L3.PY/P6E01 antibody conjugated with 1) H7c/N297A/K222R-amino-PEG6-C2-3377, 2) N297Q/K222R-AcLys-Val-Cit-PABC-Aur0101, 3) LCQ05/K222R-AcLys-Val-Cit-PABC-Aur0101, 4) H7c/N297A/K222R-amino-PEG6-C2-0131, and 5) N297Q/K222R/LCQ05-AcLys-Val-Cit-PABC-Aur0101. NNC is a control non-BCMA antibody (antibody-N297Q/K222R-AcLys-VC-PABC-0101). "LCQ05" and H7c correspond to glutamine-containing transglutaminase tag SEQ ID NO: 474 and SEQ ID NO: 454, respectively.

Figure 5 also depicts *in vivo* efficacy of an anti-BCMA ADC in the MM1S orthotopic multiple myeloma model. Anti-BCMA antibody COMBO_Rd4_0.6nM-C29 ("Combo C29 DI) is conjugated to H7c/N297A/K222R-amino-PEG6-C2-131 at doses ranging from 0.1 mg/kg, 0.38 mg/kg, 0.75 mg/kg, 1.5 mg/kg in comparison to NNC, a control non-BCMA antibody (antibody-N297Q/K222R-AcLys-VC-PABC-0101) at 3 mg/kg. H7c correspond to glutamine-containing transglutaminase tag SEQ ID NO: 454.

Figure 6A – Figure 6F depict the *in vivo* efficacy of an anti-CD3/anti-CD20 bispecific antibody in cynomolgus monkeys. B cell depletion following a single dose of bispecific antibody is shown as a percentage of prestudy counts.

Figure 7A – Figure 7F depict the *in vivo* efficacy of an anti-CD3/anti-CD20 bispecific antibody in cynomolgus monkeys. CD8+ T cell kinetics were tracked following a single dose of bispecific antibody.

Figure 8A and Figure 8B depict the *in vivo* efficacy of an anti-CD3/anti-CD20 bispecific antibody in cynomolgus monkeys. The effect of the monovalent CD3 antibody on T cell kinetics and proliferation was analyzed.

Figures 9A – Figure 9D depict the *in vivo* efficacy of an anti-CD3/anti-CD20 bispecific antibody in cynomolgus monkeys. The effect of anti-CD3 arm affinity on B cell depletion was analyzed.

Figures 10A and 10B show that the selected anti-CD3 antibodies had Thymidine incorporation reading on human and cynomolgus PBMC.

Figure 11A - Figure 11D show that all human anti-EpCam_h2B4 bispecific antibodies have cell killing activity on in vitro setting.

Figure 12 shows that a single dose of human anti-BCMA/CD3 bispecific antibody resulted in tumor regression in a dose-dependent manner in an orthotopic MM1.S myeloma model.

Figure 13 shows that two doses of human anti-BCMA/CD3 bispecific antibody resulted in increased tumor regression in an orthotopic Molp8 myeloma model.

Figure 14 shows that anti-BCMA/CD3 bispecific antibody alone or in combination with standard of care for multiple myeloma (lenalidomide or bortezomib) is more efficacious than lenalidomide and bortezomib combined in orthotopic Molp8 tumor model.

Figure 15A - Figure 15C, respectively, show that carfilzomib, lenalidomide, and doxorubicin do not have a negative effect on the function of the anti-BCMA/CD3 bispecific antibody on OPM2 cells as compared to the anti-BCMA/CD3 bispecific antibody alone.

Figure 16 shows synergistic effects on the function of anti-BCMA/CD3 bispecific antibody when combined with carfilzomib and lenalidomide in comparison to each molecule alone.

Detailed Description

The invention disclosed herein provides antibodies and antibody conjugates (e.g., antibody-drug conjugates) that specifically bind to BCMA (e.g., human BCMA). The invention also provides polynucleotides encoding these antibodies and conjugates, compositions comprising these antibodies and conjugates, and methods of making these antibodies and conjugates. Further, the invention disclosed herein provides antibodies that specifically bind to CD3 (e.g., human CD3) as well as heterodimeric antibodies (e.g., bispecific antibodies) that specifically bind to CD3 and a tumor antigen (e.g., BCMA). The invention also provides polynucleotides encoding these antibodies, compositions comprising these antibodies, and methods of making and using these antibodies.

General Techniques

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, Molecular Cloning: A Laboratory Manual, second edition (Sambrook et al., 1989) Cold Spring Harbor Press; Oligonucleotide Synthesis (M.J. Gait, ed., 1984); Methods in Molecular Biology, Humana Press; Cell Biology: A Laboratory Notebook (J.E. Cellis, ed., 1998) Academic Press; Animal Cell Culture (R.I. Freshney, ed., 1987); Introduction to Cell and Tissue Culture (J.P. Mather and P.E. Roberts, 1998) Plenum Press; Cell and Tissue Culture: Laboratory Procedures (A. Doyle, J.B. Griffiths, and D.G. Newell, eds., 1993-1998) J. Wiley and Sons; Methods in Enzymology (Academic Press, Inc.); Handbook of Experimental Immunology (D.M. Weir and C.C. Blackwell, eds.); Gene Transfer Vectors for Mammalian Cells (J.M. Miller and M.P. Calos, eds., 1987); Current Protocols in Molecular Biology (F.M. Ausubel et al., eds., 1987); PCR: The Polymerase Chain Reaction, (Mullis et al., eds., 1994); Current Protocols in Immunology (J.E. Coligan et al., eds., 1991); Short Protocols in Molecular Biology (Wiley and Sons, 1999); Immunobiology (C.A. Janeway and P. Travers, 1997); Antibodies (P. Finch, 1997); Antibodies: a practical approach (D. Catty., ed., IRL Press, 1988-1989); Monoclonal antibodies: a practical approach (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); Using antibodies: a laboratory manual (E. Harlow and D.

Lane (Cold Spring Harbor Laboratory Press, 1999); The Antibodies (M. Zanetti and J.D. Capra, eds., Harwood Academic Publishers, 1995).

Definitions

An "antibody" is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also fragments thereof (such as Fab, Fab', $F(ab')_2$, Fv), single chain (ScFv) and domain antibodies (including, for example, shark and camelid antibodies), and fusion proteins comprising an antibody, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site. An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant region of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant regions that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

The term "antigen binding fragment" or "antigen binding portion" of an antibody, as used herein, refers to one or more fragments of an intact antibody that retain the ability to specifically bind to a given antigen (e.g., BCMA or CD3). Antigen binding functions of an antibody can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term "antigen binding fragment" of an antibody include Fab; Fab'; $F(ab')_2$; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a single domain antibody (dAb) fragment (Ward et al., Nature 341:544-546, 1989), and an isolated complementarity determining region (CDR).

An antibody, an antibody conjugate, or a polypeptide that "preferentially binds" or "specifically binds" (used interchangeably herein) to a target (e.g., BCMA protein or CD3 protein) is a term well understood in the art, and methods to determine such specific or preferential binding are also well known in the art. A molecule is said to exhibit "specific binding" or "preferential binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular cell or substance than it does with alternative cells or substances. An antibody "specifically binds" or "preferentially binds" to a target if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. For example, an antibody that specifically or preferentially binds to a BCMA epitope or CD3 epitope is an antibody that binds this epitope with greater affinity, avidity, more readily, and/or with greater duration than it binds to other BCMA epitopes, non-BCMA epitopes, CD3 epitopes, or non-CD3 epitopes. It is also understood that by reading this definition, for example, an antibody (or moiety or epitope) that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means preferential binding.

A "variable region" of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. As known in the art, the variable regions of the heavy and light chain each consist of four framework regions (FR) connected by three complementarity determining regions (CDRs) also known as hypervariable regions. The CDRs in each chain are held together in close proximity by the FRs and, with the CDRs from the other chain, contribute to the formation of the antigen binding site of antibodies. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Kabat et al. Sequences of Proteins of Immunological Interest, (5th ed., 1991, National Institutes of Health, Bethesda MD)); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Al-lazikani et al., 1997, J. Molec. Biol. 273:927-948). As used herein, a CDR may refer to CDRs defined by either approach or by a combination of both approaches.

A "CDR" of a variable domain are amino acid residues within the variable region that are identified in accordance with the definitions of the Kabat, Chothia, the accumulation of both Kabat and Chothia, AbM, contact, and/or conformational definitions or any method of CDR determination well known in the art. Antibody CDRs may be identified as the hypervariable regions originally defined by Kabat et al. See, e.g., Kabat et al., 1992, Sequences of Proteins of Immunological Interest, 5th ed., Public Health Service, NIH, Washington D.C. The positions of the CDRs may also be identified as the structural loop structures originally described by Chothia and others. See, e.g., Chothia et al., Nature 342:877-883, 1989. Other approaches to CDR identification include the "AbM definition," which is a compromise between Kabat and Chothia and is derived using Oxford Molecular's AbM antibody modeling software (now Accelrys®), or the "contact definition" of CDRs based on observed antigen contacts, set forth in MacCallum et al., J. Mol. Biol., 262:732-745, 1996. In another approach, referred to herein as the "conformational definition" of CDRs, the positions of the CDRs may be identified as the residues that make enthalpic contributions to antigen binding. See, e.g., Makabe et al., Journal of Biological Chemistry, 283:1156-1166, 2008. Still other CDR boundary definitions may not strictly follow one of the above approaches, but will nonetheless overlap with at least a portion of the Kabat CDRs, although they may be shortened or lengthened in light of prediction or experimental findings that particular residues or groups of residues or even entire CDRs do not significantly impact antigen binding. As used herein, a CDR may refer to CDRs defined by any approach known in the art, including combinations of approaches. The methods used herein may utilize CDRs defined according to any of these approaches. For any given embodiment containing more than one CDR, the CDRs may be defined in accordance with any of Kabat, Chothia, extended, AbM, contact, and/or conformational definitions.

As used herein, "monoclonal antibody" refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations, which typically include different antibodies directed against different

determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler and Milstein, Nature 256:495, 1975, or may be made by recombinant DNA methods such as described in U.S. Pat. No. 4,816,567. The monoclonal antibodies may also be isolated from phage libraries generated using the techniques described in McCafferty et al., Nature 348:552-554, 1990, for example.

As used herein, "humanized" antibody refers to forms of non-human (*e.g.* murine) antibodies that are chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. Preferably, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Preferred are antibodies having Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more CDRs (CDR L1, CDR L2, CDR L3, CDR H1, CDR H2, or

CDR H3) which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody.

As used herein, "human antibody" means an antibody having an amino acid sequence corresponding to that of an antibody produced by a human and/or which has been made using any of the techniques for making human antibodies known to those skilled in the art or disclosed herein. This definition of a human antibody includes antibodies comprising at least one human heavy chain polypeptide or at least one human light chain polypeptide. One such example is an antibody comprising murine light chain and human heavy chain polypeptides. Human antibodies can be produced using various techniques known in the art. In one embodiment, the human antibody is selected from a phage library, where that phage library expresses human antibodies (Vaughan et al., Nature Biotechnology, 14:309-314, 1996; Sheets et al., Proc. Natl. Acad. Sci. (USA) 95:6157-6162, 1998; Hoogenboom and Winter, J. Mol. Biol., 227:381, 1991; Marks et al., J. Mol. Biol., 222:581, 1991). Human antibodies can also be made by immunization of animals into which human immunoglobulin loci have been transgenically introduced in place of the endogenous loci, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. This approach is described in U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016. Alternatively, the human antibody may be prepared by immortalizing human B lymphocytes that produce an antibody directed against a target antigen (such B lymphocytes may be recovered from an individual or from single cell cloning of the cDNA, or may have been immunized *in vitro).* See, e.g., Cole et al. Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77, 1985; Boerner et al., J. Immunol., 147 (1):86-95, 1991; and U.S. Pat. No. 5,750,373.

The term "chimeric antibody" is intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

The terms "polypeptide", "oligopeptide", "peptide" and "protein" are used interchangeably herein to refer to chains of amino acids of any length, preferably, relatively short (e.g., 10-100 amino acids). The chain may be linear or branched, it may comprise

modified amino acids, and/or may be interrupted by non-amino acids. The terms also encompass an amino acid chain that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that the polypeptides can occur as single chains or associated chains.

A "monovalent antibody" comprises one antigen binding site per molecule (e.g., IgG or Fab). In some instances, a monovalent antibody can have more than one antigen binding sites, but the binding sites are from different antigens.

A "monospecific antibody" comprises two identical antigen binding sites per molecule (e.g. IgG) such that the two binding sites bind identical epitope on the antigen. Thus, they compete with each other on binding to one antigen molecule. Most antibodies found in nature are monospecific. In some instances, a monospecific antibody can also be a monovalent antibody (e.g. Fab)

A "bivalent antibody" comprises two antigen binding sites per molecule (e.g., IgG). In some instances, the two binding sites have the same antigen specificities. However, bivalent antibodies may be bispecific.

A "bispecific" or "dual-specific" is a hybrid antibody having two different antigen binding sites. The two antigen binding sites of a bispecific antibody bind to two different epitopes, which may reside on the same or different protein targets.

A "bifunctional" is antibody is an antibody having identical antigen binding sites (i.e., identical amino acid sequences) in the two arms but each binding site can recognize two different antigens.

A "heteromultimer", "heteromultimeric complex", or "heteromultimeric polypeptide" is a molecule comprising at least a first polypeptide and a second polypeptide, wherein the second polypeptide differs in amino acid sequence from the first polypeptide by at least one amino acid residue. The heteromultimer can comprise a "heterodimer" formed by the first and second polypeptide or can form higher order tertiary structures where polypeptides in addition to the first and second polypeptide are present.

A "heterodimer," "heterodimeric protein," "heterodimeric complex," or "heteromultimeric polypeptide" is a molecule comprising a first polypeptide and a second polypeptide, wherein the second polypeptide differs in amino acid sequence from the first polypeptide by at least one amino acid residue.

The "hinge region," "hinge sequence", and variations thereof, as used herein, includes the meaning known in the art, which is illustrated in, for example, Janeway et al., ImmunoBiology: the immune system in health and disease, (Elsevier Science Ltd., NY) (4th ed., 1999); Bloom et al., *Protein Science* (1997), 6:407-415; Humphreys et al., *J. Immunol. Methods* (1997), 209:193-202.

The "immunoglobulin-like hinge region," "immunoglobulin-like hinge sequence," and variations thereof, as used herein, refer to the hinge region and hinge sequence of an immunoglobulin-like or an antibody-like molecule (e.g., immunoadhesins). In some embodiments, the immunoglobulin-like hinge region can be from or derived from any IgG1, IgG2, IgG3, or IgG4 subtype, or from IgA, IgE, IgD or IgM, including chimeric forms thereof, e.g., a chimeric IgG1/2 hinge region.

The term "immune effector cell" or "effector cell" as used herein refers to a cell within the natural repertoire of cells in the human immune system which can be activated to affect the viability of a target cell. The viability of a target cell can include cell survival, proliferation, and/or ability to interact with other cells.

Antibodies of the invention can be produced using techniques well known in the art, *e.g.*, recombinant technologies, phage display technologies, synthetic technologies or combinations of such technologies or other technologies readily known in the art (see, for example, Jayasena, S.D., Clin. Chem., 45: 1628-50, 1999 and Fellouse, F.A., et al, J. Mol. Biol., 373(4):924-40, 2007).

As known in the art, "polynucleotide," or "nucleic acid," as used interchangeably herein, refer to chains of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incorporated into a chain by DNA or RNA polymerase. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the chain. The sequence of

nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. Other types of modifications include, for example, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, carbamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, poly-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping group moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, alpha- or beta-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S("thioate"), P(S)S ("dithioate"), (O)NR_2 ("amidate"), P(O)R, P(O)OR', CO or CH_2 ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (-O-) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

As known in the art a "constant region" of an antibody refers to the constant region of the antibody light chain or the constant region of the antibody heavy chain, either alone or in combination.

As used herein, "substantially pure" refers to material which is at least 50% pure (i.e., free from contaminants), more preferably, at least 90% pure, more preferably, at least 95% pure, yet more preferably, at least 98% pure, and most preferably, at least 99% pure.

A "host cell" includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) of this invention.

As known in the art, the term "Fc region" is used to define a C-terminal region of an immunoglobulin heavy chain. The "Fc region" may be a native sequence Fc region or a variant Fc region. Although the boundaries of the Fc region of an immunoglobulin heavy chain might vary, the human IgG heavy chain Fc region is usually defined to stretch from an amino acid residue at position Cys226, or from Pro230, to the carboxyl-terminus thereof. The numbering of the residues in the Fc region is that of the EU index as in Kabat. Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991. The Fc region of an immunoglobulin generally comprises two constant regions, CH2 and CH3.

As used in the art, "Fc receptor" and "FcR" describe a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. FcRs are reviewed in Ravetch and Kinet, Ann. Rev. Immunol., 9:457-92, 1991; Capel et al., Immunomethods, 4:25-34, 1994; and de Haas et al., J. Lab. Clin. Med., 126:330-41, 1995. "FcR" also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal

IgGs to the fetus (Guyer et al., J. Immunol., 117:587, 1976; and Kim et al., J. Immunol., 24:249, 1994).

The term "compete", as used herein with regard to an antibody, means that a first antibody, or an antigen binding fragment (or portion) thereof, binds to an epitope in a manner sufficiently similar to the binding of a second antibody, or an antigen binding portion thereof, such that the result of binding of the first antibody with its cognate epitope is detectably decreased in the presence of the second antibody compared to the binding of the first antibody in the absence of the second antibody. The alternative, where the binding of the second antibody to its epitope is also detectably decreased in the presence of the first antibody, can, but need not be the case. That is, a first antibody can inhibit the binding of a second antibody to its epitope without that second antibody inhibiting the binding of the first antibody to its respective epitope. However, where each antibody detectably inhibits the binding of the other antibody with its cognate epitope or ligand, whether to the same, greater, or lesser extent, the antibodies are said to "cross-compete" with each other for binding of their respective epitope(s). Both competing and cross-competing antibodies are encompassed by the present invention. Regardless of the mechanism by which such competition or cross-competition occurs (e.g., steric hindrance, conformational change, or binding to a common epitope, or portion thereof), the skilled artisan would appreciate, based upon the teachings provided herein, that such competing and/or cross-competing antibodies are encompassed and can be useful for the methods disclosed herein.

A "functional Fc region" possesses at least one effector function of a native sequence Fc region. Exemplary "effector functions" include C1q binding; complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity; phagocytosis; down-regulation of cell surface receptors (e.g. B cell receptor), etc. Such effector functions generally require the Fc region to be combined with a binding domain (e.g. an antibody variable domain) and can be assessed using various assays known in the art for evaluating such antibody effector functions.

A "native sequence Fc region" comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. A "variant Fc region" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at

least one amino acid modification, yet retains at least one effector function of the native sequence Fc region. In some embodiments, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or to the Fc region of a parent polypeptide, e.g. from about one to about ten amino acid substitutions, and preferably, from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% sequence identity with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably, at least about 90% sequence identity therewith, more preferably, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99% sequence identity therewith.

The term "effector function" refers to the biological activities attributable to the Fc region of an antibody. Examples of antibody effector functions include, but are not limited to, antibody-dependent cell-mediated cytotoxicity (ADCC), Fc receptor binding, complement dependent cytotoxicity (CDC), phagocytosis, C1q binding, and down regulation of cell surface receptors (e.g., B cell receptor; BCR). See, e.g., U.S. Pat No. 6,737,056. Such effector functions generally require the Fc region to be combined with a binding domain (e.g., an antibody variable domain) and can be assessed using various assays known in the art for evaluating such antibody effector functions. An exemplary measurement of effector function is through Fcγ3 and/or C1q binding.

As used herein "antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a cell-mediated reaction in which nonspecific cytotoxic cells that express Fc receptors (FcRs) (e.g. natural killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and subsequently cause lysis of the target cell. ADCC activity of a molecule of interest can be assessed using an *in vitro* ADCC assay, such as that described in U.S. Patent No. 5,500,362 or 5,821,337. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and NK cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g., in an animal model such as that disclosed in Clynes et al., 1998, *PNAS (USA)*, 95:652-656.

"Complement dependent cytotoxicity" or "CDC" refers to the lysing of a target in the presence of complement. The complement activation pathway is initiated by the binding of the first component of the complement system (C1q) to a molecule (e.g. an antibody)

complexed with a cognate antigen. To assess complement activation, a CDC assay, e.g. as described in Gazzano-Santoro et al., *J. Immunol. Methods*, 202: 163 (1996), may be performed.

A "subject" is a mammal. Mammals may include, but are not limited to, humans, farm animals, sport animals, pets, primates, horses, dogs, cats, mice and rats.

As used herein, "vector" means a construct, which is capable of delivering, and, preferably, expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, DNA or RNA expression vectors encapsulated in liposomes, and certain eukaryotic cells, such as producer cells.

As used herein, "expression control sequence" means a nucleic acid sequence that directs transcription of a nucleic acid. An expression control sequence can be a promoter, such as a constitutive or an inducible promoter, or an enhancer. The expression control sequence is operably linked to the nucleic acid sequence to be transcribed.

As used herein, "pharmaceutically acceptable carrier" or "pharmaceutical acceptable excipient" includes any material which, when combined with an active ingredient, allows the ingredient to retain biological activity and is non-reactive with the subject's immune system. Examples include, but are not limited to, any of the standard pharmaceutical carriers such as a phosphate buffered saline solution, water, emulsions such as oil/water emulsion, and various types of wetting agents. Preferred diluents for aerosol or parenteral formulation are phosphate buffered saline (PBS) or normal (0.9%) saline. Compositions comprising such carriers are formulated by well known conventional methods (see, for example, Remington's Pharmaceutical Sciences, 18th edition, A. Gennaro, ed., Mack Publishing Co., Easton, PA, 1990; and Remington, The Science and Practice of Pharmacy 21st Ed. Mack Publishing, 2005).

The term "acyl donor glutamine-containing tag" or "glutamine tag" as used herein refers to a polypeptide or a protein containing one or more Gln residue(s) that acts as a transglutaminase amine acceptor. See, e.g., WO2012059882 and WO2015015448.

The term "k_{on}" or "k_a", as used herein, refers to the rate constant for association of an antibody to an antigen. Specifically, the rate constants (k_{on}/k_a and k_{off}/k_d) and equilibrium dissociation constants are measured using whole antibody (i.e. bivalent) and monomeric BCMA proteins.

The term "k_{off} " or "k_d", as used herein, refers to the rate constant for dissociation of an antibody from the antibody/antigen complex.

The term "K_D", as used herein, refers to the equilibrium dissociation constant of an antibody-antigen interaction.

Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X." Numeric ranges are inclusive of the numbers defining the range.

It is understood that wherever embodiments are described herein with the language "comprising," otherwise analogous embodiments described in terms of "consisting of" and/or "consisting essentially of" are also provided.

Where aspects or embodiments of the invention are described in terms of a Markush group or other grouping of alternatives, the present invention encompasses not only the entire group listed as a whole, but each member of the group individually and all possible subgroups of the main group, but also the main group absent one or more of the group members. The present invention also envisages the explicit exclusion of one or more of any of the group members in the claimed invention.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In case of conflict, the present specification, including definitions, will control. Throughout this specification and claims, the word "comprise," or variations such as "comprises" or "comprising" will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

Exemplary methods and materials are described herein, although methods and materials similar or equivalent to those described herein can also be used in the practice or

testing of the present invention. The materials, methods, and examples are illustrative only and not intended to be limiting.

BCMA Antibodies and Methods of Making Thereof

The present invention provides an antibody or an antigen binding fragment that binds to BCMA (e.g., human BCMA (e.g., SEQ ID NO: 353 or accession number: Q02223-2). In some embodiments, the present invention provides an antibody or an antigen binding fragment, which specifically binds to BCMA and exerts cytotoxic activity in malignant cells expressing BCMA.

In one aspect, provided is an isolated antibody, or an antigen binding fragment thereof, which specifically binds to B-Cell Maturation Antigen (BCMA), wherein the antibody comprises (a) a heavy chain variable (VH) region comprising (i) a VH complementary determining region one (CDR1) comprising the sequence SYX_1MX_2, wherein X_1 is A or P; and X_2 is T, N, or S (SEQ ID NO: 301), $GFTFX_1SY$, wherein X_1 is G or S (SEQ ID NO: 302), or $GFTFX_1SYX_2MX_3$, wherein X_1 is G or S, X_2 is A or P; and X_3 is T, N, or S (SEQ ID NO: 303); (ii) a VH CDR2 comprising the sequence $AX_1X_2X_3X_4GX_5X_6X_7X_8YADX_9X_{10}KG$, wherein X_1 is I, V, T, H, L, A, or C; X_2 is S, D, G, T, I, L, F, M, or V; X_3 is G, Y, L, H, D, A, S, or M; X_4 is S, Q, T, A, F, or W; X_5 is G or T;X_6 is N, S, P, Y, W, or F; X_7 is S, T, I, L, T, A, R, V, K, G, or C; X_8 is F, Y, P, W, H, or G; X_9 is V, R, or L; and X_{10} is G or T (SEQ ID NO: 305), or $X_1X_2X_3X_4X_5X_6$, wherein X_1 is S, V, I, D, G, T, L, F, or M; X_2 is G, Y, L, H, D, A, S, or M; X_3 is S, G, F, or W; X_4 is G or S; X_5 is G or T; and X_6 is N, S, P, Y, or W (SEQ ID NO: 306); and iii) a VH CDR3 comprising the sequence $VSPIX_1X_2X_3X_4$, wherein X_1 is A or Y; X_2 is A or S; and X_3 is G, Q, L, P, or E (SEQ ID NO: 307), or $YWPMX_1X_2$, wherein X_1 is D, S, T, or A; and X_2 is I, S, L, P, or D (SEQ ID NO: 308); and/or a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$, wherein X_1 is R, G, W, A, or C; X_2 is A, P, G, L, C, or S; X_3 is S, G, or R; X_4 is Q, C, E, V, or I; X_5 is S, P, G, A, R, or D; X_6 is V, G, I, or L; X_7 is S, E, D, P, or G; X_8 is S, P, F, A, M, E, V, N, D, or Y; X_9 is I, T, V, E, S, A, M, Q, Y, H, R, or F; X_{10} is Y or F; X_{11} is L, W, or P; and X_{12} is A, S, or G (SEQ ID NO: 309); (ii) a VL CDR2 comprising the sequence $X_1ASX_2RAX_3$, wherein X_1 is G or D; X_2 is S or I; and X_3 is T or P (SEQ ID NO: 310); and (iii) a VL CDR3 comprising the sequence $QQYX_1X_2X_3PX_4T$,

wherein X_1 is G, Q, E, L, F, A, S, M, K, R, or Y; X_2 is S, R, T, G, V, F, Y, D, A, H, V, E, K, or C; X_3 is W, F, or S; and X_4 is L or I (SEQ ID NO: 311), or $QQYX_1X_2X_3PX_4$, wherein X_1 is G, Q, E, L, F, A, S, M, R, K, or Y; X_2 is S, R, T, G, R, V, D, A, H, E, K, C, F, or Y; X_3 is W, S, or F; and X_4 is L or I (SEQ ID NO: 312).

In another aspect, provided is an isolated antibody, or an antigen binding fragment thereof, which specifically binds to BCMA, wherein the antibody comprises: a VH region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 2, 3, 7, 8, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 37, 39, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 83, 87, 92, 95, 97, 99, 101, 104, 106, 110, 112, 114, 118, 120, 122, 112, 125, 127, 313, 314, 363, or 365; and/or a VL region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 1, 4, 5, 6, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 34, 36, 38, 40, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 317, 80, 81, 82, 84, 85, 86, 88, 89, 90, 91, 93, 94, 96, 98, 100, 102, 103, 105, 107, 108, 109, 111, 113, 115, 116, 117, 119, 121, 123, 124, 126, 128, 315, 316, or 364.

In some embodiments, provided is an antibody having any one of partial light chain sequence as listed in Table 1 and/or any one of partial heavy chain sequence as listed in Table 1.

Table 1

mAb	Light Chain	Heavy Chain
P6E01/ P6E01	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YGSPPSFT**FGQGTKVEIK (SEQ ID NO: 1)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
P6E01/ H3.AQ	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH**	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV

mAb	Light Chain	Heavy Chain
	YGSPPSFTFGQGTKVEIK (SEQ ID NO: 1)	YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)
L1.LG F/L3.K W/P6E 01	EIVLTQSPGTLSLSPGERATLSC **RASQSLGSFYLA**WYQQKPGQA PRLLIY**GASSRAT**GIPDRFSGSG SGTDFTLTISRLEPEDFAVYYC**KH YGWPPSFT**FGQGTKVEIK (SEQ ID NO: 4)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L1.LG F/L3.N Y/P6E 01	EIVLTQSPGTLSLSPGERATLSC**R ASQSLGSFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YNYPPSFT**FGQGTKVEIK (SEQ ID NO: 5)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L1.GD F/L3.N Y/P6E 01	EIVLTQSPGTLSLSPGERATLSC**R ASQSVGDFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YNYPPSFT**FGQGTKVEIK (SEQ ID NO: 6)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L1.LG F/L3.K W/H3. AL	EIVLTQSPGTLSLSPGERATLSC**R ASQSLGSFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KHY GWPPSFT**FGQGTKVEIK (SEQ ID NO: 4)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**ARVSPIAALMDY**WGQGTL VTVSS (SEQ ID NO: 7)
L1.LG F/L3.K	EIVLTQSPGTLSLSPGERATLSC**R ASQSLGSFYLA**WYQQKPGQAP	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE

mAb	Light Chain	Heavy Chain
W/H3.AP	RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KHY GWPPSFT**FGQGTKVEIK (SEQ ID NO: 4)	WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAPMDY**WGQGTLVT VSS (SEQ ID NO: 8)
L1.LGF/L3.KW/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**R ASQSLGSFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KHY GWPPSFT**FGQGTKVEIK (SEQ ID NO: 4)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)
L1.LGF/L3.PY/H3.AP	EIVLTQSPGTLSLSPGERATLSC**R ASQSLGSFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 9)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAPMDY**WGQGTLVT VSS (SEQ ID NO: 8)
L1.LGF/L3.PY/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**R ASQSLGSFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 9)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)
L1.LGF/L3.NY/H3.AL	EIVLTQSPGTLSLSPGERATLSC**R ASQSLGSFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YNYPPSFT**FGQGTKVEIK (SEQ ID NO: 10)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAALMDY**WGQGTLVT VSS (SEQ ID NO: 7)
L1.LG	EIVLTQSPGTLSLSPGERATLSC**R**	EVQLLESGGGLVQPGGSLRLSCA

mAb	Light Chain	Heavy Chain
F/L3.NY/H3.AP	**ASQSLGSFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YNYPPSFT**FGQGTKVEIK (SEQ ID NO: 10)	ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAPMDY**WGQGTLVT VSS (SEQ ID NO: 8)
L1.LGF/L3.NY/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**R ASQSLGSFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YNYPPSFT**FGQGTKVEIK (SEQ ID NO: 10)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)
L1.GDF/L3.KW/H3.AL	EIVLTQSPGTLSLSPGERATLSC**R ASQSVGDFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KHY GWPPSFT**FGQGTKVEIK (SEQ ID NO: 11)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAALMDY**WGQGTLVT VSS (SEQ ID NO: 7)
L1.GDF/L3.KW/H3.AP	EIVLTQSPGTLSLSPGERATLSC**R ASQSVGDFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KHY GWPPSFT**FGQGTKVEIK (SEQ ID NO: 11)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAPMDY**WGQGTLVT VSS (SEQ ID NO: 8)
L1.GDF/L3.KW/H3.AQ	EIVLTQSPGTLSLSPGERATLSC**R ASQSVGDFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KHY GWPPSFT**FGQGTKVEIK (SEQ ID NO: 11)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)

mAb	Light Chain	Heavy Chain
L1.GD F/L3.P Y/H3.A Q	EIVLTQSPGTLSLSPGERATLSCR **ASQSVGDFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 12)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)
L1.GD F/L3.N Y/H3.A L	EIVLTQSPGTLSLSPGERATLSCR **ASQSVGDFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YNYPPSFT**FGQGTKVEIK (SEQ ID NO: 13)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAALMDY**WGQGTLVT VSS (SEQ ID NO: 7)
L1.GD F/L3.N Y/H3.A P	EIVLTQSPGTLSLSPGERATLSCR **ASQSVGDFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YNYPPSFT**FGQGTKVEIK (SEQ ID NO: 13)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAPMDY**WGQGTLVT VSS (SEQ ID NO: 8)
L1.GD F/L3.N Y/H3.A Q	EIVLTQSPGTLSLSPGERATLSCR **ASQSVGDFYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YNYPPSFT**FGQGTKVEIK (SEQ ID NO: 14)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)
L3.KW/ P6E01	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KHY GWPPSFT**FGQGTKVEIK (SEQ ID	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT

mAb	Light Chain	Heavy Chain
	NO: 15)	VSS (SEQ ID NO: 2)
L3.PY/ P6E01	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L3.NY/ P6E01	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YNYPPSFT**FGQGTKVEIK (SEQ ID NO: 17)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L3.PY/ L1.PS/ P6E01	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L3.PY/ L1.AH/ P6E01	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L3.PY/ L1.FF/ P6E01	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP**	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV

mAb	Light Chain	Heavy Chain
	YPPSFTFGQGTKVEIK (SEQ ID NO: 20)	YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L3.PY/ L1.PH/ P6E01	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSPHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L3.PY/ L3.KY/ P6E01	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KYY** **PYPPSFT**FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L3.PY/ L3.KF/ P6E01	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KFY** **PYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L3.PY/ H2.QR	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADQRKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 24)
L3.PY/ H2.DY	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**DYSGGN**TFYADSVKGRFTI

mAb	Light Chain	Heavy Chain
	GTDFTLTISRLEPEDFAVYYC**QH** **YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 25)
L3.PY/ H2.YQ	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSA**ISYQGGNT**FYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 26)
L3.PY/ H2.LT	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSA**ISLTGGNT**FYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 27)
L3.PY/ H2.HA	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSA**ISHAGGNT**FYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 28)
L3.PY/ H2.QL	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAPRLLI Y**GASSRAT**GIPDRFSGSGSGTDFT LTISRLEPEDFAVYYC**QHYPYPPSFT** FGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSA**ISGSGGNT**FYADQLKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 29)
L3.PY/ H3.YA	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE

mAb	Light Chain	Heavy Chain
	RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIYAGMDY**WGQGTLVT VSS (SEQ ID NO: 30)
L3.PY/ H3.AE	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFGSYAMT**WVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAEMDY**WGQGTLVT VSS (SEQ ID NO: 31)
L3.PY/ H3.AQ	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFGSYAMT**WVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)
L3.PY/ H3.TA Q	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFGSYAMT**WVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCTR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 32)
L3.PY/ P6E01	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 16)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFGSYAMT**WVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 2)
L3.PY/	EIVLTQSPGTLSLSPGERATLSCR	EVQLLESGGGLVQPGGSLRLSCA

mAb	Light Chain	Heavy Chain
L1.PS/ H2.QR	**ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	ASGFTFG**SY**AMTWVRQAPGKGLE WVSA**ISGSGGN**TFYADQRKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 24)
L3.PY/ L1.PS/ H2.DY	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFG**SY**AMTWVRQAPGKGLE WVSAIDYSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 25)
L3.PY/ L1.PS/ H2.YQ	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFG**SY**AMTWVRQAPGKGLE WVSA**ISYQGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 26)
L3.PY/ L1.PS/ H2.LT	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFG**SY**AMTWVRQAPGKGLE WVSA**ISLTGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 27)
L3.PY/ L1.PS/ H2.HA	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFG**SY**AMTWVRQAPGKGLE WVSA**ISHAGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 28)

mAb	Light Chain	Heavy Chain
L3.PY/ L1.PS/ H2.QL	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADQLKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 29)
L3.PY/ L1.PS/ H3.YA	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIYAGMDY**WGQGTLVT VSS (SEQ ID NO: 30)
L3.PY/ L1.PS/ H3.AE	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAEMDY**WGQGTLVT VSS (SEQ ID NO: 31)
L3.PY/ L1.PS/ H3.AQ	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 18)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)
L3.PY/ L1.PS/ H3.TA Q	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYPS**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCTR**VSPIAAQMDY**WGQGTLVT

mAb	Light Chain	Heavy Chain
	ID NO: 18)	VSS (SEQ ID NO: 32)
L3.PY/ L1.AH/ H2.QR	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADQRKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 24)
L3.PY/ L1.AH/ H2.DY	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAIDYSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 25)
L3.PY/ L1.AH/ H2.YQ	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SYQGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 26)
L3.PY/ L1.AH/ H2.LT	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SLTGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 27)
L3.PY/ L1.AH/ H2.HA	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH**	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SHAGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV

mAb	Light Chain	Heavy Chain
	YPYPPSFTFGQGTKVEIK (SEQ ID NO: 19)	YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 28)
L3.PY/ L1.AH/ H2.QL	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADQLKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 29)
L3.PY/ L1.AH/ H3.YA	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIYAGMDY**WGQGTLVT VSS (SEQ ID NO: 30)
L3.PY/ L1.AH/ H3.AE	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAEMDY**WGQGTLVT VSS (SEQ ID NO: 31)
L3.PY/ L1.AH/ H3.AQ	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)
L3.PY/ L1.AH/ H3.TA	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSAHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI

mAb	Light Chain	Heavy Chain
Q	GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 19)	SRDNSKNTLYLQMNSLRAEDTAV YYCTR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 32)
L3.PY/ L1.FF/ H2.QR	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP YPPSFT**FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFGSY**AMTWVRQAPGKGLE WVSA**ISGSGGN**TFYADQRKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 24)
L3.PY/ L1.FF/ H2.DY	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP YPPSFT**FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFGSY**AMTWVRQAPGKGLE WVSAIDYSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 25)
L3.PY/ L1.FF/ H2.YQ	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP YPPSFT**FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFGSY**AMTWVRQAPGKGLE WVSA**ISYQGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 26)
L3.PY/ L1.FF/ H2.LT	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP YPPSFT**FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFGSY**AMTWVRQAPGKGLE WVSA**ISLTGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 27)
L3.PY/	EIVLTQSPGTLSLSPGERATLSCR	EVQLLESGGGLVQPGGSLRLSCA

mAb	Light Chain	Heavy Chain
L1.FF/ H2.HA	**ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP YPPSFT**FGQGTKVEIK (SEQ ID NO: 20)	ASGFTFG**SY**AMTWVRQAPGKGLE WVSAI**SHAGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 28)
L3.PY/ L1.FF/ H2.QL	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP YPPSFT**FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFG**SY**AMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADQLKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 29)
L3.PY/ L1.FF/ H3.YA	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP YPPSFT**FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFG**SY**AMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIYAGMDY**WGQGTLVT VSS (SEQ ID NO: 30)
L3.PY/ L1.FF/ H3.AE	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP YPPSFT**FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFG**SY**AMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAEMDY**WGQGTLVT VSS (SEQ ID NO: 31)
L3.PY/ L1.FF/ H3.AQ	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP YPPSFT**FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFG**SY**AMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)

mAb	Light Chain	Heavy Chain
L3.PY/ L1.FF/ H3.TA Q	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSFFLA**WYQQKPGQAPR LLIY**GASSRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QHYP YPPSFT**FGQGTKVEIK (SEQ ID NO: 20)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCTR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 32)
L3.PY/ L1.PH/ H2.QR	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSPHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADQRKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 24)
L3.PY/ L1.PH/ H2.HA	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSPHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SHAGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 28)
L3.PY/ L1.PH/ H3.AE	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSPHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAEMDY**WGQGTLVT VSS (SEQ ID NO: 31)
L3.PY/ L1.PH/ H3.AQ	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSPHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAISGSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT

mAb	Light Chain	Heavy Chain
	ID NO: 21)	VSS (SEQ ID NO: 3)
L3.PY/ L1.PH/ H3.TA Q	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSPHYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH YPYPPSFT**FGQGTKVEIK (SEQ ID NO: 21)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCTR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 32)
L3.PY/ L3.KY/ H2.QR	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KYY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADQRKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 24)
L3.PY/ L3.KY/ H2.DY	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KYY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAIDYSGGNTFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 25)
L3.PY/ L3.KY/ H2.YQ	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KYY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SYQGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 26)
L3.PY/ L3.KY/ H2.LT	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KYY**	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SLTGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV

mAb	Light Chain	Heavy Chain
	PYPPSFTFGQGTKVEIK (SEQ ID NO: 22)	YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 27)
L3.PY/ L3.KY/ H2.HA	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KYY** **PYPPSFT**FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SHAGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 28)
L3.PY/ L3.KY/ H2.QL	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KYY** **PYPPSFT**FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADQLKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 29)
L3.PY/ L3.KY/ H3.YA	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KYY** **PYPPSFT**FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIYAGMDY**WGQGTLVT VSS (SEQ ID NO: 30)
L3.PY/ L3.KY/ H3.TA Q	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KYY** **PYPPSFT**FGQGTKVEIK (SEQ ID NO: 22)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCTR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 32)
L3.PY/ L3.KF/ H2.DY	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAIDYSGGNTFYADSVKGRFTI

mAb	Light Chain	Heavy Chain
	GTDFTLTISRLEPEDFAVYYC**KFY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 25)
L3.PY/ L3.KF/ H2.YQ	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KFY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SYQGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 26)
L3.PY/ L3.KF/ H2.LT	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KFY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SLTGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 27)
L3.PY/ L3.KF/ H2.QL	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KFY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADQLKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIASGMDY**WGQGTLVT VSS (SEQ ID NO: 29)
L3.PY/ L3.KF/ H3.YA	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KFY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFGSYAMTWVRQAPGKGLE WVSAI**SGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIYAGMDY**WGQGTLVT VSS (SEQ ID NO: 30)
L3.PY/	EIVLTQSPGTLSLSPGERATLSC**R**	EVQLLESGGGLVQPGGSLRLSCA

mAb	Light Chain	Heavy Chain
L3.KF/ H3.AE	**ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KFY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	AS**GFTFGSY**AMTWVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAEMDY**WGQGTLVT VSS (SEQ ID NO: 31)
L3.PY/ L3.KF/ H3.AQ	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KFY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFGSY**AMTWVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 3)
L3.PY/ L3.KF/ H3.TA Q	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**KFY PYPPSFT**FGQGTKVEIK (SEQ ID NO: 23)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFGSY**AMTWVRQAPGKGLE WVSA**ISGSGGN**TFYADSVKGRFTI SRDNSKNTLYLQMNSLRAEDTAV YYCTR**VSPIAAQMDY**WGQGTLVT VSS (SEQ ID NO: 32)
P5A2_ VHVL	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YGSWPLT**FGQGTKVEIK (SEQ ID NO: 34)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFSSY**AMNWVRQAPGKGLE WVS**AISDSGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDI**WGQGTLVTVSS (SEQ ID NO: 33)
A02_R d4_0.6 nM_C0 6	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSVIYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY QRWPLT**FGQGTKVEIK (SEQ ID NO: 36)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFSSY**AMNWVRQAPGKGLE WVS**AISDSGGSAWYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMSL**WGQGTLVTVSS (SEQ ID NO: 35)

mAb	Light Chain	Heavy Chain
A02_Rd4_0.6nM_C09	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSSYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YQSWPLT**FGQGTKVEIK (SEQ ID NO: 38)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AISDSGGSMWYADSVKG**RF TISRDNSKNTLYLQMNSLRAEDTA VYYCAR**YWPMSL**WGQGTLVTVS S (SEQ ID NO: 37)
A02_Rd4_6nM_C16	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSDIYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY QTWPLT**FGQGTKVEIK (SEQ ID NO: 40)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AISdFGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDI**WGQGTLVTVSS (SEQ ID NO: 39)
A02_Rd4_6nM_C03	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSNLYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YQGWPLT**FGQGTKVEIK (SEQ ID NO: 41)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AISDSGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDI**WGQGTLVTVSS (SEQ ID NO: 33)
A02_Rd4_6nM_C01	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSAYYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YERWPLT**FGQGTKVEIK (SEQ ID NO: 43)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AITASGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMSL**WGQGTLVTVSS (SEQ ID NO: 42)
A02_Rd4_6nM_C26	EIVLTQSPGTLSLSPGERATLSCR **ASQSVSSLYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY QVWPLT**FGQGTKVEIK (SEQ ID	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AISDSGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMSL**WGQGTLVTVSS

mAb	Light Chain	Heavy Chain
	NO: 45)	(SEQ ID NO: 44)
A02_Rd4_6nM_C25	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YLDWPLT**FGQGTKVEIK (SEQ ID NO: 47)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AISdSGGSRWYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMTP**WGQGTLVTVSS (SEQ ID NO: 46)
A02_Rd4_6nM_C22	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YQVWPLT**FGQGTKVEIK (SEQ ID NO: 49)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AVLdSGGSTYYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMTP**WGQGTLVTVSS (SEQ ID NO: 48)
A02_Rd4_6nM_C19	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSVIYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYL AWPLT**FGQGTKVEIK (SEQ ID NO: 51)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AISdSGGSRWYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMSD**WGQGTLVTVSS (SEQ ID NO: 50)
A02_Rd4_0.6nM_C03	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YFTWPLT**FGQGTKVEIK (SEQ ID NO: 53)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AISdSGGSKWYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMSL**WGQGTLVTVSS (SEQ ID NO: 52)
A02_Rd4_6nM_C07	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSPyYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYE**	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AIGGSGGSLPYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV

mAb	Light Chain	Heavy Chain
	RWPLTFGQGTKVEIK (SEQ ID NO: 55)	YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 54)
A02_Rd4_6nM_C23	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSVEYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YARWPLT**FGQGTKVEIK (SEQ ID NO: 57)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFS**SY**AMN**W**VRQAPGKGLE WVS**AISdSGGSGWYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMSL**WGQGTLVTVSS (SEQ ID NO: 56)
A02_Rd4_0.6nM_C18	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSEIYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYF GWPLT**FGQGTKVEIK (SEQ ID NO: 59)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFS**SY**AMN**W**VRQAPGKGLE WVS**AVLdSGGSTYYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMSL**WGQGTLVTVSS (SEQ ID NO: 58)
A02_Rd4_6nM_C10	EIVLTQSPGTLSLSPGERATLSC**R ASQSVEMSYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YAHWPLT**FGQGTKVEIK (SEQ ID NO: 61)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFS**SY**AMN**W**VRQAPGKGLE WVS**AISdSGGSCWYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMTP**WGQGTLVTVSS (SEQ ID NO: 60)
A02_Rd4_6nM_C05	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YQRWPLT**FGQGTKVEIK (SEQ ID NO: 63)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFS**SY**AMN**W**VRQAPGKGLE WVS**AIFaSGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMTP**WGQGTLVTVSS (SEQ ID NO: 62)
A02_Rd4_0.6nM_C1	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSAQYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS	EVQLLESGGGLVQPGGSLRLSCA ASGFTFS**SY**AMN**W**VRQAPGKGLE WVS**AISgWGGSLPYADSVKG**RFT

mAb	Light Chain	Heavy Chain
0	GTDFTLTISRLEPEDFAVYYC**QQ YQRWPLT**FGQGTKVEIK (SEQ ID NO: 65)	ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 64)
A02_Rd4_6nM_C04	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSAIYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY QVWPLT**FGQGTKVEIK (SEQ ID NO: 67)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AIMsSGGPLYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMAL**WGQGTLVTVSS (SEQ ID NO: 66)
A02_Rd4_0.6nM_C26	EIVLTQSPGTLSLSPGERATLSC**G PSQSVSSSYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY QSWPLT**FGQGTKVEIK (SEQ ID NO: 69)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AILmSGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMSL**WGQGTLVTVSS (SEQ ID NO: 68)
A02_Rd4_0.6nM_C13	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYWA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YESWPLT**FGQGTKVEIK (SEQ ID NO: 71)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AISdSGGYRYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMSL**WGQGTLVTVSS (SEQ ID NO: 70)
A02_Rd4_0.6nM_C01	EIVLTQSPGTLSLSPGERATLSC**R GGQSVSSSYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YQSWPLT**FGQGTKVEIK (SEQ ID NO: 73)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AILsSGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDI**WGQGTLVTVSS (SEQ ID NO: 72)
A02_Rd4_6n	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSFIYLA**WYQQKPGQAPR	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE

mAb	Light Chain	Heavy Chain
M_C08	LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY GSWPLT**FGQGTKVEIK (SEQ ID NO: 75)	WVS**AILdSGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMSP**WGQGTLVTVSS (SEQ ID NO: 74)
P5C1_ VHVL	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSTYLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYS TSPLT**FGQGTKVEIK (SEQ ID NO: 77)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGGSGGSTYYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 76)
C01_R d4_6n M_C24	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSPEYLA**WYQQKPGQAP RLLIY**DASSRAP**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YSVWPLT**FGQGTKVEIK (SEQ ID NO: 79)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGGSGGSLPYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
C01_R d4_6n M_C26	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSAIYLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYS AWPLT**FGQGTKVEIK (SEQ ID NO: 317)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGGSGGSLPYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
C01_R d4_6n M_C10	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSvYLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYS TWPLT**FGQGTKVEIK (SEQ ID NO: 79)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGgSGGSLPYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
C01_R	EIVLTQSPGTLSLSPGERATLSC**R**	EVQLLESGGGLVQPGGSLRLSCA

mAb	Light Chain	Heavy Chain
d4_0.6 nM_C27	**ASQSVSSTYLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYS RWPLT**FGQGTKVEIK (SEQ ID NO: 81)	ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGgSGGSLPYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4_6nM_C20	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSPIYLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYS AFPLT**FGQGTKVEIK (SEQ ID NO: 82)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGgSGGSLPYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4_6nM_C12	EIVLTQSPGTLSLSPGERATLSC **WLSQSVSSTYLA**WYQQKPGQA PRLLIY**DASSRAP**GIPDRFSGSG SGTDFTLTISRLEPEDFAVYYC**Q QYSEWPLT**FGQGTKVEIK (SEQ ID NO: 84)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGgSGGWSYYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 83)
C01_Rd4_0.6nM_C16	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSTYLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYS SWPLT**FGQGTKVEIK (SEQ ID NO: 85)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGgSGGSLPYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4_0.6nM_C09	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSIFLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYS AWPLT**FGQGTKVEIK (SEQ ID NO: 86)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGgSGGSLPYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)

mAb	Light Chain	Heavy Chain
C01_Rd4_6nM_C09	EIVLTQSPGTLSLSPGERATLSC**A CSQSVSSTYLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYS AWPLT**FGQGTKVEIK (SEQ ID NO: 88)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**ATVgSGGSIGYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 87)
C01_Rd4_0.6nM_C03	EIVLTQSPGTLSLSPGERATLSC**R ASCDVSSTYLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY MRSPLT**FGQGTKVEIK (SEQ ID NO: 89)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGgSGGSLPYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4_0.6nM_C06	EIVLTQSPGTLSLSPGERATLSC**R ASEAVPSTYLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYS AFPLT**FGQGTKVEIK (SEQ ID NO: 90)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGgSGGSLPYADSVKGT**ISR DNSKNTLYLQMNSLRAEDTAVYY CAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
C01_Rd4_6nM_C04	EIVLTQSPGTLSLSPGERATLSC**C SSQSVSSTYLA**WYQQKPGQAPR LLIY**DASSRAP**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQYS AFPLT**FGQGTKVEIK (SEQ ID NO: 91)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVS**AIGgSGGSLPYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
COMBO_Rd4_0.6nM_C22	EIVLTQSPGTLSLSPGERATLSC**R ASVRVSSTYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY MKWPLT**FGQGTKVEIK (SEQ ID	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVS**AISdSGGSRWYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCTR**YWPMDI**WGQGTLVTVSS

mAb	Light Chain	Heavy Chain
	NO: 93)	(SEQ ID NO: 92)
COMBO_Rd4_6nM_C21	EIVLTQSPGTLSLSPGERATLSCR**ASQSVSAAYLA**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYMCWPLT**FGQGTKVEIK (SEQ ID NO: 94)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSY**PMSWVRQAPGKGLEWVS**AIGgSGGSLPYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
COMBO_Rd4_6nM_C10	EIVLTQSPGTLSLSPGERATLSCR**ASQSVSSSYWG**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYQCWPLT**FGQGTKVEIK (SEQ ID NO: 96)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSY**PMSWVRQAPGKGLEWVS**AIGgSGGSIHYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 95)
COMBO_Rd4_0.6nM_C04	EIVLTQSPGTLSLSPGERATLSCR**ASQSVSSTYLA**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYQSWPLT**FGQGTKVEIK (SEQ ID NO: 98)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSY**PMSWVRQAPGKGLEWVS**AHIgSGGSTYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 97)
COMBO_Rd4_6nM_C25	EIVLTQSPGTLSLSPGERATLSCR**ASQSVSSpYLA**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYQSWPLT**FGQGTKVEIK (SEQ ID NO: 100)	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSY**PMSWVRQAPGKGLEWVS**AIGgSGGSTYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWPMDP**WGQGTLVTVSS (SEQ ID NO: 99)
COMBO_Rd4_0.6nM_C21	EIVLTQSPGTLSLSPGERATLSCR**ASQSVSSSYLA**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQ**	EVQLLESGGGLVQPGGSLRLSCAAS**GFTFSSY**PMSWVRQAPGKGLEWVS**AIGgSGGSLPYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAV

mAb	Light Chain	Heavy Chain
	YQSWPLTFGQGTKVEIK (SEQ ID NO: 38)	YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
COMBO_Rd4_6nM_C11	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSPIYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY KAWPLT**FGQGTKVEIK (SEQ ID NO: 102)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFS**SY**PMSWVRQAPGKGLE WVS**AIGGSGGSLGYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 101)
COMBO_Rd4_0.6nM_C20	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSYLYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY MEWPLT**FGQGTKVEIK (SEQ ID NO: 103)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFS**SY**PMSWVRQAPGKGLE WVS**AIGGSGGSLPYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 78)
COMBO_Rd4_6nM_C09	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSAQYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YQAWPLT**FGQGTKVEIK (SEQ ID NO: 105)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFS**SY**PMSWVRQAPGKGLE WVS**AIFASGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 104)
COMBO_Rd4_6nM_C08	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YQKWPLT**FGQGTKVEIK (SEQ ID NO: 107)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFS**SY**PMSWVRQAPGKGLE WVS**AIGGSGTWTYYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 106)
COMBO_Rd4_0.6n	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSAVYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS	EVQLLESGGGLVQPGGSLRLSCA ASGFTFS**SY**PMSWVRQAPGKGLE WVS**AIGGSGGSLPYADSVKG**RFT

mAb	Light Chain	Heavy Chain
M_C19	GTDFTLTISRLEPEDFAVYYCQQ YRAWPLTFGQGTKVEIK (SEQ ID NO: 108)	ISRDNSKNTLYLQMNSLRAEDTAV YYCARYWPMDSWGQGTLVTVSS (SEQ ID NO: 78)
COMB O_Rd4 _0.6n M_C02	EIVLTQSPGTLSLSPGERATLSCR ASIAVSSTYLAWYQQKPGQAPR LLMYDASIRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQY MVWPLTFGQGTKVEIK (SEQ ID NO: 109)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVSAIGGSGGSLPYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAV YYCARYWPMDSWGQGTLVTVSS (SEQ ID NO: 78)
COMB O_Rd4 _0.6n M_C23	EIVLTQSPGTLSLSPGERATLSCR PRQSVSSSYLAWYQQKPGQAP RLLMYDASIRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYCQQ YQDWPLTFGQGTKVEIK (SEQ ID NO: 111)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVSALFGSGGSTYYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAV YYCARYWPMDSWGQGTLVTVSS (SEQ ID NO: 110)
COMB O_Rd4 _0.6n M_C29	EIVLTQSPGTLSLSPGERATLSCR ASQSVSSSYLAWYQQKPGQAP RLLMYDASIRATGIPDRFSGSGS GTDFTLTISRLEPEDFAVYYCQQ YQSWPLTFGQGTKVEIK (SEQ ID NO: 38)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVSAIGGSGGSLPYADIVKGRFT ISRDNSKNTLYLQMNSLRAEDTAV YYCARYWPMDIWGQGTLVTVSS (SEQ ID NO: 112)
COMB O_Rd4 _0.6n M_C09	EIVLTQSPGTLSLSPGERATLSCR ASQSVSSTYLAWYQQKPGQAPR LLMYDASIRATGIPDRFSGSGSG TDFTLTISRLEPEDFAVYYCQQY QEWPLTFGQGTKVEIK (SEQ ID NO: 113)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVSAIGGSGGSLPYADSVKGRFT ISRDNSKNTLYLQMNSLRAEDTAV YYCARYWPMDIWGQGTLVTVSS (SEQ ID NO: 503)
COMB O_Rd4	EIVLTQSPGTLSLSPGERATLSCR ASQSVSASYLAWYQQKPGQAP	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE

mAb	Light Chain	Heavy Chain
_6nM_ C12	RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YMSWPLT**FGQGTKVEIK (SEQ ID NO: 115)	WVSA**ALGSGGSTYYADSVKG**RF TISRDNSKNTLYLQMNSLRAEDTA VYYCAR**YWPMDS**WGQGTLVTVS S (SEQ ID NO: 114)
COMB O_Rd4 _0.6n M_C30	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSYMYLA**WYQQKPGQAP RLLIY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY KSWPLT**FGQGTKVEIK (SEQ ID NO: 116)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVSA**IGGSGGSTYYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 76)
COMB O_Rd4 _0.6n M_C14	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSALYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YYGWPLT**FGQGTKVEIK (SEQ ID NO: 117)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVSA**IGGSGGSLPYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDIW**GQGTLVTVSS (SEQ ID NO: 503)
COMB O_Rd4 _6nM_ C07	EIVLTQSPGTLSLSPGERATLSC**R ASQPISSSYLA**WYQQKPGQAPR LLMY**DASIRAT**GIPDRFSGSGSG TDFTLTISRLEPEDFAVYYC**QQY QGWPLT**FGQGTKVEIK (SEQ ID NO: 119)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYPMSWVRQAPGKGLE WVSA**IGGSGGSLPYADSVKG**RFT ISRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMAD**WGQGTLVTVSS (SEQ ID NO: 118)
COMB O_Rd4 _6nM_ C02	EIVLTQSPGTLSLSPGERATLSC**R ASQSVSSSYLA**WYQQKPGQAP RLLMY**DASIRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QQ YEFWPLT**FGQGTKVEIK (SEQ ID NO: 121)	EVQLLESGGGLVQPGGSLRLSCA ASGFTFSSYAMNWVRQAPGKGLE WVSA**ISDSGGFVYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 120)
COMB	EIVLTQSPGTLSLSPGERATLSC**R**	EVQLLESGGGLVQPGGSLRLSCA

mAb	Light Chain	Heavy Chain
O_Rd4_0.6nM_C05	**ASQSVSSTYLA**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYMSWPLT**FGQGTKVEIK (SEQ ID NO: 123)	ASGFTFS**SYA**MN**W**VRQAPGKGLEWVSA**IGGSGGSTYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWPMSL**WGQGTLVTVSS (SEQ ID NO: 122)
COMBO_Rd4_0.6nM_C17	EIVLTQSPGTLSLSPGERATLSC**RASQGISSTYLA**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYAYWPLT**FGQGTKVEIK (SEQ ID NO: 124)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS**SY**PMS**W**VRQAPGKGLEWVSA**IGGSGGSLPYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWPMDI**WGQGTLVTVSS (SEQ ID NO: 503)
COMBO_Rd4_6nM_C22	EIVLTQSPGTLSLSPGERATLSC**RASQSVSSSYLA**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYQGWPLT**FGQGTKVEIK (SEQ ID NO: 126)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS**SYA**MN**W**VRQAPGKGLEWVS**ACLDSGGSTYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWPMDS**WGQGTLVTVSS (SEQ ID NO: 125)
COMBO_Rd4_0.6nM_C11	EIVLTQSPGTLSLSPGERATLSC**RASQSVSVRYLA**WYQQKPGQAPRLLMY**DASIRAT**GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYC**QQYGSWPIT**FGQGTKVEIK (SEQ ID NO: 128)	EVQLLESGGGLVQPGGSLRLSCAASGFTFS**SY**PMS**W**VRQAPGKGLEWVS**AALGSGGSTYYADSVKG**RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR**YWPMSL**WGQGTLVTVSS (SEQ ID NO: 127)
Consensus	EIVLTQSPGTLSLSPGERATLSC$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$WYQQKPGQAPRLLMY$X_{13}ASX_{14}RAX_{15}$GIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCX$_{16}$X$_{17}$YX$_{18}$X$_{19}$PPSFTFGQGTKVEIK, wherein X_1 is R,	EVQLLESGGGLVQPGGSLRLSCAASGFTFX$_1$SYX$_2$MX$_3$WVRQAPGKGLEWVSAX$_4$X$_5$X$_6$X$_7$GX$_8$X$_9$X$_{10}$X$_{11}$YADX$_{12}$X$_{13}$KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARVSPIX$_{14}$X$_{15}$X$_{16}$MDYWGQGTLVTVSS, wherein X_1

mAb	Light Chain	Heavy Chain
	G, W, A, or C; X_2 is A, P, G, L, C, or S; X_3 is S, G, or R; X_4 is Q, C, E, V, or I; X_5 is S, P, G, A, R, or D; X_6 is V, G, I, or L; X_7 is S, E, D, P, or G; X_8 is S, P, F, A, M, E, V, N, D, or Y; X_9 is I, T, V, E, S, A, M, Q, Y, H, R, or F; X_{10} is Y or F; X_{11} is L, W, or P; X_{12} is A, S, or G, X_{13} is G or D; X_{14} is S or I; X_{15} is T or P; X_{16} is Q or K; X_{17} is H or Y; X_{18} is G, N, or P; and X_{19} is S, W, or Y (SEQ ID NO: 315); or EIVLTQSPGTLSLSPGERATLSC $X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$WY QQKPGQAPRLLMY$X_{13}ASX_{14}$RAX $_{15}$GIPDRFSGSGSGTDFTLTISRLE PEDFAVYYCQQY$X_{16}X_{17}X_{18}$PX_{19}F GQGTKVEIK, wherein X_1 is R, G, W, A, or C; X_2 is A, P, G, L, C, or S; X_3 is S, G, or R; X_4 is Q, C, E, V, or I; X_5 is S, L, P, G, A, R, or D; X_6 is V, G, or I; X_7 is S, E, D, or P; X_8 is S, P, F, A, M, E, V, N, D, or Y; X_9 is I, T, V, E, S, A, M, Q, Y, H, or R; X_{10} is Y or F; X_{11} is L, W, or P; X_{12} is A, S, or G, X_{13} is G or D; X_{14} is S or I; X_{15} is T or P; X_{16} is G, Q, E, L, F, A, S, M, R, K, or Y; X_{17} is S, R, T, G, R, V, D, A, H, E, K,	is G or S, X_2 is A or P; X_3 is T, N, or S; X_4 is I, V, T, H, L, A, or C; X_5 is S, D, G, T, I, L, F, M, or V; X_6 is G, Y, L, H, D, A, S, or M; X_7 is S, Q, T, A, F, or W; X_8 is G or T; X_9 is N, S, P, Y, W, or F; X_{10} is S, T, I, L, T, A, R, V, K, G, or C; X_{11} is F, Y, P, W, H, or G; X_{12} is V, R, or L; X_{13} is G or T; X_{14} is A or Y; X_{15} is A or S; and X_{16} is G, Q, L, P, or E (SEQ ID NO: 313); or EVQLLESGGGLVQPGGSLRLSCA ASGFTFX$_1$SYX$_2$MX$_3$WVRQAPGKG LEWVSAX$_4$X$_5$X$_6$X$_7$GX$_8$X$_9$X$_{10}$X$_{11}$YAD X$_{12}$X$_{13}$KGRFTISRDNSKNTLYLQMN SLRAEDTAVYYCARYWPMX$_{14}$X$_{15}$ WGQGTLVTVSS, wherein X_1 is G or S, X_2 is A or P; X_3 is T, N, or S; X_4 is I, V, T, H, L, A, or C; X_5 is S, D, G, T, I, L, F, M, or V; X_6 is G, Y, L, H, D, A, S, or M; X_7 is S, Q, T, A, F, or W; X_8 is G or T; X_9 is N, S, P, Y, W, or F; X_{10} is S, T, I, L, T, A, R, V, K, G, or C; X_{11} is F, Y, P, W, H, or G; X_{12} is V, R, or L; X_{13} is G or T; X_{14} is D, S, T, or A; and X_{15} is I, S, L, P, or D (SEQ ID NO: 314)

mAb	Light Chain	Heavy Chain
	C, F, or Y; X_{18} is W, S, or F; and X_{19} is L or I (SEQ ID NO: 316)	
P4G4	EIVLTQSPGTLSLSPGERATLSC**R** **ASQSVSSSYLA**WYQQKPGQAP RLLIY**GASSRAY**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YGSPPLFT**FGQGTKVEIK (SEQ ID NO: 80)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFSSYAMS**WVRQAPGKGLE WVSAI**SASGGSTYYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAR**LSWSGAFDN**WGQGTLVT VSS (SEQ ID NO: 363)
P1A11	EIVLTQSPGTLSLSPGERATLSC**R** **ASQNVSSSYLA**WYQQKPGQAP RLLIY**GASYRAT**GIPDRFSGSGS GTDFTLTISRLEPEDFAVYYC**QH** **YGSPPSFT**FGQGTKVEIK (SEQ ID NO: 364)	EVQLLESGGGLVQPGGSLRLSCA AS**GFTFRSYAMS**WVRQAPGKGLE WVSAI**SGSGGSTFYADSVKG**RFTI SRDNSKNTLYLQMNSLRAEDTAV YYCAT**VGTSGAFGI**WGQGTLVTV SS (SEQ ID NO: 365)

In Table 1, the underlined sequences are CDR sequences according to Kabat and in bold according to Chothia, except for the heavy chain CDR2 sequences, the Chothia CDR sequence is underlined and the Kabat CDR sequence is in bold

The invention also provides CDR portions of antibodies to BCMA (including Chothia, Kabat CDRs, and CDR contact regions). Determination of CDR regions is well within the skill of the art. It is understood that in some embodiments, CDRs can be a combination of the Kabat and Chothia CDR (also termed "combined CRs" or "extended CDRs"). In some embodiments, the CDRs are the Kabat CDRs. In other embodiments, the CDRs are the Chothia CDRs. In other words, in embodiments with more than one CDR, the CDRs may be any of Kabat, Chothia, combination CDRs, or combinations thereof. Table 2 provides examples of CDR sequences provided herein.

Table 2

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

H3.AQ For the following mAbs: P6E01/H3.AQ; L1.LGF/L3.KW/H3.AQ; L1.LGF/L3.PY/H3.AQ; L1.LGF/L3.NY/H3.AQ; L1.GDF/L3.KW/H3.AQ; L1.GDF/L3.PY/H3.AQ; L1.GDF/L3.NY/H3.AQ; L3.PY/H3.AQ; L3.PY/L1.PS/H3.AQ; L3.PY/L1.AH/H3.AQ; L3.PY/L1.FF/H3.AQ; L3.PY/L1.PH/H3.AQ; and L3.PY/L3.KF/H3.AQ.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYADSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIAAQMDY (SEQ ID NO: 135)

H3.AL For the following mAbs: L1.LGF/L3.KW/H3.AL; L1.LGF/L3.NY/H3.AL; and L1.GDF/L3.NY/H3.AL.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYADSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIAALMDY (SEQ ID NO: 136)
H3.AP For the following mAbs: L1.LGF/L3.KW/H3.AP; L1.LGF/L3.PY/H3.AP; L1.LGF/L3 NY/H3.AP; L1.GDF/L3.KW/H3.AP; and L1.GDF/L3 NY/H3.AP.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYADSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIAAPMDY (SEQ ID NO: 137)
H2.QR For the following mAbs: L3.PY/H2.QR; L3.PY/L1.PS/H2.QR; L3.PY/L1.A	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYADQRKG (SEQ ID NO: 138) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIASGMDY (SEQ ID NO: 134)

H/H2.QR; L3.PY/L1.FF/H2.QR; L3.PY/L1.PH/H2.QR; and L3.PY/L3.KY/H2.QR.			
H2.DY For the following mAbs: L3.PY/H2.DY; L3.PY/L1.PS/H2.DY; L3.PY/L1.AH/H2.DY; L3.PY/L1.FF/H2.DY; L3.PY/L3.KY/H2.DY; and L3.PY/L3.KF/H2.DY.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AIDYSGGNTFYADSVKG (SEQ ID NO: 139) (Kabat) DYSSGN (SEQ ID NO:140) (Chothia)	VSPIASGMDY (SEQ ID NO: 134)
H2.YQ For the following mAbs: L3.PY/H2.YQ;	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131)	AISYQGGNTFYADSVKG (SEQ ID NO: 141) (Kabat) SYQGGN (SEQ ID NO:142) (Chothia)	VSPIASGMDY (SEQ ID NO: 134)

L3.PY/L1.PS/H2.YQ; L3.PY/L1.AH/H2.YQ; L3.PY/L1.FF/H2.YQ; L3.PY/L3.KY/H2.YQ; and L3.PY/L3.KF/H2.YQ.	(extended)		
H2.LT For the following mAbs: L3.PY/H2.LT; L3.PY/L1.PS/H2.LT; L3.PY/L1.AH/H2.LT; L3.PY/L1.FF/H2.LT; L3.PY/L3.KY/H2.LT; and L3.PY/L3.KF/H2.LT.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISLTGGNTFYADSVKG (SEQ ID NO: 143) (Kabat) SLTGGN (SEQ ID NO:144) (Chothia)	VSPIASGMDY (SEQ ID NO: 134)
H2.HA For the following mAbs: L3.PY/H2.H	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ	AISHAGGNTFYADSVKG (SEQ ID NO: 145) (Kabat) SHAGGN (SEQ ID NO:146) (Chothia)	VSPIASGMDY (SEQ ID NO: 134)

A; L3.PY/L1.AH/H2.HA; L3.PY/L1.FF/H2.HA; L3.PY/L1.PH/H2.HA; and L3.PY/L3.KY/H2.HA.	ID NO: 131) (extended)		
H2.QL For the following mAbs: L3.PY/H2.QL; L3.PY/L1.PS/H2.QL; L3.PY/L1.AH/H2.QL; L3.PY/L1.FF/H2.QL; L3.PY/L3.KY/H2.QL; and L3.PY/L3.KF/H2.QL.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYADQLKG (SEQ ID NO: 147) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIASGMDY (SEQ ID NO: 134)
H3.YA For the following mAbs: L3.PY/H3.Y	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ	AISGSGGNTFYADSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIYAGMDY (SEQ ID NO: 148)

A; L3.PY/L1.PS/H3.YA; L3.PY/L1.AH/H3.YA; L3.PY/L1.FF/H3.YA; L3.PY/L3.KY/H3.YA; and L3.PY/L3.KF/H3.YA.	ID NO: 131) (extended)		
H3.AE For the following mAbs: L3.PY/H3.AE; L3.PY/L1.AH/H3.AE; L3.PY/L1.FF/H3.AE; L3.PY/L1.PH/H3.AE; and L3.PY/L3.KF/H3.AE.	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131) (extended)	AISGSGGNTFYADSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIAAEMDY (SEQ ID NO: 149)
H3.TAQ For the following mAbs: L3.PY/H3.TAQ;	SYAMT (SEQ ID NO: 129) (Kabat); GFTFGSY (SEQ ID NO: 130) (Chothia); GFTFGSYAMT (SEQ ID NO: 131)	AISGSGGNTFYADSVKG (SEQ ID NO: 132) (Kabat) SGSGGN (SEQ ID NO:133) (Chothia)	VSPIAAQMDY (SEQ ID NO: 135)

L3.PY/L1.PS/H3.TAQ; L3.PY/L1.AH/H3.TAQ; L3.PY/L1.FF/H3.TAQ; L3.PY/L1.PH/H3.TAQ; and L3.PY/L3.KF/H3.TAQ.	(extended)		
P5A2_VHVL and A02_Rd4_6nM_C03	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSTYYADSVKG (SEQ ID NO: 153) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMDI (SEQ ID NO: 155)
COMBO_Rd4_0.6nM_C17; COMBO_Rd4_0.6nM_C14; and COMBO_Rd4_0.6nM_C09	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLPYADSVKG (SEQ ID NO: 504) (Kabat) GGSGGS (SEQ ID NO: 159)(Chothia)	YWPMDI (SEQ ID NO: 155)

COMBO_Rd4_0.6nM_C29	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLPYADIVKG (SEQ ID NO:158) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDI (SEQ ID NO: 155)

C01_Rd4_6nM_C04; C01_Rd4_0.6nM_C03; C01_Rd4_0.6nM_C06; COMBO_Rd4_0.6nM_C02; COMBO_Rd4_6nM_C21; C01_Rd4_6nM_C26; COMBO_Rd4_0.6nM_C19; C01_Rd4_6nM_C24; C01_Rd4_6nM_C20; C01_Rd4_0.6nM_C09;	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLPYADSVKG (SEQ ID NO: 504) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)

COMBO_Rd4_0.6nM_C21; C01_Rd4_0.6nM_C04_C27; C01_Rd4_0.6nM_C16; C01_Rd4_6nM_C10; COMBO_Rd4_0.6nM_C20			
P5C1_VHVL and COMBO_Rd4_0.6nM_C30	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSTYYADSVKG (SEQ ID NO: 162) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)
A02_Rd4_0.6nM_C06	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152)	AISDSGGSAWYADSVKG (SEQ ID NO: 163) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMSL (SEQ ID NO: 164)

	(extended)		
A02_Rd4_0.6nM_C09	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSAWYADSVKG (SEQ ID NO: 163) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_0.6nM_C16	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDFGGSTYYADSVKG (SEQ ID NO: 165) (Kabat) SDFGGS (SEQ ID NO: 166) (Chothia)	YWPMDI (SEQ ID NO: 155)
A02_Rd4_6nM_C01	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AITASGGSTYYADSVKG (SEQ ID NO: 167) (Kabat) TASGGS (SEQ ID NO: 168) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_6nM_C26	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ	AISDSGGSTYYADSVKG (SEQ ID NO: 153) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMSL (SEQ ID NO: 164)

	ID NO: 152) (extended)		
A02_Rd4_6nM_C25	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSRWYADSVKG (SEQ ID NO: 169) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMTP (SEQ ID NO: 170)
A02_Rd4_6nM_C22	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AVLDSGGSTYYADSVKG (SEQ ID NO: 171) (Kabat) LDSGGS (SEQ ID NO: 172) (Chothia)	YWPMTP (SEQ ID NO: 170)
A02_Rd4_6nM_C19	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSRWYADSVKG (SEQ ID NO: 169) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMSD (SEQ ID NO: 173)
A02_Rd4_0.6nM_C03	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID	AISDSGGSKWYADSVKG (SEQ ID NO: 174) (Kabat) SDSGGS (SEQ ID NO: 154)	YWPMSL (SEQ ID NO: 164)

	NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	(Chothia)	
A02_Rd4_6nM_C07	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AIGGSGGSLPYADSVKG(SEQ ID NO: 504) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)
A02_Rd4_6nM_C23	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSGWYADSVKG (SEQ ID NO: 175) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_0.6nM_C18	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AVLDSGGSTYYADSVKG (SEQ ID NO: 171) (Kabat) LDSGGS (SEQ ID NO: 172) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_6nM_C1	SYAMN (SEQ ID NO: 150) (Kabat);	AISDSGGSCWYADSVKG (SEQ ID NO: 176) (Kabat)	YWPMTP (SEQ ID NO: 170)

0	GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	SDSGGS (SEQ ID NO: 154) (Chothia)	
A02_Rd4_6nM_C05	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AIFASGGSTYYADSVKG (SEQ ID NO: 177) (Kabat) FASGGS (SEQ ID NO: 178) (Chothia)	YWPMTP (SEQ ID NO: 170)
A02_Rd4_0.6nM_C10	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISGWGGSLPYADSVKG (SEQ ID NO: 304) (Kabat) SGWGGS (SEQ ID NO: 179) (Chothia)	YWPMDS (SEQ ID NO: 161)
A02_Rd4_6nM_C04	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AIMSSGGPLYYADSVKG (SEQ ID NO: 180) (Kabat) MSSGGP (SEQ ID NO: 181) (Chothia)	YWPMAL (SEQ ID NO: 182)
A02_Rd4_0.6nM_C26	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia);	AILMSGGSTYYADSVKG (SEQ ID NO: 183) (Kabat) LMSGGS (SEQ ID NO: 184) (Chothia)	YWPMSL (SEQ ID NO: 164)

	GFTFSSYAMN (SEQ ID NO: 152) (extended)		
A02_Rd4_0.6nM_C13	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGYRYYADSVKG (SEQ ID NO: 185) (Kabat) SDSGGY (SEQ ID NO: 186) (Chothia)	YWPMSL (SEQ ID NO: 164)
A02_Rd4_0.6nM_C01	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AILSSGGSTYYADSVKG (SEQ ID NO: 187) (Kabat) LSSGGS (SEQ ID NO: 188) (Chothia)	YWPMDI (SEQ ID NO: 155)
A02_Rd4_6nM_C08	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AILDSGGSTYYADSVKG (SEQ ID NO: 160) (Kabat) LDSGGS (SEQ ID NO: 172) (Chothia)	YWPMSP (SEQ ID NO: 189)
C01_Rd4_6nM_C12	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157)	AIGGSGGWSYYADSVKG (SEQ ID NO: 190) (Kabat) GGSGGW (SEQ ID NO: 191) (Chothia)	YWPMDS (SEQ ID NO: 161)

	(extended)		
C01_Rd4_6nM_C09	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	ATVGSGGSIGYADSVKG (SEQ ID NO: 192) (Kabat) VGSGGS (SEQ ID NO: 193) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_0.6nM_C22	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGSRWYADSVKG (SEQ ID NO: 169) (Kabat) SDSGGS (SEQ ID NO: 154) (Chothia)	YWPMDI (SEQ ID NO: 155)
COMBO_Rd4_0.6nM_C10	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSIHYADSVKG (SEQ ID NO: 194) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_0.6nM_C04	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ	AHIGSGGSTYYADSVKG (SEQ ID NO: 195) (Kabat) IGSGGS (SEQ ID NO: 196) (Chothia)	YWPMDS (SEQ ID NO: 161)

	ID NO: 157) (extended)		
COMBO_Rd4_0.6nM_C25	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSTYYADSVKG (SEQ ID NO: 162) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDP (SEQ ID NO: 197)
COMBO_Rd4_6nM_C21	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLPYADSVKG (SEQ ID NO: 504) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_6nM_C11	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLGYADSVKG (SEQ ID NO: 198) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_6nM_C09	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ	AIFASGGSTYYADSVKG (SEQ ID NO: 177) (Kabat) FASGGS (SEQ ID NO: 178) (Chothia)	YWPMDS (SEQ ID NO: 161)

	ID NO: 157) (extended)		
COMBO_Rd4_6nM_C08	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGTWTYYADSVKG (SEQ ID NO: 199) (Kabat) GGSGTW (SEQ ID NO: 200) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_0.6nM_C23	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	ALFGSGGSTYYADSVKG (SEQ ID NO: 201) (Kabat) FGSGGS (SEQ ID NO: 202) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_0.6nM_C12	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AALGSGGSTYYADSVKG (SEQ ID NO: 203) (Kabat) LGSGGS (SEQ ID NO: 204) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_6nM_C07	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AIGGSGGSLPYADSVKG (SEQ ID NO: 504) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMAD (SEQ ID NO: 205)

COMBO_Rd4_6nM_C02	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AISDSGGFVYYADSVKG (SEQ ID NO: 206) (Kabat) SDSGGF (SEQ ID NO: 207) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_6nM_C05	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	AIGGSGGSTYYADSVKG (SEQ ID NO: 162) (Kabat) GGSGGS (SEQ ID NO: 159) (Chothia)	YWPMSL (SEQ ID NO: 164)
COMBO_Rd4_6nM_C22 .	SYAMN (SEQ ID NO: 150) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMN (SEQ ID NO: 152) (extended)	ACLDSGGSTYYADSVKG (SEQ ID NO: 208) (Kabat) LDSGGS (SEQ ID NO: 172) (Chothia)	YWPMDS (SEQ ID NO: 161)
COMBO_Rd4_6nM_C11	SYPMS (SEQ ID NO: 156) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYPMS (SEQ ID NO: 157) (extended)	AALGSGGSTYYADSVKG (SEQ ID NO: 203) (Kabat) LGSGGS (SEQ ID NO: 204) (Chothia)	YWPMSL (SEQ ID NO: 164)
Heavy chain	SYX_1MX_2, wherein X_1 is A or P; and X_2	$AX_1X_2X_3X_4GX_5X_6X_7X_8YADX_9$ $X_{10}KG$, wherein X_1 is I, V, T,	$VSPIX_1X_2X_3MDY$; wherein X_1 is A or

consensus	is T, N, or S (Kabat) (SEQ ID NO: 301) GFTFX$_1$SY, wherein X$_1$ is G or S (Chothia) (SEQ ID NO: 302) GFTFX$_1$SYX$_2$MX$_3$, wherein X$_1$ is G or S, X$_2$ is A or P; and X$_3$ is T, N, or S (SEQ ID NO: 303) (extended)	H, L, A, or C; X$_2$ is S, D, G, T, I, L, F, M, or V; X$_3$ is G, Y, L, H, D, A, S, or M; X$_4$ is S, Q, T, A, F, or W; X$_5$ is G or T; X$_6$ is N, S, P, Y, W, or F; X$_7$ is S, T, I, L, A, R, V, K, G, or C; X$_8$ is F, Y, P, W, H, or G; X$_9$ is V, R, or L; and X$_{10}$ is G or T (Kabat) (SEQ ID NO: 305) X$_1$X$_2$X$_3$X$_4$X$_5$X$_6$, wherein X$_1$ is S, V, I, D, G, T, L, F, or M; X$_2$ is G, Y, L, H, D, A, S, or M; X$_3$ is S, G, F, or W; X$_4$ is G or S; X$_5$ is G or T; and X$_6$ is N, S, P, Y, or W (Chothia) (SEQ ID NO: 306)	Y; X$_2$ is A or S; and X$_3$ is G, Q, L, P, or E (SEQ ID NO: 307) YWPMX$_1$X$_2$, wherein X$_1$ is D, S, T, or A; and X$_2$ is I, S, L, P, or D (SEQ ID NO: 308)
P4G4	SYAMS (SEQ ID NO: 366) (Kabat); GFTFSSY (SEQ ID NO: 151) (Chothia); GFTFSSYAMS (SEQ ID NO: 367) (extended)	SASGGS (SEQ ID NO: 368) (Chothia) AISASGGSTYYADSVKG (SEQ ID NO: 369) (Kabat)	LSWSGAFDN (SEQ ID NO: 370)
P1A11	SYAMS (SEQ ID NO: 366) (Kabat); GFTFRSY (SEQ ID NO: 371) GFTFRSYAMS (SEQ ID NO: 372)	SGSGGS (SEQ ID NO: 359) (Chothia) AISGSGGSTFYADSVKG (SEQ ID NO: 360) (Kabat)	VGTSGAFGI (SEQ ID NO: 361)

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

L1.LGF/L3.NY/H3.AL; L1.LGF/L3.NY/H3.AP; and L1.LGF/L3.NY/H3AQ			
L1.GDF/L3.NY For the following mAbs: L1.GDF/L3.NY/P6E01; L1.GDF/L3.NY/H3.AL; L1.GDF/L3.NY/H3.AP; and L1.GDF/L3.NY/H3.AQ	RASQSVGDFYLA (SEQ ID NO: 215)	GASSRAT (SEQ ID NO: 210)	QHYNYPPSFT (SEQ ID NO: 214)
L1.LGF/L3.PY For the following mAbs: L1.LGF/L3.PY/H3.AP; and L1.LGF/L3	RASQSLGSFYLA (SEQ ID NO: 212)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)

.PY/H3.AQ			
L1.GDF/L3.KW For the following mAbs: L1.GDF/L3.KW/H3.AL; L1.GDF/L3.KW/H3.AP; and L1.GDF/L3.KW/H3.AQ	RASQSVGDFYLA (SEQ ID NO: 215)	GASSRAT (SEQ ID NO: 210)	KHYGWPPSFT (SEQ ID NO: 213)
L1.GDF/L3.PY/H3.AQ	RASQSVGDFYLA (SEQ ID NO: 215)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)
L3.KW/P6E01	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	KHYGWPPSFT (SEQ ID NO: 213)
L3.PY For the following mAbs: L3.PY/P6E01; L3.PY/H2.QR; L3.PY/H2.DY;	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)

L3.PY/H2.YQ; L3.PY/H2.LT; L3.PY/H2.HA; L3.PY/H2.QL; L3.PY/H3.YA; L3.PY/H3.AE; L3.PY/H3.AQ; L3.PY/H3.TAQ			
L3.NY/P6E01	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	QHYNYPPSFT (SEQ ID NO: 214)
L3.PY/L1.PS For the following mAbs: L3.PY/L1.PS/P6E01; L3.PY/L1.PS/H2.QR; L3.PY/L1.PS/H2.DY; L3.PY/L1.PS/H2.YQ;	RASQSVSSSYPS (SEQ ID NO: 217)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)

L3.PY/L1.PS/H2.LT; L3.PY/L1.PS/H2.HA; L3.PY/L1.PS/H2.QL; L3.PY/L1.PS/H3.YA; L3.PY/L1.PS/H3.AE; L3.PY/L1.PS/H3.AQ; L3.PY/L1.PS/H3.TAQ			
L3.PY/L1.AH For the following mAbs: L3.PY/L1.AH/P6E01; L3.PY/L1.AH/H2.QR; L3.PY/L1.AH/H2.DY; L3.PY/L1.AH/H2.YQ; L3.PY/L1.AH/H2.LT;	RASQSVSAHYLA (SEQ ID NO: 218)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)

L3.PY/L1.AH/H2.HA; L3.PY/L1.AH/H2.QL; L3.PY/L1.AH/H3.YA; L3.PY/L1.AH/H3.AE; L3.PY/L1.AH/H3.AQ; L3.PY/L1.AH/H3.TAQ			
L3.PY/L1.FF For the following mAbs: L3.PY/L1.FF/P6E01; L3.PY/L1.FF/H2.QR; L3.PY/L1.FF/H2.DY; L3.PY/L1.FF/H2.YQ; L3.PY/L1.FF/H2.LT; L3.PY/L1.FF/H2.HA;	RASQSVSSFFLA (SEQ ID NO: 219)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)

L3.PY/L1.FF/H2.QL; L3.PY/L1.FF/H3.YA; L3.PY/L1.FF/H3.AE; L3.PY/L1.FF/H3.AQ; and L3.PY/L1.FF/H3.TAQ			
L3.PY/L1.PH For the following mAbs: L3.PY/L1.PH/P6E01; L3.PY/L1.PH/H2.QR; L3.PY/L1.PH/H2.HA; L3.PY/L1.PH/H3.AE; L3.PY/L1.PH/H3.AQ; and L3.PY/L1.PH/H3.TAQ	RASQSVSPHYLA (SEQ ID NO: 219)	GASSRAT (SEQ ID NO: 210)	QHYPYPPSFT (SEQ ID NO: 216)

L3.PY/L3.KY For the following mAbs: L3.PY/L3.KY/P6E01; L3.PY/L3.KY/H2.QR; L3.PY/L3.KY/H2.DY; L3.PY/L3.KY/H2.YQ; L3.PY/L3.KY/H2.LT; L3.PY/L3.KY/H2.HA; L3.PY/L3.KY/H2.QL; L3.PY/L3.KY/H3.YA; and L3.PY/L3.KY/H3.TAQ	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	KYYPYPPSFT (SEQ ID NO: 220)

L3.PY/L3.KF For the following mAbs: L3.PY/L3.KF/H2.DY; L3.PY/L3.KF/H2.YQ; L3.PY/L3.KF/H2.LT; L3.PY/L3.KF/H2.QL; L3.PY/L3.KF/H3.YA; L3.PY/L3.KF/H3.AE; L3.PY/L3.KF/H3.AQ; and L3.PY/L3.KF/H3.TAQ	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAT (SEQ ID NO: 210)	KFYPYPPSFT (SEQ ID NO: 220)
P5A2_VHVL	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYGSWPLT (SEQ ID NO: 222)
A02_Rd4_0.6nM_C06	RASQSVSVIYLA (SEQ ID NO: 223)	DASIRAT (SEQ ID NO: 221)	QQYQRWPLT (SEQ ID NO: 224)
A02_Rd4_0.6nM	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)

_C09; COMBO _Rd_0.6 nM_C29 ; and COMBO _Rd4_0. 6nM_C2 1			
A02_Rd 4_6nM_ C16	RASQSVSDIYLA (SEQ ID NO: 226)	DASIRAT (SEQ ID NO: 221)	QQYQTWPLT (SEQ ID NO: 227)
A02_Rd 4_6nM_ C03	RASQSVSNIYLA (SEQ ID NO: 228)	DASIRAT (SEQ ID NO: 221)	QQYQGWPLT (SEQ ID NO: 229)
A02_Rd 4_6nM_ C01	RASQSVSAYYLA (SEQ ID NO: 230)	DASIRAT (SEQ ID NO: 221)	QQYERWPLT (SEQ ID NO: 231)
A02_Rd 4_6nM_ C26	RASQSVSSIYLA (SEQ ID NO: 232)	DASIRAT (SEQ ID NO: 221)	QQYQVWPLT (SEQ ID NO: 233)
A02_Rd 4_6nM_ C25	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYLDWPLT (SEQ ID NO: 234)
A02_Rd 4_6nM_ C22	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQVWPLT (SEQ ID NO: 233)
A02_Rd 4_6nM_ C19	RASQSVSVIYLA (SEQ ID NO: 223)	DASIRAT (SEQ ID NO: 221)	QQYLAWPLT (SEQ ID NO: 236)

A02_Rd 4_0.6nM _C03	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYFTWPLT (SEQ ID NO: 237)
A02_Rd 4_6nM_ C07	RASQSVSPYYLA (SEQ ID NO: 238)	DASIRAT (SEQ ID NO: 221)	QQYERWPLT (SEQ ID NO: 231)
A02_Rd 4_6nM_ C23	RASQSVSVEYLA (SEQ ID NO: 239)	DASIRAT (SEQ ID NO: 221)	QQYARWPLT (SEQ ID NO: 240)
A02_Rd 4_0.6nM _C18	RASQSVSEIYLA (SEQ ID NO: 241)	DASIRAT (SEQ ID NO: 221)	QQYFGWPLT (SEQ ID NO: 242)
A02_Rd 4_6nM_ C10	RASQSVEMSYLA (SEQ ID NO: 243)	DASIRAT (SEQ ID NO: 221)	QQYAHWPLT (SEQ ID NO: 244)
A02_Rd 4_6nM_ C05	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQRWPLT (SEQ ID NO: 224)
A02_Rd 4_0.6nM _C10	RASQSVSAQYLA (SEQ ID NO: 245)	DASIRAT (SEQ ID NO: 221)	QQYQRWPLT (SEQ ID NO: 224)
A02_Rd 4_6nM_ C04	RASQSVSAIYLA (SEQ ID NO: 235)	DASIRAT (SEQ ID NO: 221)	QQYQVWPLT (SEQ ID NO: 233)
A02_Rd 4_0.6nM _C26	GPSQSVSSSYLA (SEQ ID NO: 246)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
A02_Rd 4_0.6nM _C13	RASQSVSSSYWA (SEQ ID NO: 247)	DASIRAT (SEQ ID NO: 221)	QQYESWPLT (SEQ ID NO: 248)

A02_Rd 4_0.6nM _C01	RGGQSVSSSYLA (SEQ ID NO: 249)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
A02_Rd 4_6nM_ C08	RASQSVSFIYLA (SEQ ID NO: 250)	DASIRAT (SEQ ID NO: 221)	QQYGSWPLT (SEQ ID NO: 222)
P5C1_V HVL	RASQSVSSTYLA (SEQ ID NO: 251)	DASSRAP (SEQ ID NO: 252)	QQYSTSPLT (SEQ ID NO: 253)
C01_Rd 4_6nM_ C24	RASQSVSPEYLA (SEQ ID NO: 254)	DASSRAP (SEQ ID NO: 252)	QQYSVWPLT (SEQ ID NO: 255)
C01_Rd 4_6nM_ C26	RASQSVSAIYLA (SEQ ID NO: 235)	DASSRAP (SEQ ID NO: 252)	QQYSAWPLT (SEQ ID NO: 256)
C01_Rd 4_6nM_ C10	RASQSVSSVYLA (SEQ ID NO: 257)	DASSRAP (SEQ ID NO: 252)	QQYSTWPLT (SEQ ID NO: 258)
C01_Rd 4_0.6nM _C27	RASQSVSSTYLA (SEQ ID NO: 251)	DASSRAP (SEQ ID NO: 252)	QQYSRWPLT (SEQ ID NO: 259)
C01_Rd 4_6nM_ C20	RASQSVSPIYLA (SEQ ID NO: 260)	DASSRAP (SEQ ID NO: 252)	QQYSAFPLT (SEQ ID NO: 261)
C01_Rd 4_6nM_ C12	WLSQSVSSTYLA (SEQ ID NO: 262)	DASSRAP (SEQ ID NO: 252)	QQYSEWPLT (SEQ ID NO: 263)
C01_Rd 4_0.6nM _C16	RASQSVSSTYLA (SEQ ID NO: 251)	DASSRAP (SEQ ID NO: 252)	QQYSSWPLT (SEQ ID NO: 264)
C01_Rd	RASQSVSSIFLA	DASSRAP	QQYSAWPLT

4_0.6nM_C09	(SEQ ID NO: 265)	(SEQ ID NO: 252)	(SEQ ID NO: 256)
C01_Rd4_6nM_C09	ACSQSVSSTYLA (SEQ ID NO: 266)	DASSRAP (SEQ ID NO: 252)	QQYSAWPLT (SEQ ID NO: 256)
C01_Rd4_0.6nM_C03	RASCDVSSTYLA (SEQ ID NO: 267)	DASSRAP (SEQ ID NO: 252)	QQYMRSPLT (SEQ ID NO: 268)
C01_Rd4_0.6nM_C06	RASEAVPSTYLA (SEQ ID NO: 269)	DASSRAP (SEQ ID NO: 252)	QQYSAFPLT (SEQ ID NO: 261)
C01_Rd4_0.6nM_C04	CSSQSVSSTYLA (SEQ ID NO: 270)	DASSRAP (SEQ ID NO: 252)	QQYSAFPLT (SEQ ID NO: 261)
COMBO_Rd4_0.6nM_C22	RASVRVSSTYLA (SEQ ID NO: 271)	DASIRAT (SEQ ID NO: 221)	QQYMKWPLT (SEQ ID NO: 272)
COMBO_Rd4_6nM_C21	RASQSVSAAYLA (SEQ ID NO: 273)	DASIRAT (SEQ ID NO: 221)	QQYMCWPLT (SEQ ID NO: 274)
COMBO_Rd4_6nM_C10	RASQSVSSSYWG (SEQ ID NO: 275)	DASIRAT (SEQ ID NO: 221)	QQYQCWPLT (SEQ ID NO: 276)
COMBO_Rd4_0.6nM_C04	RASQSVSSTYLA (SEQ ID NO: 251)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)
COMBO_Rd4_6	RASQSVSSPYLA (SEQ ID NO: 277)	DASIRAT (SEQ ID NO: 221)	QQYQSWPLT (SEQ ID NO: 225)

nM_C25			
COMBO_Rd4_6nM_C11	RASQSVSPIYLA (SEQ ID NO: 260)	DASIRAT (SEQ ID NO: 221)	QQYKAWPLT (SEQ ID NO: 278)
COMBO_Rd4_0.6nM_C20	RASQSVSYLYLA (SEQ ID NO: 279)	DASIRAT (SEQ ID NO: 221)	QQYMEWPLT (SEQ ID NO: 280)
COMBO_Rd4_6nM_C09	RASQSVSAQYLA (SEQ ID NO: 245)	DASIRAT (SEQ ID NO: 221)	QQYQAWPLT (SEQ ID NO: 281)
COMBO_Rd4_6nM_C08	RASQSVSSSYLA (SEQ ID NO: 209)	DASIRAT (SEQ ID NO: 221)	QQYQKWPLT (SEQ ID NO: 282)
COMBO_Rd4_0.6nM_C19	RASQSVSAVYLA (SEQ ID NO: 283)	DASIRAT (SEQ ID NO: 221)	QQYRAWPLT (SEQ ID NO: 284)
COMBO_Rd4_0.6nM_C02	RASIAVSSTYLA (SEQ ID NO: 285)	DASIRAT (SEQ ID NO: 221)	QQYMVWPLT (SEQ ID NO: 286)
COMBO_Rd4_0.6nM_C23	RPRQSVSSSYLA (SEQ ID NO: 287)	DASIRAT (SEQ ID NO: 221)	QQYQDWPLT (SEQ ID NO: 288)
COMBO_Rd4_0.6nM_C09	RASQSVSSTYLA (SEQ ID NO: 251)	DASIRAT (SEQ ID NO: 221)	QQYQEWPLT (SEQ ID NO: 289)

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

6nM_C11			
Light chain consensus	$X_1X_2X_3X_4X_5X_6X_7X_8X_9X_{10}X_{11}X_{12}$, wherein X_1 is R, G, W, A, or C; X_2 is A, P, G, L, C, or S; X_3 is S, G, or R; X_4 is Q, C, E, V, or I; X_5 is S, P, G, A, R, or D; X_6 is V, G, I, or L; X_7 is S, E, D, P, or G; X_8 is S, P, F, A, M, E, V, N, D, or Y; X_9 is I, T, V, E, F S, A, M, Q, Y, H, or R; X_{10} is Y or F; X_{11} is L, W, or P; and X_{12} is A, S, or G (SEQ ID NO: 309)	$X_1ASX_2RAX_3$, wherein X_1 is G or D; X_2 is S or I; and X_3 is T or P (SEQ ID NO: 310)	$X_1X_2YX_3X_4PPSFT$, wherein X_1 is Q or K; X_2 is H or Y; X_3 is G, N, or P; and X_4 is S, W, or Y (SEQ ID NO: 311) $QQYX_1X_2X_3PX_4T$, wherein X_1 is G, Q, E, L, F, A, S, M, K, R, or Y; X_2 is S, R, T, G, V, F, Y, D, A, H, V, E, K, or C; X_3 is W, F, or S; and X_4 is L or I (SEQ ID NO: 312)
P4G4	RASQSVSSSYLA (SEQ ID NO: 209)	GASSRAY (SEQ ID NO: 362)	QHYGSPPLFT (SEQ ID NO: 499)
P1A11	RASQNVSSSYLA (SEQ ID NO: 500)	GASYRAT (SEQ ID NO: 501)	QHYGSPPSFT (SEQ ID NO: 211)

In some embodiments, the present invention provides an antibody that binds to BCMA and competes with the antibody as described herein, including P6E01/P6E01, P6E01/H3.AQ, L1.LGF/L3.KW/P6E01; L1.LGF/L3.NY/P6E01, L1.GDF/L3.NY/P6E01, L1.LGF/L3.KW/H3.AL, L1.LGF/L3.KW/H3.AP, L1.LGF/L3.KW/H3.AQ, L1.LGF/L3.PY/H3.AP, L1.LGF/L3.PY/H3.AQ, L1.LGF/L3.NY/H3.AL, L1.LGF/L3.NY/H3.AP, L1.LGF/L3.NY/H3.AQ, L1.GDF/L3.KW/H3.AL, L1.GDF/L3.KW/H3.AP, L1.GDF/L3.KW/H3.AQ, L1.GDF/L3.PY/H3.AQ,

L1.GDF/L3.NY/H3.AL, L1.GDF/L3.NY/H3.AP, L1.GDF/L3.NY/H3.AQ, L3.KW/P6E01, L3.PY/P6E01, L3.NY/P6E01,
L3.PY/L1.PS/P6E01, L3.PY/L1.AH/P6E01, L3.PY/L1.FF/P6E01, L3.PY/L1.PH/P6E01, L3.PY/L3.KY/P6E01, L3.PY/L3.KF/P6E01, L3.PY/H2.QR, L3.PY/H2.DY, L3.PY/H2.YQ, L3.PY/H2.LT, L3.PY/H2.HA, L3.PY/H2.QL, L3.PY/H3.YA, L3.PY/H3.AE, L3.PY/H3.AQ, L3.PY/H3.TAQ, L3.PY/P6E01, L3.PY/L1.PS/H2.QR, L3.PY/L1.PS/H2.DY, L3.PY/L1.PS/H2.YQ, L3.PY/L1.PS/H2.LT, L3.PY/L1.PS/H2.HA, L3.PY/L1.PS/H2.QL, L3.PY/L1.PS/H3.YA, L3.PY/L1.PS/H3.AE, L3.PY/L1.PS/H3.AQ, L3.PY/L1.PS/H3.TAQ, L3.PY/L1.AH/H2.QR, L3.PY/L1.AH/H2.DY, L3.PY/L1.AH/H2.YQ, L3.PY/L1.AH/H2.LT, L3.PY/L1.AH/H2.HA, L3.PY/L1.AH/H2.QL, L3.PY/L1.AH/H3.YA, L3.PY/L1.AH/H3.AE, L3.PY/L1.AH/H3.AQ, L3.PY/L1.AH/H3.TAQ, L3.PY/L1.FF/H2.QR, L3.PY/L1.FF/H2.DY, L3.PY/L1.FF/H2.YQ, L3.PY/L1.FF/H2.LT, L3.PY/L1.FF/H2.HA, L3.PY/L1.FF/H2.QL, L3.PY/L1.FF/H3.YA, L3.PY/L1.FF/H3.AE, L3.PY/L1.FF/H3.AQ, L3.PY/L1.FF/H3.TAQ, L3.PY/L1.PH/H2.QR, L3.PY/L1.PH/H2.HA, L3.PY/L1.PH/H3.AE, L3.PY/L1.PH/H3.AQ, L3.PY/L1.PH/H3.TAQ, L3.PY/L3.KY/H2.QR, L3.PY/L3.KY/H2.DY, L3.PY/L3.KY/H2.YQ L3.PY/L3.KY/H2.LT, L3.PY/L3.KY/H2.HA, L3.PY/L3.KY/H2.QL, L3.PY/L3.KY/H3.YA L3.PY/L3.KY/H3.TAQ, L3.PY/L3.KF/H2.DY, L3.PY/L3.KF/H2.YQ, L3.PY/L3.KF/H2.LT L3.PY/L3.KF/H2.QL, L3.PY/L3.KF/H3.YA, L3.PY/L3.KF/H3.AE, L3.PY/L3.KF/H3.AQ L3.PY/L3.KF/H3.TAQ, P5A2_VHVL, A02_Rd4_0.6nM_C06, A02_Rd4_0.6nM_C09 A02_Rd4_6nM_C16, A02_Rd4_6nM_C03, A02_Rd4_6nM_C01, A02_Rd4_6nM_C26 A02_Rd4_6nM_C25, A02_Rd4_6nM_C22, A02_Rd4_6nM_C19, A02_Rd4_0.6nM_C03 A02_Rd4_6nM_C07, A02_Rd4_6nM_C23, A02_Rd4_0.6nM_C18, A02_Rd4_6nM_C10 A02_Rd4_6nM_C05, A02_Rd4_0.6nM_C10, A02_Rd4_6nM_C04, A02_Rd4_0.6nM_C26 A02_Rd4_0.6nM_C13, A02_Rd4_0.6nM_C01, A02_Rd4_6nM_C08, P5C1_VHVL, C01_Rd4_6nM_C24, C01_Rd4_6nM_C26, C01_Rd4_6nM_C10, C01_Rd4_0.6nM_C27 C01_Rd4_6nM_C20, C01_Rd4_6nM_C12, C01_Rd4_0.6nM_C16, C01_Rd4_0.6nM_C09 C01_Rd4_6nM_C09, C01_Rd4_0.6nM_C03, C01_Rd4_0.6nM_C06, C01_Rd4_6nM_C04 COMBO_Rd4_0.6nM_C22, COMBO_Rd4_6nM_C21, COMBO_Rd4_6nM_C10, COMBO_Rd4_0.6nM_C04, COMBO_Rd4_6nM_C25, COMBO_Rd4_0.6nM_C21, COMBO_Rd4_6nM_C11, COMBO_Rd4_0.6nM_C20, COMBO_Rd4_6nM_C09, COMBO_Rd4_6nM_C08, COMBO_Rd4_0.6nM_C19, COMBO_Rd4_0.6nM_C02,

COMBO_Rd4_0.6nM_C23, COMBO_Rd4_0.6nM_C29, COMBO_Rd4_0.6nM_C09, COMBO_Rd4_6nM_C12, COMBO_Rd4_0.6nM_C30, COMBO_Rd4_0.6nM_C14, COMBO_Rd4_6nM_C07, COMBO_Rd4_6nM_C02, COMBO_Rd4_0.6nM_C05, COMBO_Rd4_0.6nM_C17, COMBO_Rd4_6nM_C22, COMBO_Rd4_0.6nM_C11, COMBO_Rd4_0.6nM_C29, P4G4, or P1A11.

In some embodiments, the present invention provides an antibody or an antigen binding fragment, which specifically binds to BCMA, wherein the antibody comprises a VH region comprising a sequence shown in SEQ ID NO: 112; and/or a VL region comprising a sequence shown in SEQ ID NO: 38. In some embodiments, the antibody comprises a light chain comprising the sequence EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLMYDASIRATGIP DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYQSWPLTFGQGTKVEIKRTVAAPSVFIFPP SDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTL TLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC (SEQ ID NO: 357) and a heavy chain comprising the sequence EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYPMSWVRQAPGKGLEWVSAIGGSGGSL PYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARYWPMDIWGQGTLVTVSSAS TKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPS VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEM TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRW QQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 358).

In some embodiments, the present invention provides an antibody or an antigen binding fragment, which specifically bind to BCMA, wherein the antibody comprises a VH region comprising a sequence shown in SEQ ID NO: 2, 32, 42, or 78; and/or a VL region comprising a sequence shown in SEQ ID NO: 6, 16, 43, or 85, .

The binding affinity (K_D) of the BCMA antibody as described herein to BCMA (such as human BCMA (e.g., (SEQ ID NO: 353) can be about 0.002 nM to about 6500 nM. In some embodiments, the binding affinity is about any of 6500 nm, 6000 nm, 5986 nm, 5567

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

In some embodiments, the invention encompasses compositions, including pharmaceutical compositions, comprising antibodies described herein or made by the methods and having the characteristics described herein. As used herein, compositions comprise one or more antibodies that bind to BCMA, and/or one or more polynucleotides comprising sequences encoding one or more these antibodies. These compositions may further comprise suitable excipients, such as pharmaceutically acceptable excipients including buffers, which are well known in the art.

The invention also provides methods of making any of these antibodies. The antibodies of this invention can be made by procedures known in the art. The polypeptides can be produced by proteolytic or other degradation of the antibodies, by recombinant methods (i.e., single or fusion polypeptides) as described above or by chemical synthesis. Polypeptides of the antibodies, especially shorter polypeptides up to about 50 amino acids, are conveniently made by chemical synthesis. Methods of chemical synthesis are known in the art and are commercially available. For example, an antibody could be produced by an automated polypeptide synthesizer employing the solid phase method. See also, U.S. Pat. Nos. 5,807,715; 4,816,567; and 6,331,415.

The invention also encompasses fusion proteins comprising one or more fragments or regions from the antibodies of this invention. In one embodiment, a fusion polypeptide is provided that comprises at least 10 contiguous amino acids of the variable light chain region shown in SEQ ID NOs: 1, 4, 5, 6, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 34, 36, 38, 40, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 317, 81, 82, 84, 85, 86, 88, 89, 90, 91, 93, 94, 96, 98, 100, 102, 103, 105, 107,

108, 109, 111, 113, 115, 116, 117, 119, 121, 123, 124, 126, 128, 80, 315, 36, or 364, and/or at least 10 amino acids of the variable heavy chain region shown in SEQ ID NOs: 2, 3, 7, 8, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 37, 39, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 83, 87, 92, 95, 97, 99, 101, 104, 106, 110, 112, 114, 118, 120, 122, 112, 125, 127, 313, 314, 363, or 365. In other embodiments, a fusion polypeptide is provided that comprises at least about 10, at least about 15, at least about 20, at least about 25, or at least about 30 contiguous amino acids of the variable light chain region and/or at least about 10, at least about 15, at least about 20, at least about 25, or at least about 30 contiguous amino acids of the variable heavy chain region. In another embodiment, the fusion polypeptide comprises a light chain variable region and/or a heavy chain variable region, as shown in any of the sequence pairs selected from among SEQ ID NOs: 1 and 2, 1 and 3, 4 and 2, 5 and 2, 6 and 2, 4 and 7, 4 and 8, 4 and 3, 9 and 8, 9 and 3, 10 and 7, 10 and 8, 10 and 3, 11 and 7, 11 and 8, 11 and 3, 12 and 3, 13 and 7, 13 and 8, 14 and 3, 15 and 2, 16 and 2, 17 and 2, 18 and 2, 19 and 2, 20 and 2, 21 and 2, 22 and 2, 23 and 2, 16 and 24, 16 and 25, 16 and 26, 16 and 27, 16 and 28, 16 and 29, 16 and 30, 16 and 31, 16 and 3, 16 and 32, 16 and 2, 18 and 24, 18 and 25, 18 and 26, 18 and 27, 18 and 28, 18 and 29, 18 and 30, 18 and 31, 18 and 3, 18 and 32, 19 and 24, 19 and 25, 19 and 26, 19 and 27, 19 and 28, 19 and 29, 19 and 30, 19 and 31, 19 and 3, 19 and 32, 20 and 24, 20 and 25, 20 and 26, 20 and 27, 20 and 28, 20 and 29, 20 and 30, 20 and 31, 20 and 3, 20 and 32, 21 and 24, 21 and 28, 21 and 31, 21 and 3, 21 and 32, 22 and 24, 22 and 25, 22 and 26, 22 and 27, 22 and 28, 22 and 29, 22 and 30, 22 and 32, 23 and 25, 23 and 26, 23 and 27, 23 and 29, 23 and 30, 23 and 31, 23 and 3, 23 and 32, 34 and 33, 36 and 35, 38 and 37, 40 and 39, 41 and 33, 43 and 42, 45 and 44, 47 and 46, 49 and 48, 51 and 50, 53 and 52, 55 and 54, 57 and 56, 59 and 58, 61 and 60, 63 and 62, 65 and 64, 67 and 66, 69 and 68, 71 and 70, 73 and 72, 75 and 74, 77 and 76, 79 and 78, 317 and 78, 79 and 78, 81 and 78, 82 and 78, 84 and 83, 85 and 78, 86 and 78, 88 and 87, 89 and 78, 90 and 78, 91 and 78, 93 and 92, 94 and 78, 96 and 95, 98 and 97, 38 and 78, 102 and 101, 103 and 78, 105 and 104, 107 and 106, 108 and 78, 109 and 78, 111 and 110, 38 and 112, 113 and 112, 115 and 114, 116 and 76, 117 and 112, 119 and 118, 121 and 120, 123 and 122, 124 and 112, 126 and 125,

128 and 127, 80 and 363, or 364 and 365. In another embodiment, the fusion polypeptide comprises one or more CDR(s). In still other embodiments, the fusion polypeptide comprises CDR H3 (VH CDR3) and/or CDR L3 (VL CDR3). For purposes of this invention, a fusion protein contains one or more antibodies and another amino acid sequence to which it is not attached in the native molecule, for example, a heterologous sequence or a homologous sequence from another region. Exemplary heterologous sequences include, but are not limited to a "tag" such as a FLAG tag or a 6His tag. Tags are well known in the art.

The invention also provides isolated polynucleotides encoding the antibodies of the invention, and vectors and host cells comprising the polynucleotide.

In one embodiment, a polynucleotide comprises a sequence encoding the heavy chain and/or the light chain variable regions of antibody P6E01/P6E01, P6E01/H3.AQ, L1.LGF/L3.KW/P6E01; L1.LGF/L3.NY/P6E01, L1.GDF/L3.NY/P6E01, L1.LGF/L3.KW/H3.AL, L1.LGF/L3.KW/H3.AP, L1.LGF/L3.KW/H3.AQ, L1.LGF/L3.PY/H3.AP, L1.LGF/L3.PY/H3.AQ, L1.LGF/L3.NY/H3.AL, L1.LGF/L3.NY/H3.AP, L1.LGF/L3.NY/H3.AQ, L1.GDF/L3.KW/H3.AL, L1.GDF/L3.KW/H3.AP, L1.GDF/L3.KW/H3.AQ, L1.GDF/L3.PY/H3.AQ, L1.GDF/L3.NY/H3.AL, L1.GDF/L3.NY/H3.AP, L1.GDF/L3.NY/H3.AQ, L3.KW/P6E01, L3.PY/P6E01, L3.NY/P6E01, L3.PY/L1.PS/P6E01, L3.PY/L1.AH/P6E01, L3.PY/L1.FF/P6E01, L3.PY/L1.PH/P6E01, L3.PY/L3.KY/P6E01, L3.PY/L3.KF/P6E01, L3.PY/H2.QR, L3.PY/H2.DY, L3.PY/H2.YQ, L3.PY/H2.LT, L3.PY/H2.HA, L3.PY/H2.QL, L3.PY/H3.YA, L3.PY/H3.AE, L3.PY/H3.AQ, L3.PY/H3.TAQ, L3.PY/P6E01, L3.PY/L1.PS/H2.QR, L3.PY/L1.PS/H2.DY, L3.PY/L1.PS/H2.YQ, L3.PY/L1.PS/H2.LT, L3.PY/L1.PS/H2.HA, L3.PY/L1.PS/H2.QL, L3.PY/L1.PS/H3.YA, L3.PY/L1.PS/H3.AE, L3.PY/L1.PS/H3.AQ, L3.PY/L1.PS/H3.TAQ, L3.PY/L1.AH/H2.QR, L3.PY/L1.AH/H2.DY, L3.PY/L1.AH/H2.YQ, L3.PY/L1.AH/H2.LT, L3.PY/L1.AH/H2.HA, L3.PY/L1.AH/H2.QL, L3.PY/L1.AH/H3.YA, L3.PY/L1.AH/H3.AE, L3.PY/L1.AH/H3.AQ, L3.PY/L1.AH/H3.TAQ, L3.PY/L1.FF/H2.QR, L3.PY/L1.FF/H2.DY, L3.PY/L1.FF/H2.YQ, L3.PY/L1.FF/H2.LT, L3.PY/L1.FF/H2.HA, L3.PY/L1.FF/H2.QL, L3.PY/L1.FF/H3.YA, L3.PY/L1.FF/H3.AE, L3.PY/L1.FF/H3.AQ, L3.PY/L1.FF/H3.TAQ,

L3.PY/L1.PH/H2.QR, L3.PY/L1.PH/H2.HA, L3.PY/L1.PH/H3.AE, L3.PY/L1.PH/H3.AQ, L3.PY/L1.PH/H3.TAQ, L3.PY/L3.KY/H2.QR, L3.PY/L3.KY/H2.DY, L3.PY/L3.KY/H2.YQ L3.PY/L3.KY/H2.LT, L3.PY/L3.KY/H2.HA, L3.PY/L3.KY/H2.QL, L3.PY/L3.KY/H3.YA L3.PY/L3.KY/H3.TAQ, L3.PY/L3.KF/H2.DY, L3.PY/L3.KF/H2.YQ, L3.PY/L3.KF/H2.LT L3.PY/L3.KF/H2.QL, L3.PY/L3.KF/H3.YA, L3.PY/L3.KF/H3.AE, L3.PY/L3.KF/H3.AQ L3.PY/L3.KF/H3.TAQ, P5A2_VHVL, A02_Rd4_0.6nM_C06, A02_Rd4_0.6nM_C09 A02_Rd4_6nM_C16, A02_Rd4_6nM_C03, A02_Rd4_6nM_C01, A02_Rd4_6nM_C26 A02_Rd4_6nM_C25, A02_Rd4_6nM_C22, A02_Rd4_6nM_C19, A02_Rd4_0.6nM_C03 A02_Rd4_6nM_C07, A02_Rd4_6nM_C23, A02_Rd4_0.6nM_C18, A02_Rd4_6nM_C10 A02_Rd4_6nM_C05, A02_Rd4_0.6nM_C10, A02_Rd4_6nM_C04, A02_Rd4_0.6nM_C26 A02_Rd4_0.6nM_C13, A02_Rd4_0.6nM_C01, A02_Rd4_6nM_C08, P5C1_VHVL, C01_Rd4_6nM_C24, C01_Rd4_6nM_C26, C01_Rd4_6nM_C10, C01_Rd4_0.6nM_C27 C01_Rd4_6nM_C20, C01_Rd4_6nM_C12, C01_Rd4_0.6nM_C16, C01_Rd4_0.6nM_C09 C01_Rd4_6nM_C09, C01_Rd4_0.6nM_C03, C01_Rd4_0.6nM_C06, C01_Rd4_6nM_C04 COMBO_Rd4_0.6nM_C22, COMBO_Rd4_6nM_C21, COMBO_Rd4_6nM_C10, COMBO_Rd4_0.6nM_C04, COMBO_Rd4_6nM_C25, COMBO_Rd4_0.6nM_C21, COMBO_Rd4_6nM_C11, COMBO_Rd4_0.6nM_C20, COMBO_Rd4_6nM_C09, COMBO_Rd4_6nM_C08, COMBO_Rd4_0.6nM_C19, COMBO_Rd4_0.6nM_C02, COMBO_Rd4_0.6nM_C23, COMBO_Rd4_0.6nM_C29, COMBO_Rd4_0.6nM_C09, COMBO_Rd4_6nM_C12, COMBO_Rd4_0.6nM_C30, COMBO_Rd4_0.6nM_C14, COMBO_Rd4_6nM_C07, COMBO_Rd4_6nM_C02, COMBO_Rd4_0.6nM_C05, COMBO_Rd4_0.6nM_C17, COMBO_Rd4_6nM_C22, COMBO_Rd4_0.6nM_C11, COMBO_Rd4_0.6nM_C29, P4G4, or P1A11. The sequence encoding the antibody of interest may be maintained in a vector in a host cell and the host cell can then be expanded and frozen for future use. Vectors (including expression vectors) and host cells are further described herein.

The invention also encompasses scFv of antibodies of this invention. Single chain variable region fragments are made by linking light and/or heavy chain variable regions by using a short linking peptide (Bird et al., Science 242:423-426, 1988). An example of a linking peptide is $(GGGGS)_3$ (SEQ ID NO: 498), which bridges approximately 3.5 nm between the carboxy terminus of one variable region and the amino terminus of the other

variable region. Linkers of other sequences have been designed and used (Bird et al., 1988, supra). Linkers should be short, flexible polypeptides and preferably comprised of less than about 20 amino acid residues. Linkers can in turn be modified for additional functions, such as attachment of drugs or attachment to solid supports. The single chain variants can be produced either recombinantly or synthetically. For synthetic production of scFv, an automated synthesizer can be used. For recombinant production of scFv, a suitable plasmid containing polynucleotide that encodes the scFv can be introduced into a suitable host cell, either eukaryotic, such as yeast, plant, insect or mammalian cells, or prokaryotic, such as E. coli. Polynucleotides encoding the scFv of interest can be made by routine manipulations such as ligation of polynucleotides. The resultant scFv can be isolated using standard protein purification techniques known in the art.

Other forms of single chain antibodies, such as diabodies or minibodies are also encompassed. Diabodies are bivalent, bispecific antibodies in which heavy chain variable (VH) and light chain variable (VL) domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see e.g., Holliger, P., et al., Proc. Natl. Acad Sci. USA 90:6444-6448, 1993; Poljak, R. J., et al., Structure 2:1121-1123, 1994). Minibody includes the VL and VH domains of a native antibody fused to the hinge region and CH3 domain of the immunoglobulin molecule. See, e.g., US5,837,821.

In another aspect, the invention provides compositions (such as a pharmaceutical compositions) comprising any of the polynucleotides of the invention. In some embodiments, the composition comprises an expression vector comprising a polynucleotide encoding any of the antibodies described herein. In still other embodiments, the composition comprises either or both of the polynucleotides shown in SEQ ID NO: 486 and SEQ ID NO: 485 below:

COMBO_Rd4_0.6nM_C29 heavy chain variable region

GAAGTCCAACTCCTCGAATCCGGTGGCGGCCTTGTCCAGCCTGGAGGTTCCTTGCGC
CTGTCATGTGCCGCCAGCGGATTCACCTTCTCGTCCTACCCGATGTCGTGGGTCCGC
CAGGCTCCGGGAAAGGGCCTGGAATGGGTGTCAGCCATCGGAGGATCGGGGGGCT
CCCTGCCCTACGCCGATATCGTGAAGGGAAGGTTCACCATTAGCCGGGACAACTCCA

AGAACACTCTGTACCTCCAAATGAACAGCCTGAGAGCGGAGGACACCGCAGTGTACT
ATTGCGCCCGGTACTGGCCAATGGACATCTGGGGCCAGGGGACTCTGGTCACCGTC
TCCTCA (SEQ ID NO: 486)

COMBO_Rd4_0.6nM_C29 light chain variable region

GAGATCGTGCTGACTCAGTCCCCTGGAACCCTGTCCCTGTCACCTGGCGAAAGAGCT
ACCTTGTCCTGTCGCGCATCACAATCCGTGTCGTCGAGCTATCTCGCGTGGTACCAG
CAGAAGCCCGGACAGGCCCCAAGGCTGCTTATGTACGACGCCTCCATCCGGGCCAC
TGGTATCCCCGACCGCTTCTCGGGCTCCGGAAGCGGCACCGACTTCACCCTGACTAT
TTCCCGGCTCGAACCGGAGGATTTCGCCGTGTACTACTGCCAACAGTACCAGAGCTG
GCCGCTGACGTTTGGGCAGGGGACCAAGGTCGAAATCAAA
(SEQ ID NO: 485)

In other embodiments, the composition comprises either or both of the polynucleotides shown in SEQ ID NO: 488 and SEQ ID NO: 487 below:

L3.PY/H3TAQ heavy chain variable region

GAAGTGCAGCTGCTGGAATCTGGCGGAGGACTGGTGCAGCCTGGCGGCTCTCTGAG
ACTGTCTTGTGCCGCCAGCGGCTTCACCTTCGGCAGCTACGCTATGACCTGGGTGCG
CCAGGCCCCTGGCAAAGGACTGGAATGGGTGTCCGCCATCTCTGGCAGCGGCGGCA
ATACCTTCTACGCCGAGAGCGTGAAGGGCCGGTTCACCATCAGCCGGGACAACAGC
AAGAACACCCTGTACCTGCAGATGAACAGCCTGCGGGCCGAGGACACCGCCGTGTA
CTATTGTACACGGGTGTCCCCTATCGCCGCGCAGATGGATTATTGGGGCCAGGGCAC
TCTGGTCACCGTCTCCTCA
(SEQ ID NO: 488)

L3.PY/H3TAQ heavy chain variable region

GAGATCGTGCTGACACAGAGCCCTGGCACCCTGAGCCTGTCTCCAGGCGAAAGAGC
CACCCTGTCCTGCAGAGCCAGCCAGAGCGTGTCCAGCAGCTACCTGGCCTGGTATC
AGCAGAAGCCCGGCCAGGCTCCCCGGCTGCTGATCTATGGCGCCTCTTCTAGAGCC
ACCGGCATCCCCGATAGATTCAGCGGCTCTGGCAGCGGCACCGACTTCACCCTGAC
CATCAGCAGACTGGAACCCGAGGACTTCGCCGTGTACTACTGCCAGCACTACCCTTA
TCCCCCCAGCTTCACATTTGGCCAGGGCACCAAGGTGGAGATCAAA
(SEQ ID NO: 487)

In still other embodiments, the composition comprises either or both of the polynucleotides shown in SEQ ID NO: 490 and SEQ ID NO: 489 below:

A02_Rd4_0.6nM_C01 *heavy chain variable region*

GAAGTTCAATTATTGGAATCTGGTGGAGGACTGGTGCAGCCTGGCGGCTCTCTGAGA
CTGTCTTGTGCCGCCAGCGGCTTCACCTTCAGCAGCTACGCCATGAACTGGGTGCGC
CAGGCCCCTGGTAAAGGTTTGGAATGGGTTTCTGCTATTACTGCGTCTGGTGGTTCTA
CTTACTATGCCGATGTGGTTAAGGGTAGATTCACCATTTCTAGAGACAACTCTAAGAA
CACCTTGTACTTGCAAATGAACTCCTTGAGAGCTGAAGATACTGCTGTTTATTACTGTG
CTAGATACTGGCCAATGTCGTTGTGGGGTCAAGGTACTCTGGTCACCGTCTCCTCA
(SEQ ID NO: 490)

A02_Rd4_0.6nM_C01 *light chain variable region*

GAGATCGTGCTGACACAGAGCCCTGGCACCCTGAGCCTGTCTCCTGGTGAAAGAGCT
ACTTTGTCTTGTAGAGCTTCTCAATCCGTTTCCGCGTATTATTTGGCTTGGTATCAACA
AAAACCAGGTCAAGCTCCAAGATTATTGATGTACGATGCTTCTATTAGAGCCACCGGT
ATTCCAGATAGATTTTCTGGTTCTGGTTCCGGTACTGATTTCACTTTGACTATCTCTAG
ATTGGAACCAGAAGATTTCGCTGTTTACTACTGTCAACAATATGAGCGTTGGCCATTG
ACTTTTGGTCAAGGTACAAAGGTTGAAATCAAACGTGAG
(SEQ ID NO: 489)

In other embodiments, the composition comprises either or both of the polynucleotides shown in SEQ ID NO: 492 and SEQ ID NO: 491 below:

A02_Rd4_0.6nM_C16 *heavy chain variable region*

GAAGTTCAATTATTGGAATCTGGTGGAGGACTGGTGCAGCCTGGCGGCTCTCTGAGA
CTGTCTTGTGCCGCCAGCGGCTTCACCTTCAGCAGCTACGCCATGAACTGGGTGCGC
CAGGCCCCTGGTAAAGGTTTGGAATGGGTTTCTGCTATTTCTGATTTTGGTGGTTCTA
CTTACTATGCCGATATCGTTAAGGGTAGATTCACCATTTCTAGAGACAACTCTAAGAAC
ACCTTGTACTTGCAAATGAACTCCTTGAGAGCTGAAGATACTGCTGTTTATTACTGTGC
TAGATACTGGCCAATGGATATTTGGGGTCAAGGTACTCTGGTCACCGTCTCCTCA
(SEQ ID NO: 492)

A02_Rd4_0.6nM_C16 *light chain variable region*

GAGATCGTGCTGACACAGAGCCCTGGCACCCTGAGCCTGTCTCCTGGTGAAAGAGCT
ACTTTGTCTTGTAGAGCTTCTCAATCCGTTTCCGATCTGTATTTGGCTTGGTATCAACA

AAAACCAGGTCAAGCTCCAAGATTATTGATGTACGATGCTTCTATTAGAGCCACCGGT
ATTCCAGATAGATTTTCTGGTTCTGGTTCCGGTACTGATTTCACTTTGACTATCTCTAG
ATTGGAACCAGAAGATTTCGCTGTTTACTACTGTCAACAATATCAGACTTGGCCATTGA
CTTTTGGTCAAGGTACAAAGGTTGAAATCAAACGTGAG

(SEQ ID NO: 491).

Expression vectors are further described herein.

In another aspect, the invention provides a method of making any of the polynucleotides described herein.

Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes an antibody or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants contain one or more substitutions, additions, deletions and/or insertions such that the immunoreactivity of the encoded polypeptide is not diminished, relative to a native immunoreactive molecule. The effect on the immunoreactivity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably, at least about 80% identity, yet more preferably, at least about 90% identity, and most preferably, at least about 95% identity to a polynucleotide sequence that encodes a native antibody or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein,

refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, or 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O., 1978, A model of evolutionary change in proteins - Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J., 1990, Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M., 1989, CABIOS 5:151-153; Myers, E.W. and Muller W., 1988, CABIOS 4:11-17; Robinson, E.D., 1971, Comb. Theor. 11:105; Santou, N., Nes, M., 1987, Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R., 1973, Numerical Taxonomy the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J., 1983, Proc. Natl. Acad. Sci. USA 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e., gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing

under moderately stringent conditions to a naturally occurring DNA sequence encoding a native antibody (or a complementary sequence).

Suitable "moderately stringent conditions" include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1 % SDS.

As used herein, "highly stringent conditions" or "high stringency conditions" are those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

The polynucleotides of this invention can be obtained using chemical synthesis, recombinant methods, or PCR. Methods of chemical polynucleotide synthesis are well known in the art and need not be described in detail herein. One of skill in the art can use the sequences provided herein and a commercial DNA synthesizer to produce a desired DNA sequence.

For preparing polynucleotides using recombinant methods, a polynucleotide comprising a desired sequence can be inserted into a suitable vector, and the vector in turn can be introduced into a suitable host cell for replication and amplification, as further discussed herein. Polynucleotides may be inserted into host cells by any means known in the art. Cells are transformed by introducing an exogenous polynucleotide by direct uptake, endocytosis, transfection, F-mating or electroporation. Once introduced, the exogenous polynucleotide can be maintained within the cell as a non-integrated vector (such as a plasmid) or integrated into the host cell genome. The polynucleotide so amplified can be isolated from the host cell by methods well known within the art. See, e.g., Sambrook et al., 1989.

Alternatively, PCR allows reproduction of DNA sequences. PCR technology is well known in the art and is described in U.S. Patent Nos. 4,683,195, 4,800,159, 4,754,065 and 4,683,202, as well as PCR: The Polymerase Chain Reaction, Mullis et al. eds., Birkauswer Press, Boston, 1994.

RNA can be obtained by using the isolated DNA in an appropriate vector and inserting it into a suitable host cell. When the cell replicates and the DNA is transcribed into RNA, the RNA can then be isolated using methods well known to those of skill in the art, as set forth in Sambrook et al., 1989, supra, for example.

Suitable cloning vectors may be constructed according to standard techniques, or may be selected from a large number of cloning vectors available in the art. While the cloning vector selected may vary according to the host cell intended to be used, useful cloning vectors will generally have the ability to self-replicate, may possess a single target for a particular restriction endonuclease, and/or may carry genes for a marker that can be used in selecting clones containing the vector. Suitable examples include plasmids and bacterial viruses, e.g., pUC18, pUC19, Bluescript (e.g., pBS SK+) and its derivatives, mp18, mp19, pBR322, pMB9, ColE1, pCR1, RP4, phage DNAs, and shuttle vectors such

as pSA3 and pAT28. These and many other cloning vectors are available from commercial vendors such as BioRad, Strategene, and Invitrogen.

Expression vectors generally are replicable polynucleotide constructs that contain a polynucleotide according to the invention. It is implied that an expression vector must be replicable in the host cells either as episomes or as an integral part of the chromosomal DNA. Suitable expression vectors include but are not limited to plasmids, viral vectors, including adenoviruses, adeno-associated viruses, retroviruses, cosmids, and expression vector(s) disclosed in PCT Publication No. WO 87/04462. Vector components may generally include, but are not limited to, one or more of the following: a signal sequence; an origin of replication; one or more marker genes; suitable transcriptional controlling elements (such as promoters, enhancers and terminator). For expression (i.e., translation), one or more translational controlling elements are also usually required, such as ribosome binding sites, translation initiation sites, and stop codons.

The vectors containing the polynucleotides of interest can be introduced into the host cell by any of a number of appropriate means, including electroporation, transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (e.g., where the vector is an infectious agent such as vaccinia virus). The choice of introducing vectors or polynucleotides will often depend on features of the host cell.

The invention also provides host cells comprising any of the polynucleotides described herein. Any host cells capable of over-expressing heterologous DNAs can be used for the purpose of isolating the genes encoding the antibody, polypeptide or protein of interest. Non-limiting examples of mammalian host cells include but not limited to COS, HeLa, and CHO cells. See also PCT Publication No. WO 87/04462. Suitable non-mammalian host cells include prokaryotes (such as *E. coli* or *B. subtillis*) and yeast (such as *S. cerevisae*, *S. pombe*; or *K. lactis*). Preferably, the host cells express the cDNAs at a level of about 5 fold higher, more preferably, 10 fold higher, even more preferably, 20 fold higher than that of the corresponding endogenous antibody or protein of interest, if present, in the host cells. Screening the host cells for a specific binding to BCMA or an BCMA domain (e.g., domains 1-4) is effected by an immunoassay or FACS. A cell overexpressing the antibody or protein of interest can be identified.

Representative materials of the present invention were deposited in the American Type Culture Collection (ATCC) on April 15, 2015. Vector having ATCC Accession No. PTA-122094 is a polynucleotide encoding the heavy chain variable region of humanized BCMA antibody COMBO_Rd4_0.6nM_C29, and vector having ATCC Accession No. PTA-122093 is a polynucleotide encoding the light chain variable region of humanized BCMA antibody COMBO_Rd4_0.6nM_C29. The deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposit will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Pfizer, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 U.S.C. Section 122 and the Commissioner's rules pursuant thereto (including 37 C.F.R. Section 1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

BCMA Antibody Conjugates

The present invention also provides a conjugate (or immunoconjugate) of the BCMA antibody as described herein, or of the antigen binding fragment thereof, wherein the antibody or the antigen binding fragment is conjugated to an agent (e.g., a cytotoxic agent) (e.g., antibody-drug conjugates) either directly or indirectly via a linker. For example, a cytotoxic agent can be linked or conjugated to the BCMA antibody or the antigen binding fragment thereof as described herein.

Methods for conjugating cytotoxic agent or other therapeutic agents to antibodies have been described in various publications. For example, chemical modification can be made in the antibodies either through lysine side chain amines or through cysteine sulfhydryl groups activated by reducing interchain disulfide bonds for the conjugation reaction to occur. See, e.g., Tanaka et al., FEBS Letters 579:2092-2096, 2005, and Gentle et al., Bioconjugate Chem. 15:658-663, 2004. Reactive cysteine residues engineered at specific sites of antibodies for specific drug conjugation with defined stoichiometry have also been described. See, e.g., Junutula et al., Nature Biotechnology, 26:925-932, 2008. Conjugation using an acyl donor glutamine-containing tag or an endogenous glutamine made reactive (i.e., the ability to form a covalent bond as an acyl donor) by polypeptide engineering in the presence of transglutaminase and an amine (e.g., a cytotoxic agent comprising or attached to a reactive amine) is also described in international applications WO2012/059882 and WO2015015448 .

In some embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag engineered at a specific site of the antibody (e.g., a carboxyl terminus, an amino terminus, or at another site in the BCMA antibody). In some embodiments, the tag comprises an amino acid glutamine (Q) or an amino acid sequence LQG, LLQGG (SEQ ID NO:318), LLQG (SEQ ID NO:454), LSLSQG (SEQ ID NO: 455), GGGLLQGG (SEQ ID NO: 456), GLLQG (SEQ ID NO: 457), LLQ, GSPLAQSHGG (SEQ ID NO: 458), GLLQGGG (SEQ ID NO: 459), GLLQGG (SEQ ID NO: 460), GLLQ (SEQ ID NO: 461), LLQLLQGA (SEQ ID NO: 462), LLQGA (SEQ ID NO: 463), LLQYQGA (SEQ ID NO: 464), LLQGSG (SEQ ID NO: 465), LLQYQG (SEQ ID NO: 466), LLQLLQG (SEQ ID NO: 467), SLLQG (SEQ ID NO: 468), LLQLQ (SEQ ID NO: 469), LLQLLQ (SEQ ID NO: 470), LLQGR (SEQ ID NO: 471), LLQGPP (SEQ ID NO: 472), LLQGPA (SEQ ID NO: 473), GGLLQGPP (SEQ ID NO: 474), GGLLQGA (SEQ ID NO: 475), LLQGPGK (SEQ ID NO: 476), LLQGPG (SEQ ID NO: 477), LLQGP (SEQ ID NO: 478), LLQP (SEQ ID NO: 479), LLQPGK (SEQ ID NO: 480), LLQAPGK (SEQ ID NO: 481), LLQGAPG (SEQ ID NO: 482), LLQGAP (SEQ ID NO: 483), and LLQLQG (SEQ ID NO: 484).

In some embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag engineered at a specific site of the

antibody, wherein the tag comprises an amino acid sequence GGLLQGPP (SEQ ID NO: 474) or GGLLQGA (SEQ ID NO: 475) engineered at the light chain carboxyl terminus of the BCMA antibody. In some embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag engineered at a specific site of the antibody, wherein the tag comprises an amino acid sequence LLQG (SEQ ID NO: 454) engineered after residue T135 in the heavy chain of the BCMA antibody. In other embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag engineered at a specific site of the antibody, wherein the tag comprises an amino acid sequence LLQGA (SEQ ID NO: 463) or LLQGPP (SEQ ID NO: 472) engineered at the heavy chain carboxyl terminus of the BCMA antibody and wherein the lysine residue at the heavy chain carboxyl terminus is deleted. In some embodiments, the BCMA antibody or the conjugate as described herein comprises an amino acid substitution at position 297 of the BCMA antibody (EU numbering scheme). For example, the amino acid asparagine (N) can be substituted with glutamine (Q) or alanine (A) at position 297 of the BCMA antibody.

Also provided is an isolated antibody comprising an acyl donor glutamine-containing tag and an amino acid modification at position 222, 340, or 370 of the antibody (EU numbering scheme) wherein the modification is an amino acid deletion, insertion, substitution, mutation, or any combination thereof. Accordingly, in some embodiments, provided is the BCMA antibody or the conjugate as described herein comprising the acyl donor glutamine-containing tag (e.g., Q, LQG, LLQGG (SEQ ID NO:318), LLQG (SEQ ID NO:454), LSLSQG (SEQ ID NO: 455), GGGLLQGG (SEQ ID NO: 456), GLLQG (SEQ ID NO: 457), LLQ, GSPLAQSHGG (SEQ ID NO: 458), GLLQGGG (SEQ ID NO: 459), GLLQGG (SEQ ID NO: 460), GLLQ (SEQ ID NO: 461), LLQLLQGA (SEQ ID NO: 462), LLQGA (SEQ ID NO: 463), LLQYQGA (SEQ ID NO: 464), LLQGSG (SEQ ID NO: 465), LLQYQG (SEQ ID NO: 466), LLQLLQG (SEQ ID NO: 467), SLLQG (SEQ ID NO: 468), LLQLQ (SEQ ID NO: 469), LLQLLQ (SEQ ID NO: 470), LLQGR (SEQ ID NO: 471), LLQGPP (SEQ ID NO: 472), LLQGPA (SEQ ID NO: 473), GGLLQGPP (SEQ ID NO: 474), GGLLQGA (SEQ ID NO: 475), LLQGPGK (SEQ ID NO: 476), LLQGPG (SEQ ID NO: 477), LLQGP (SEQ ID NO: 478), LLQP (SEQ ID NO: 479), LLQPGK (SEQ ID NO: 480), LLQAPGK (SEQ ID NO: 481), LLQGAPG (SEQ ID NO: 482), LLQGAP (SEQ ID NO: 483),

and LLQLQG (SEQ ID NO: 484)) conjugated at a specific site (e.g., at a carboxyl terminus of the heavy or light chain, residue T135 in the antibody heavy chain, or at another site) of the BCMA antibody and an amino acid modification at position 222, 340, or 370 of the antibody (EU numbering scheme). In some embodiments, the amino acid modification is a substitution from lysine to arginine (e.g., K222R, K340R, or K370R).

In some embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag comprising the sequence GGLLQGPP (SEQ ID NO: 474) engineered at the C-terminus of the BCMA antibody light chain and an amino acid substitution from lysine to arginine at position 222 of the antibody (EU numbering scheme). In some embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag comprising the sequence GGLLQGA (SEQ ID NO: 475) engineered at the C-terminus of the BCMA antibody light chain and an amino acid substitution from lysine to arginine at position 222 of the antibody (EU numbering scheme). In some embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag comprising the sequence LLQGA (SEQ ID NO: 463) engineered at the C-terminus of the BCMA antibody heavy chain and an amino acid substitution from lysine to arginine at position 222 of the antibody (EU numbering scheme), wherein the lysine residue at the heavy chain carboxyl terminus is deleted. In some embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag comprising the sequence LLQG (SEQ ID NO: 454) engineered after residue T135 in the heavy chain of the BCMA antibody and an amino acid substitution from lysine to arginine at position 222 of the antibody (EU numbering scheme).

In some embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag comprising a glutamine engineered at position 297 or an amino acid substitution at position 297 from asparagine (N) to another amino acid in the BCMA antibody and an amino acid substitution from lysine to arginine at position 222 of the antibody (EU numbering scheme). For example, in some embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag comprising the sequence GGLLQGPP (SEQ ID NO: 474) engineered at the C-terminus of the BCMA antibody light chain, an amino acid substitution

at position 297 of the BCMA antibody from asparagine (N) to glutamine (Q), and an amino acid substitution from lysine to arginine at position 222 of the antibody (EU numbering scheme). In some embodiments, the BCMA antibody or the conjugate as described herein comprises an acyl donor glutamine-containing tag comprising the sequence LLQG (SEQ ID NO: 454) engineered after residue T135 in the heavy chain of the BCMA antibody, an amino acid substitution at position 297 of the BCMA antibody from asparagine (N) to alanine (A), and an amino acid substitution from lysine to arginine at position 222 of the antibody (EU numbering scheme).

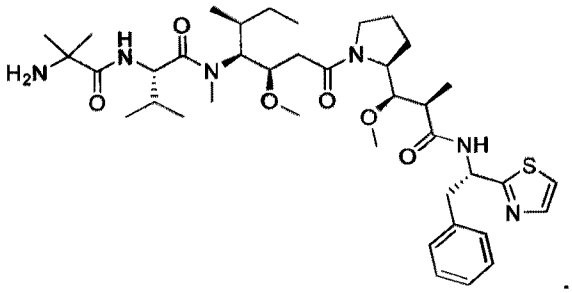
The agents that can be conjugated to the BCMA antibodies or the antigen binding fragments of the present invention include, but are not limited to, cytotoxic agents, immunomodulating agents, imaging agents, therapeutic proteins, biopolymers, or oligonucleotides.

Examples of a cytotoxic agent include, but are not limited to, anthracycline, an auristatin, a dolastatin, a combretastatin, a duocarmycin, a pyrrolobenzodiazepine dimer, an indolino-benzodiazepine dimer, an enediyne, a geldanamycin, a maytansine, a puromycin, a taxane, a vinca alkaloid, a camptothecin, a tubulysin, a hemiasterlin, a spliceostatin, a pladienolide, and stereoisomers, isosteres, analogs, or derivatives thereof.

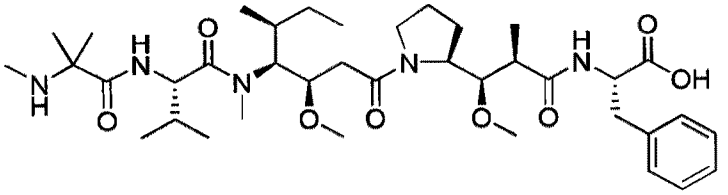
The anthracyclines are derived from bacteria *Strepomyces* and have been used to treat a wide range of cancers, such as leukemias, lymphomas, breast, uterine, ovarian, and lung cancers. Exemplary anthracyclines include, but are not limited to, daunorubicin, doxorubicin (i.e., adriamycin), epirubicin, idarubicin, valrubicin, and mitoxantrone.

Dolastatins and their peptidic analogs and derivatives, auristatins, are highly potent antimitotic agents that have been shown to have anticancer and antifungal activity. See, e.g., U.S. Pat. No. 5,663,149 and Pettit et al., *Antimicrob. Agents Chemother.* 42:2961-2965, 1998. Exemplary dolastatins and auristatins include, but are not limited to, dolastatin 10, auristatin E, auristatin EB (AEB), auristatin EFP (AEFP), MMAD (Monomethyl Auristatin D or monomethyl dolastatin 10), MMAF (Monomethyl Auristatin F or N-methylvaline-valine-dolaisoleuine-dolaproine-phenylalanine), MMAE (Monomethyl Auristatin E or N-methylvaline-valine-dolaisoleuine-dolaproine-norephedrine), 5-benzoylvaleric acid-AE ester (AEVB), and other novel auristatins (such as the ones described in U.S. Publication No. 2013/0129753). In some embodiments, the auristatin is

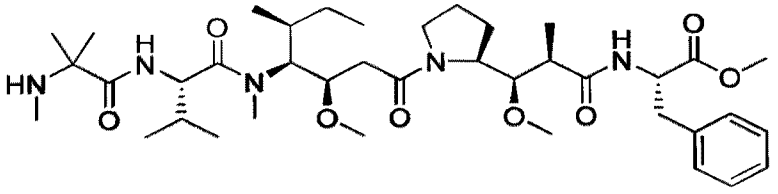
0101 (2-methylalanyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-{[(1*S*)-2-phenyl-1-(1,3-thiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide) having the following structure:



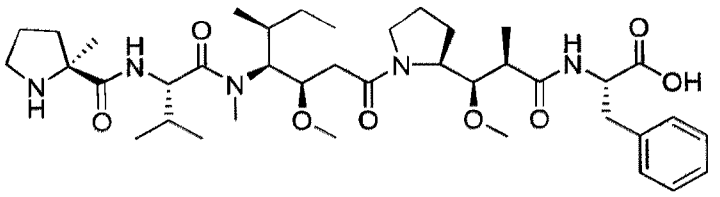
In some embodiments, the auristatin is 3377 (N,2-dimethylalanyl-N-{(1S,2R)-4-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxyl-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxobutyl}-N-methyl-L-valinamide) having the following structure:



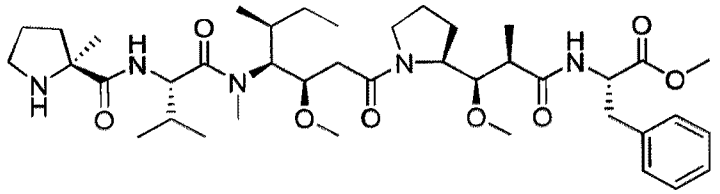
In some embodiments, the auristatin is 0131-OMe (N,2-dimethylalanyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-3-{[(2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino}-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methylL-valinamide) having the following structure:



In other embodiments, the auristatin is 0131 (2-methyl-L-proly-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide) having the following structure:



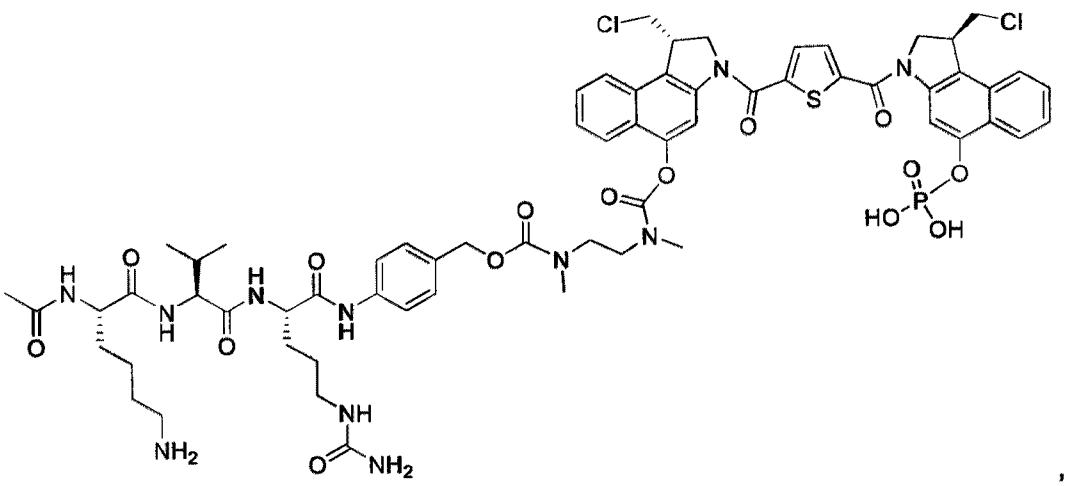
In other embodiments, the auristatin is 0121 (2-methyl-L-proly-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide) having the following structure:



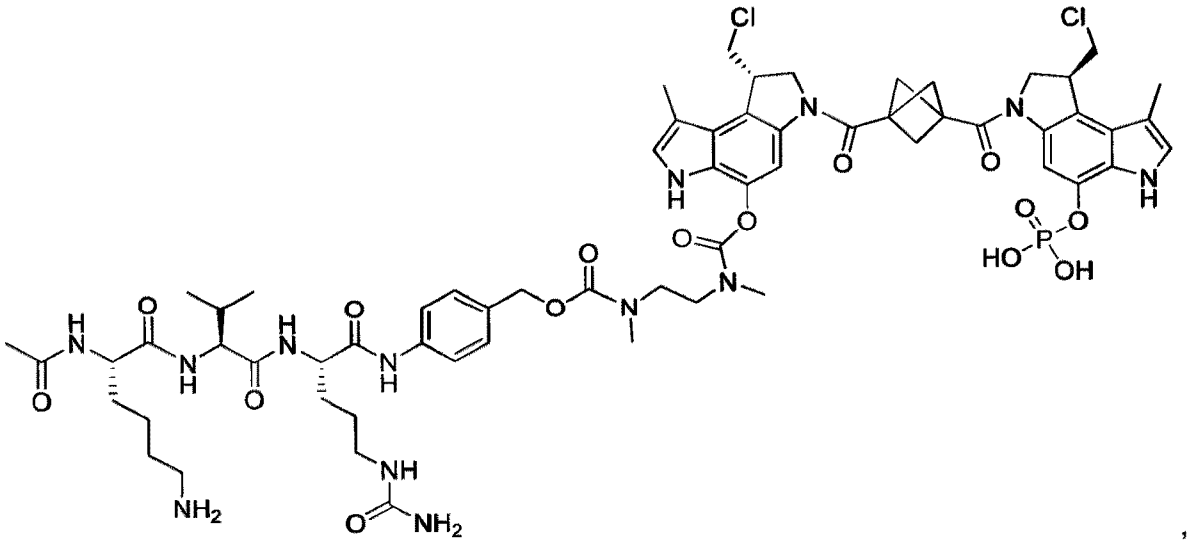
Camptothecin is a cytotoxic quinoline alkaloid which inhibits the enzyme topoisomerase I. Examples of camptothecin and its derivatives include, but are not limited to, topotecan and irinotecan, and their metabolites, such as SN-38.

Combretastatins are natural phenols with vascular disruption properties in tumors. Exemplary combretastatins and their derivatives include, but are not limited to, combretastatin A-4 (CA-4) and ombrabulin.

Duocarmycin and CC-1065 are DNA alkylating agents with cytotoxic potency. See Boger and Johnson, *PNAS* 92:3642-3649 (1995). Exemplary duocarmycin and CC-1065 include, but are not limited to, (+)-duocarmycin A and (+)-duocarmycin SA, (+)-CC-1065, and the compounds as disclosed in the international application PCT/IB2015/050280 including, but not limited to, N~2~-acetyl-L-lysyl-L-valyl-N~5~-carbamoyl-N-[4-({[(2-{[({(1S)-1-(chloromethyl)-3-[(5-{[(1S)-1-(chloromethyl)-5-(phosphonooxy)-1,2-dihydro-3H-benzo[e]indol-3-yl]carbonyl}thiophen-2-yl)carbonyl]-2,3-di hydro-1H-benzo[e]indol-5-yl}oxy)carbonyl](methyl)amino}ethyl)(methyl)carbamoyl]oxy}methyl)phenyl]-L-ornithinamide having the structure:

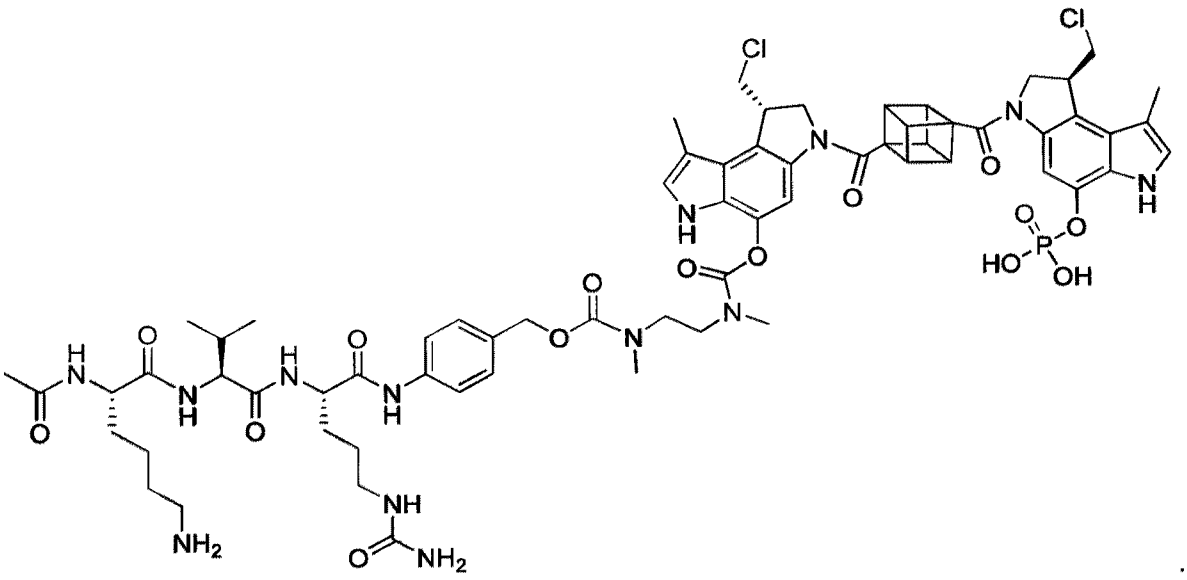


, N~2~-acetyl-L-lysyl-L-valyl-N~5~-carbamoyl-N-[4-({[(2-{[({(8S)-8-(chloromethyl)-6-[(3-{[(1S)-1-(chloromethyl)-8-methyl-5-(phosphonooxy)-1,6-dihydropyrrolo[3,2-e]indol-3(2H)-yl]carbonyl}bicyclo[1.1.1]p ent-1-yl)carbonyl]-1-methyl-3,6,7,8-tetrahydropyrrolo[3,2-e]indol-4-yl}oxy)carbonyl](methyl)amino}ethyl)(methyl)carbamoyl]oxy}methyl)phenyl]-L-ornithinamide having the structure:



, N~2~-acetyl-L-lysyl-L-valyl-N~5~-carbamoyl-N-[4-({[(2-{[({(8S)-8-(chloromethyl)-6-[(4-{[(1S)-1-(chloromethyl)-8-methyl-5-(phosphonooxy)-1,6-dihydropyrrolo[3,2-e]indol-3(2H)-yl]carbonyl}pentacyclo[4.2.0.0~2,5~.0~3,8~.0~4,7~]oct-1-yl)carbonyl]-1-methyl-3,6,7,8-tetrahydropyrrolo[3,2-e]indol-4-

yl}oxy)carbonyl](methyl)amino}ethyl)(methyl)carbamoyl]oxy}methyl)phenyl]-L-ornithinamide having the structure:



Enediynes are a class of anti-tumor bacterial products characterized by either nine- and ten-membered rings or the presence of a cyclic system of conjugated triple-double-triple bonds. Exemplary enediynes include, but are not limited to, calicheamicin, esperamicin, uncialamicin, dynemicin, and their derivatives.

Geldanamycins are benzoquinone ansamycin antibiotic that bind to Hsp90 (Heat Shock Protein 90) and have been used antitumor drugs. Exemplary geldanamycins include, but are not limited to, 17-AAG (17-N-Allylamino-17-Demethoxygeldanamycin) and 17-DMAG (17-Dimethylaminoethylamino-17-demethoxygeldanamycin).

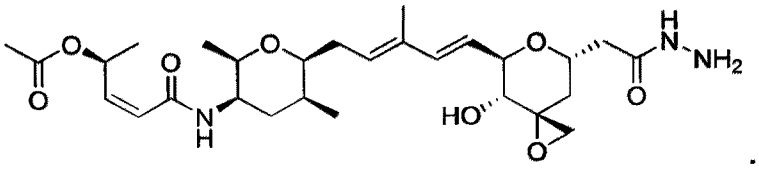
Hemiasterlin and its analogues (e.g., HTI-286) bind to the tubulin, disrupt normal microtubule dynamics, and, at stoichiometric amounts, depolymerize microtubules.

Maytansines or their derivatives maytansinoids inhibit cell proliferation by inhibiting the microtubules formation during mitosis through inhibition of polymerization of tubulin. See Remillard et al., Science 189:1002-1005, 1975. Exemplary maytansines and maytansinoids include, but are not limited to, mertansine (DM1) and its derivatives as well as ansamitocin.

Pyrrolobenzodiazepine dimers (PBDs) and indolino-benzodiazepine dimers (IGNs) are anti-tumor agents that contain one or more immine functional groups, or their

equivalents, that bind to duplex DNA. PBD and IGN molecules are based on the natural product athramycin, and interact with DNA in a sequence-selective manner, with a preference for purine-guanine-purine sequences. Exemplary PBDs and their analogs include, but are not limited to, SJG-136.

Spliceostatins and pladienolides are anti-tumor compounds which inhibit splicing and interacts with spliceosome, SF3b. Examples of spliceostatins include, but are not limited to, spliceostatin A, FR901464, and (2S,3Z)-5-{[(2R,3R,5S,6S)-6-{(2E,4E)-5-[(3R,4R,5R,7S)-7-(2-hydrazinyl-2-oxoethyl)-4-hydroxy-1,6-dioxaspiro[2.5]oct-5-yl]-3-methylpenta-2,4-dien-1-yl}-2,5-dimethyltetrahydro-2H-pyran-3-yl]amino}-5-oxopent-3-en-2-yl acetate having the structure of



. Examples of pladienolides include, but are not limited to, Pladienolide B, Pladienolide D, or E7107.

Taxanes are diterpenes that act as anti-tubulin agents or mitotic inhibitors. Exemplary taxanes include, but are not limited to, paclitaxel (e.g., TAXOL®) and docetaxel (TAXOTERE®).

Tubulysins are natural products isolated from a strain of myxobacteria that has been shown to depolymerize microtubules and induce mitotic arrest. Exemplary tubulysins include, but are not limited to, tubulysin A, tubulysin B, and tubulysin D.

Vinca alkyloids are also anti-tubulin agents. Exemplary vinca alkyloids include, but are not limited to, vincristine, vinblastine, vindesine, and vinorelbine.

Accordingly, in some embodiments, the cytotoxic agent is selected from the group consisting of MMAD (Monomethyl Auristatin D), 0101 (2-methylalanyl-*N*-[(3*R*,4*S*,5*S*)-3-methoxy-1-{(2*S*)-2-[(1*R*,2*R*)-1-methoxy-2-methyl-3-oxo-3-{[(1*S*)-2-phenyl-1-(1,3-thiazol-2-yl)ethyl]amino}propyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-*N*-methyl-L-valinamide), 3377 (N,2-dimethylalanyl-N-{(1S,2R)-4-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxyl-2-phenylethyl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-2-methoxy-1-[(1S)-1-methylpropyl]-4-oxobutyl}-N-methyl-L-valinamide), 0131 (2-methyl-L-proly-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S)-1-carboxy-2-phenylethyl]amino}-1-methoxy-2-methyl-3-

oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide), 0131-OMe (N,2-dimethylalanyl-N-[(3R,4S,5S)-3-methoxy-1-{(2S)-2-[(1R,2R)-1-methoxy-3-{[(2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino}-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-5-methyl-1-oxoheptan-4-yl]-N-methylL-valinamide), 0121(2-methyl-L-proly-N-[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(2S)-1-methoxy-1-oxo-3-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl]-N-methyl-L-valinamide), and (2S,3Z)-5-{[(2R,3R,5S,6S)-6-{(2E,4E)-5-[(3R,4R,5R,7S)-7-(2-hydrazinyl-2-oxoethyl)-4-hydroxy-1,6-dioxaspiro[2.5]oct-5-yl]-3-methylpenta-2,4-dien-1-yl}-2,5-dimethyltetrahydro-2H-pyran-3-yl]amino}-5-oxopent-3-en-2-yl acetate.

In some embodiments, the agent is an immunomodulating agent. Examples of an immunomodulating agent include, but are not limited to, gancyclovier, etanercept, tacrolimus, sirolimus, voclosporin, cyclosporine, rapamycin, cyclophosphamide, azathioprine, mycophenolgate mofetil, methotrextrate, glucocorticoid and its analogs, cytokines, stem cell growth factors, lymphotoxins, tumor necrosis factor (TNF), hematopoietic factors, interleukins (e.g., interleukin-1 (IL-1), IL-2, IL-3, IL-6, IL-10, IL-12, IL-18, and IL-21), colony stimulating factors (e.g., granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF)), interferons (e.g., interferons-α, -β and -γ), the stem cell growth factor designated "S 1 factor," erythropoietin and thrombopoietin, or a combination thereof.

In some embodiments, the agent moiety is an imaging agent (e.g., a fluorophore or a chelator), such as fluorescein, rhodamine, lanthanide phosphors, and their derivatives thereof, or a radioisotope bound to a chelator. Examples of fluorophores include, but are not limited to, fluorescein isothiocyanate (FITC) (e.g., 5-FITC), fluorescein amidite (FAM) (e.g., 5-FAM), eosin, carboxyfluorescein, erythrosine, Alexa Fluor® (e.g., Alexa 350, 405, 430, 488, 500, 514, 532, 546, 555, 568, 594, 610, 633, 647, 660, 680, 700, or 750), carboxytetramethylrhodamine (TAMRA) (e.g., 5,-TAMRA), tetramethylrhodamine (TMR), and sulforhodamine (SR) (e.g., SR101). Examples of chelators include, but are not limited to, 1,4,7,10-tetraazacyclododecane-N,N',N",N"'-tetraacetic acid (DOTA), 1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA), 1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid (deferoxamine), diethylenetriaminepentaacetic acid (DTPA), and 1,2-bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid) (BAPTA).

Examples of fluorophores include, but are not limited to, fluorescein isothiocyanate (FITC) (e.g., 5-FITC), fluorescein amidite (FAM) (e.g., 5-FAM), eosin, carboxyfluorescein, erythrosine, Alexa Fluor® (e.g., Alexa 350, 405, 430, 488, 500, 514, 532, 546, 555, 568, 594, 610, 633, 647, 660, 680, 700, or 750), carboxytetramethylrhodamine (TAMRA) (e.g., 5,-TAMRA), tetramethylrhodamine (TMR), and sulforhodamine (SR) (e.g., SR101).

In some embodiments, therapeutic or diagnostic radioisotopes or other labels (e.g., PET or SPECT labels) can be incorporated in the agent for conjugation to the BCMA antibodies or the antigen binding fragments as described herein. Examples of a radioisotope or other labels include, but are not limited to, ^{3}H, ^{11}C, ^{13}N, ^{14}C, ^{15}N, ^{15}O, ^{35}S, ^{18}F, ^{32}P, ^{33}P, ^{47}Sc, ^{51}Cr, ^{57}Co, ^{58}Co, ^{59}Fe, ^{62}Cu, ^{64}Cu, ^{67}Cu, ^{67}Ga, ^{68}Ga, ^{75}Se, ^{76}Br, ^{77}Br, ^{86}Y, ^{89}Zr, ^{90}Y, ^{94}Tc, ^{95}Ru, ^{97}Ru, ^{99}Tc, ^{103}Ru, ^{105}Rh, ^{105}Ru, ^{107}Hg, ^{109}Pd, ^{111}Ag, ^{111}In, ^{113}In, ^{121}Te, ^{122}Te, ^{123}I, ^{124}I, ^{125}I, ^{125}Te, ^{126}I, ^{131}I, ^{131}In, ^{133}I, ^{142}Pr, ^{143}Pr, ^{153}Pb, ^{153}Sm, ^{161}Tb, ^{165}Tm, ^{166}Dy, ^{166}H, ^{167}Tm, ^{168}Tm, ^{169}Yb, ^{177}Lu, ^{186}Re, ^{188}Re, ^{189}Re, ^{197}Pt, ^{198}Au, ^{199}Au, ^{201}Tl, ^{203}Hg, ^{211}At, ^{212}Bi, ^{212}Pb, ^{213}Bi, ^{223}Ra, ^{224}Ac, or ^{225}Ac.

In some embodiments, the agent is a therapeutic protein including, but is not limited to, a toxin, a hormone, an enzyme, and a growth factor.

Examples of a toxin protein (or polypeptide) include, but are not limited to, dipththeria (e.g., diphtheria A chain), *Pseudomonas* exotoxin and endotoxin, ricin (e.g., ricin A chain), abrin (e.g., abrin A chain), modeccin (e.g., modeccin A chain), alpha-sarcin, Aleurites fordii proteins, dianthin proteins, ribonuclease (RNase), DNase I, *Staphylococcal* enterotoxin-A, pokeweed antiviral protein, gelonin, diphtherin toxin, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, mitogellin, restrictocin, phenomycin, enomycin, tricothecenes, inhibitor cystine knot (ICK) peptides (e.g., ceratotoxins), and conotoxin (e.g., KIIIA or SmIIIa).

In some embodiments, the agent is a biocompatible polymer. The BCMA antibodies or the antigen binding fragments as described herein can be conjugated to the biocompatible polymer to increase serum half-life and bioactivity, and/or to extend *in vivo* half-lives. Examples of biocompatible polymers include water-soluble polymer, such as polyethylene glycol (PEG) or its derivatives thereof and zwitterion-containing biocompatible polymers (e.g., a phosphorylcholine containing polymer).

In some embodiments, the agent is an oligonucleotide, such as anti-sense oligonucleotides.

In another aspect, the invention provides a conjugate of the antibody or the antigen binding fragment as described herein, wherein the conjugate comprises the formula: antibody-(acyl donor glutamine-containing tag)-(linker)-(cytotoxic agent), wherein the acyl donor glutamine-containing tag is engineered at a specific site of the antibody or the antigen binding fragment (e.g., at a carboxyl terminus of the heavy or light chain, after residue T135 in the antibody heavy chain, or at an another site), wherein the tag is conjugated to a linker (e.g., a linker containing one or more reactive amines (e.g., primary amine NH_2)), and wherein the linker is conjugated to a cytotoxic agent (e.g., MMAD or other auristatins such as 0101, 0131, or 3377).

Examples of a linker containing one or more reactive amines include, but are not limited to, Ac-Lys-Gly (acetyl-lysine-glycine), aminocaproic acid, Ac-Lys-β-Ala (acetyl-lysine-β-alanine), amino-PEG2 (polyethylene glycol)-C2, amino-PEG3-C2, amino-PEG6-C2 (or amino PEG6-propionyl), Ac-Lys-Val-Cit-PABC (acetyl-lysine-valine-citrulline-*p*-aminobenzyloxycarbonyl), amino-PEG6-C2-Val-Cit-PABC, aminocaproyl-Val-Cit-PABC, [(3R,5R)-1-{3-[2-(2-aminoethoxy)ethoxy]propanoyl}piperidine-3,5-diyl]bis-Val-Cit-PABC, [(3S,5S)-1-{3-[2-(2-aminoethoxy)ethoxy]propanoyl}piperidine-3,5-diyl]bis-Val-Cit-PABC, putrescine, or Ac-Lys-putrescine.

In some embodiments, the conjugate is 1) antibody-GGLLQGPP (SEQ ID NO: 474)-AcLys-VC-PABC-0101; 2) antibody-AcLys-VC-PABC-0101 and comprises N297Q; 3) antibody-GGLLQGPP (SEQ ID NO: 474)-AcLys-VC-PABC-0101 and comprises N297Q; 4) antibody-LLQG (SEQ ID NO: 454)-amino-PEG6-C2-0131 and comprises N297A; 5) antibody–LLQG (SEQ ID NO: 454)-amino-PEG6-C2-3377 and comprises N297A; 6) antibody-GGLLQGA (SEQ ID NO: 475)-AcLys-VC-PABC-0101. In some embodiments, the acyl donor glutamine-containing tag comprising, e.g., GGLLQGPP (SEQ ID NO: 474) or GGLLQGA (SEQ ID NO: 475), is engineered at the C-terminus of the light chain of the antibody. In other embodiments, the acyl donor glutamine-containing tag (e.g., LLQGA (SEQ ID NO: 463) or LLQGPP (SEQ ID NO: 472)) is engineered at the C-terminus of the heavy chain of the antibody, wherein the lysine residue at the C-terminus is deleted. In some embodiments, the acyl donor glutamine-containing tag comprising, e.g., LLQG (SEQ

ID NO: 454) is engineered after residue T135 in the antibody heavy chain or replaces amino acid residues E294-N297 in the antibody heavy chain. Examples of the antibody include, but are not limited to, P6E01/P6E01, P6E01/H3.AQ, L1.LGF/L3.KW/P6E01; L1.LGF/L3.NY/P6E01, L1.GDF/L3.NY/P6E01, L1.LGF/L3.KW/H3.AL, L1.LGF/L3.KW/H3.AP, L1.LGF/L3.KW/H3.AQ, L1.LGF/L3.PY/H3.AP, L1.LGF/L3.PY/H3.AQ, L1.LGF/L3.NY/H3.AL, L1.LGF/L3.NY/H3.AP, L1.LGF/L3.NY/H3.AQ, L1.GDF/L3.KW/H3.AL, L1.GDF/L3.KW/H3.AP, L1.GDF/L3.KW/H3.AQ, L1.GDF/L3.PY/H3.AQ, L1.GDF/L3.NY/H3.AL, L1.GDF/L3.NY/H3.AP, L1.GDF/L3.NY/H3.AQ, L3.KW/P6E01, L3.PY/P6E01, L3.NY/P6E01, L3.PY/L1.PS/P6E01, L3.PY/L1.AH/P6E01, L3.PY/L1.FF/P6E01, L3.PY/L1.PH/P6E01, L3.PY/L3.KY/P6E01, L3.PY/L3.KF/P6E01, L3.PY/H2.QR, L3.PY/H2.DY, L3.PY/H2.YQ, L3.PY/H2.LT, L3.PY/H2.HA, L3.PY/H2.QL, L3.PY/H3.YA, L3.PY/H3.AE, L3.PY/H3.AQ, L3.PY/H3.TAQ, L3.PY/P6E01, L3.PY/L1.PS/H2.QR, L3.PY/L1.PS/H2.DY, L3.PY/L1.PS/H2.YQ, L3.PY/L1.PS/H2.LT, L3.PY/L1.PS/H2.HA, L3.PY/L1.PS/H2.QL, L3.PY/L1.PS/H3.YA, L3.PY/L1.PS/H3.AE, L3.PY/L1.PS/H3.AQ, L3.PY/L1.PS/H3.TAQ, L3.PY/L1.AH/H2.QR, L3.PY/L1.AH/H2.DY, L3.PY/L1.AH/H2.YQ, L3.PY/L1.AH/H2.LT, L3.PY/L1.AH/H2.HA, L3.PY/L1.AH/H2.QL, L3.PY/L1.AH/H3.YA, L3.PY/L1.AH/H3.AE, L3.PY/L1.AH/H3.AQ, L3.PY/L1.AH/H3.TAQ, L3.PY/L1.FF/H2.QR, L3.PY/L1.FF/H2.DY, L3.PY/L1.FF/H2.YQ, L3.PY/L1.FF/H2.LT, L3.PY/L1.FF/H2.HA, L3.PY/L1.FF/H2.QL, L3.PY/L1.FF/H3.YA, L3.PY/L1.FF/H3.AE, L3.PY/L1.FF/H3.AQ, L3.PY/L1.FF/H3.TAQ, L3.PY/L1.PH/H2.QR, L3.PY/L1.PH/H2.HA, L3.PY/L1.PH/H3.AE, L3.PY/L1.PH/H3.AQ, L3.PY/L1.PH/H3.TAQ, L3.PY/L3.KY/H2.QR, L3.PY/L3.KY/H2.DY, L3.PY/L3.KY/H2.YQ L3.PY/L3.KY/H2.LT, L3.PY/L3.KY/H2.HA, L3.PY/L3.KY/H2.QL, L3.PY/L3.KY/H3.YA L3.PY/L3.KY/H3.TAQ, L3.PY/L3.KF/H2.DY, L3.PY/L3.KF/H2.YQ, L3.PY/L3.KF/H2.LT L3.PY/L3.KF/H2.QL, L3.PY/L3.KF/H3.YA, L3.PY/L3.KF/H3.AE, L3.PY/L3.KF/H3.AQ L3.PY/L3.KF/H3.TAQ, P5A2_VHVL, A02_Rd4_0.6nM_C06, A02_Rd4_0.6nM_C09 A02_Rd4_6nM_C16, A02_Rd4_6nM_C03, A02_Rd4_6nM_C01, A02_Rd4_6nM_C26 A02_Rd4_6nM_C25, A02_Rd4_6nM_C22, A02_Rd4_6nM_C19, A02_Rd4_0.6nM_C03 A02_Rd4_6nM_C07, A02_Rd4_6nM_C23, A02_Rd4_0.6nM_C18, A02_Rd4_6nM_C10 A02_Rd4_6nM_C05, A02_Rd4_0.6nM_C10, A02_Rd4_6nM_C04, A02_Rd4_0.6nM_C26

A02_Rd4_0.6nM_C13, A02_Rd4_0.6nM_C01, A02_Rd4_6nM_C08, P5C1_VHVL, C01_Rd4_6nM_C24, C01_Rd4_6nM_C26, C01_Rd4_6nM_C10, C01_Rd4_0.6nM_C27 C01_Rd4_6nM_C20, C01_Rd4_6nM_C12, C01_Rd4_0.6nM_C16, C01_Rd4_0.6nM_C09 C01_Rd4_6nM_C09, C01_Rd4_0.6nM_C03, C01_Rd4_0.6nM_C06, C01_Rd4_6nM_C04 COMBO_Rd4_0.6nM_C22, COMBO_Rd4_6nM_C21, COMBO_Rd4_6nM_C10, COMBO_Rd4_0.6nM_C04, COMBO_Rd4_6nM_C25, COMBO_Rd4_0.6nM_C21, COMBO_Rd4_6nM_C11, COMBO_Rd4_0.6nM_C20, COMBO_Rd4_6nM_C09, COMBO_Rd4_6nM_C08, COMBO_Rd4_0.6nM_C19, COMBO_Rd4_0.6nM_C02, COMBO_Rd4_0.6nM_C23, COMBO_Rd4_0.6nM_C29, COMBO_Rd4_0.6nM_C09, COMBO_Rd4_6nM_C12, COMBO_Rd4_0.6nM_C30, COMBO_Rd4_0.6nM_C14, COMBO_Rd4_6nM_C07, COMBO_Rd4_6nM_C02, COMBO_Rd4_0.6nM_C05, COMBO_Rd4_0.6nM_C17, COMBO_Rd4_6nM_C22, COMBO_Rd4_0.6nM_C11, COMBO_Rd4_0.6nM_C29, P4G4, or P1A11.

In one variation, the conjugate further comprises an amino acid substitution from lysine to arginine at position 222. Accordingly, for example, the conjugate is 1) antibody-GGLLQGPP (SEQ ID NO: 474)- AcLys-VC-PABC-0101 and comprises K222R; 2) antibody-AcLys-VC-PABC-0101 and comprises N297Q and K222R; 3) antibody-GGLLQGPP (SEQ ID NO: 474)-AcLys-VC-PABC-0101 and comprises N297Q and K222R; 4) antibody-LLQG (SEQ ID NO: 454)-amino-PEG6-C2-0131 and comprises N297A and K222R; 5) antibody–LLQG (SEQ ID NO: 454)-amino-PEG6-C2-3377 and comprises N297A and K222R; and 6) antibody-GGLLQGA (SEQ ID NO: 475)-AcLys-VC-PABC-0101 and comprises K222R. In some embodiments, the acyl donor glutamine-containing tag comprising, e.g., GGLLQGPP (SEQ ID NO: 474) or GGLLQGA (SEQ ID NO: 475) is engineered at the C-terminus of the light chain of the antibody. In other embodiments, the acyl donor glutamine-containing tag (e.g., LLQGA (SEQ ID NO: 473) or LLQGPP (SEQ ID NO: 472)) is engineered at the C-terminus of the heavy chain of the antibody, wherein the lysine residue at the C-terminus is deleted. In some embodiments, the acyl donor glutamine-containing tag comprising, e.g., LLQG (SEQ ID NO: 454) is engineered after residue T135 in the antibody heavy chain or replaces amino acid residues E294-N297 in the antibody heavy chain. Examples of the antibody include, but are not limited to, P6E01/P6E01, P6E01/H3.AQ, L1.LGF/L3.KW/P6E01; L1.LGF/L3.NY/P6E01,

L1.GDF/L3.NY/P6E01, L1.LGF/L3.KW/H3.AL, L1.LGF/L3.KW/H3.AP, L1.LGF/L3.KW/H3.AQ, L1.LGF/L3.PY/H3.AP, L1.LGF/L3.PY/H3.AQ, L1.LGF/L3.NY/H3.AL, L1.LGF/L3.NY/H3.AP, L1.LGF/L3.NY/H3.AQ, L1.GDF/L3.KW/H3.AL, L1.GDF/L3.KW/H3.AP, L1.GDF/L3.KW/H3.AQ, L1.GDF/L3.PY/H3.AQ, L1.GDF/L3.NY/H3.AL, L1.GDF/L3.NY/H3.AP, L1.GDF/L3.NY/H3.AQ, L3.KW/P6E01, L3.PY/P6E01, L3.NY/P6E01, L3.PY/L1.PS/P6E01, L3.PY/L1.AH/P6E01, L3.PY/L1.FF/P6E01, L3.PY/L1.PH/P6E01, L3.PY/L3.KY/P6E01, L3.PY/L3.KF/P6E01, L3.PY/H2.QR, L3.PY/H2.DY, L3.PY/H2.YQ, L3.PY/H2.LT, L3.PY/H2.HA, L3.PY/H2.QL, L3.PY/H3.YA, L3.PY/H3.AE, L3.PY/H3.AQ, L3.PY/H3.TAQ, L3.PY/P6E01, L3.PY/L1.PS/H2.QR, L3.PY/L1.PS/H2.DY, L3.PY/L1.PS/H2.YQ, L3.PY/L1.PS/H2.LT, L3.PY/L1.PS/H2.HA, L3.PY/L1.PS/H2.QL, L3.PY/L1.PS/H3.YA, L3.PY/L1.PS/H3.AE, L3.PY/L1.PS/H3.AQ, L3.PY/L1.PS/H3.TAQ, L3.PY/L1.AH/H2.QR, L3.PY/L1.AH/H2.DY, L3.PY/L1.AH/H2.YQ, L3.PY/L1.AH/H2.LT, L3.PY/L1.AH/H2.HA, L3.PY/L1.AH/H2.QL, L3.PY/L1.AH/H3.YA, L3.PY/L1.AH/H3.AE, L3.PY/L1.AH/H3.AQ, L3.PY/L1.AH/H3.TAQ, L3.PY/L1.FF/H2.QR, L3.PY/L1.FF/H2.DY, L3.PY/L1.FF/H2.YQ, L3.PY/L1.FF/H2.LT, L3.PY/L1.FF/H2.HA, L3.PY/L1.FF/H2.QL, L3.PY/L1.FF/H3.YA, L3.PY/L1.FF/H3.AE, L3.PY/L1.FF/H3.AQ, L3.PY/L1.FF/H3.TAQ, L3.PY/L1.PH/H2.QR, L3.PY/L1.PH/H2.HA, L3.PY/L1.PH/H3.AE, L3.PY/L1.PH/H3.AQ, L3.PY/L1.PH/H3.TAQ, L3.PY/L3.KY/H2.QR, L3.PY/L3.KY/H2.DY, L3.PY/L3.KY/H2.YQ L3.PY/L3.KY/H2.LT, L3.PY/L3.KY/H2.HA, L3.PY/L3.KY/H2.QL, L3.PY/L3.KY/H3.YA L3.PY/L3.KY/H3.TAQ, L3.PY/L3.KF/H2.DY, L3.PY/L3.KF/H2.YQ, L3.PY/L3.KF/H2.LT L3.PY/L3.KF/H2.QL, L3.PY/L3.KF/H3.YA, L3.PY/L3.KF/H3.AE, L3.PY/L3.KF/H3.AQ L3.PY/L3.KF/H3.TAQ, P5A2_VHVL, A02_Rd4_0.6nM_C06, A02_Rd4_0.6nM_C09 A02_Rd4_6nM_C16, A02_Rd4_6nM_C03, A02_Rd4_6nM_C01, A02_Rd4_6nM_C26 A02_Rd4_6nM_C25, A02_Rd4_6nM_C22, A02_Rd4_6nM_C19, A02_Rd4_0.6nM_C03 A02_Rd4_6nM_C07, A02_Rd4_6nM_C23, A02_Rd4_0.6nM_C18, A02_Rd4_6nM_C10 A02_Rd4_6nM_C05, A02_Rd4_0.6nM_C10, A02_Rd4_6nM_C04, A02_Rd4_0.6nM_C26 A02_Rd4_0.6nM_C13, A02_Rd4_0.6nM_C01, A02_Rd4_6nM_C08, P5C1_VHVL, C01_Rd4_6nM_C24, C01_Rd4_6nM_C26, C01_Rd4_6nM_C10, C01_Rd4_0.6nM_C27 C01_Rd4_6nM_C20, C01_Rd4_6nM_C12, C01_Rd4_0.6nM_C16, C01_Rd4_0.6nM_C09 C01_Rd4_6nM_C09, C01_Rd4_0.6nM_C03, C01_Rd4_0.6nM_C06, C01_Rd4_6nM_C04

COMBO_Rd4_0.6nM_C22, COMBO_Rd4_6nM_C21, COMBO_Rd4_6nM_C10, COMBO_Rd4_0.6nM_C04, COMBO_Rd4_6nM_C25, COMBO_Rd4_0.6nM_C21, COMBO_Rd4_6nM_C11, COMBO_Rd4_0.6nM_C20, COMBO_Rd4_6nM_C09, COMBO_Rd4_6nM_C08, COMBO_Rd4_0.6nM_C19, COMBO_Rd4_0.6nM_C02, COMBO_Rd4_0.6nM_C23, COMBO_Rd4_0.6nM_C29, COMBO_Rd4_0.6nM_C09, COMBO_Rd4_6nM_C12, COMBO_Rd4_0.6nM_C30, COMBO_Rd4_0.6nM_C14, COMBO_Rd4_6nM_C07, COMBO_Rd4_6nM_C02, COMBO_Rd4_0.6nM_C05, COMBO_Rd4_0.6nM_C17, COMBO_Rd4_6nM_C22, COMBO_Rd4_0.6nM_C11, COMBO_Rd4_0.6nM_C29, or P4G4, or P1A11.

CD3 Antibodies and Methods of Making Thereof

The present invention further provides an antibody that binds to CD3 (e.g., human CD3 (SEQ ID NO: 502; or accession number: NM_000733.3).

In one aspect, provided is an isolated antibody, or an antigen binding fragment thereof, which specifically binds to CD3, wherein the antibody comprises a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 320, 322, 324, 326, 328, 330, 345, 347, 349, 351, 444, 354, 356, 378, 442, 380, 382, 384 386, 388, 390, 392, 394, 396, 398, or 400; and/or a light chain variable (VL) region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 319, 321, 323, 325, 327, 329, 344, 346, 348, 350, 352, 355, 377, 443, 445, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, or 399.

In another aspect, provided is an isolated antibody, or an antigen binding fragment thereof, which specifically binds to CD3, wherein the VH region comprises (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 331, 332, 333, 401, 402, 403, 407, 408, 415, 416, 418, 419, 420, 424, 425, 426, 446, 447, or 448 (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 334, 336, 337, 338, 339, 404, 405, 409, 410, 411, 412, 413, 414, 417, 418, 421, 422, 427, 428, 449, or 450; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 335, 406, 423, 429, or 451; and/or a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 340, 343, 430, 431, 435, or 440, 441; (ii) a VL CDR2

comprising the sequence shown in SEQ ID NO: 341, 433, 452, or 436; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 342, 432, 434, 437, 438, 439, 446, or 453.

In some embodiments, provided is an antibody having any one of partial light chain sequence as listed in Table 3 and/or any one of partial heavy chain sequence as listed in Table 3.

Table 3

mAb	Light Chain	Heavy Chain
h2B4	DIVMTQSPDSLAVSLGERATINCT **SSQSLFNVRSRKNYLA**WYQQKP GQPPKLLIS**WASTRES**GVPDRFS GSGSGTDFTLTISSLQAEDVAVY YC**KQSYDLFT**FGSGTKLEIK (SEQ ID NO: 319)	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDYYMTWVRQAPGKGLE WVAFIRNRARGYTSDHNASVKGR FTISRDNAKNSLYLQMNSLRAEDT AVYYCAR**DRPSYYVLDY**WGQGTT VTVSS (SEQ ID NO: 320)
h2B4-VH-wt VL_TK	DIVMTQSPDSLAVSLGERATINC **KSSQSLFNVRSRKNYLA**WYQQK PGQPPKLLIS**WASTRES**GVPDRF SGSGSGTDFTLTISSLQAEDVAV YYC**KQSYDLFT**FGSGTKLEIK (SEQ ID NO: 321)	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDYYMTWVRQAPGKGLE WVAFIRNRARGYTSDHNASVKGR FTISRDNAKNSLYLQMNSLRAEDT AVYYCAR**DRPSYYVLDY**WGQGTT VTVSS (SEQ ID NO: 322)
h2B4-VH-hnps VL_TK	DIVMTQSPDSLAVSLGERATINC **KSSQSLFNVRSRKNYLA**WYQQK PGQPPKLLIS**WASTRES**GVPDRF SGSGSGTDFTLTISSLQAEDVAV YYC**KQSYDLFT**FGSGTKLEIK (SEQ ID NO: 323)	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDYYMTWVRQAPGKGLE WVAFIRNRARGYTSDHNPSVKGR FTISRDNAKNSLYLQMNSLRAEDT AVYYCAR**DRPSYYVLDY**WGQGTT VTVSS (SEQ ID NO: 324)
h2B4-VH-yaes VL_TK	DIVMTQSPDSLAVSLGERATINC **KSSQSLFNVRSRKNYLA**WYQQK PGQPPKLLIS**WASTRES**GVPDRF SGSGSGTDFTLTISSLQAEDVAV YYC**KQSYDLFT**FGSGTKLEIK (SEQ ID NO: 325)	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDYYMTWVRQAPGKGLE WVAFIRNRARGYTSDYAESVKGR FTISRDNAKNSLYLQMNSLRAEDT AVYYCAR**DRPSYYVLDY**WGQGTT VTVSS (SEQ ID NO: 326)
h2B4-VH-yads VL_TK	DIVMTQSPDSLAVSLGERATINC **KSSQSLFNVRSRKNYLA**WYQQK PGQPPKLLIS**WASTRES**GVPDRF SGSGSGTDFTLTISSLQAEDVAV YYC**KQSYDLFT**FGSGTKLEIK	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDYYMTWVRQAPGKGLE WVAFIRNRARGYTSDYADSVKGR FTISRDNAKNSLYLQMNSLRAEDT AVYYCAR**DRPSYYVLDY**WGQGTT

mAb	Light Chain	Heavy Chain
	(SEQ ID NO: 327)	VTVSS (SEQ ID NO: 328)
h2B4-VH-yaps VL_TK	DIVMTQSPDSLAVSLGERATINCT SSQSLFNVRSRKNYLAWYQQKP GQPPKLLISWASTRESGVPDRFS GSGSGTDFTLTISSLQAEDVAVY YCKQSYDLFTFGSGTKLEIK (SEQ ID NO: 329)	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDYYMTWVRQAPGKGLE WVAFIRNRARGYTSDYAPSVKGR FTISRDNAKNSLYLQMNSLRAEDT AVYYCARDRPSYYVLDYWGQGTT VTVSS (SEQ ID NO: 330)
h2B4-VH-hnps VL_TK-S55Y	DIVMTQSPDSLAVSLGERATINC KSSQSLFNVRSRKNYLAWYQQK PGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTISSLQAEDVAV YYCKQSYDLFTFGSGTKLEIK (SEQ ID NO: 344)	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDYYMTWVRQAPGKGLE WVAFIRNRARGYTSDHNPSVKGR FTISRDNAKNSLYLQMNSLRAEDT AVYYCARDRPSYYVLDYWGQGTT VTVSS (SEQ ID NO: 345)
h2B4-VH-hnps VL_TK-S105Q	DIVMTQSPDSLAVSLGERATINC KSSQSLFNVRSRKNYLAWYQQK PGQPPKLLISWASTRESGVPDRF SGSGSGTDFTLTISSLQAEDVAV YYCKQSYDLFTFGQGTKLEIK (SEQ ID NO: 346)	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDYYMTWVRQAPGKGLE WVAFIRNRARGYTSDHNPSVKGR FTISRDNAKNSLYLQMNSLRAEDT AVYYCARDRPSYYVLDYWGQGTT VTVSS (SEQ ID NO: 347)
h2B4-VH-hnps VL_TK-S55Y/S105Q	DIVMTQSPDSLAVSLGERATINC KSSQSLFNVRSRKNYLAWYQQK PGQPPKLLIYWASTRESGVPDRF SGSGSGTDFTLTISSLQAEDVAV YYCKQSYDLFTFGQGTKLEIK (SEQ ID NO: 348)	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDYYMTWVRQAPGKGLE WVAFIRNRARGYTSDHNPSVKGR FTISRDNAKNSLYLQMNSLRAEDT AVYYCARDRPSYYVLDYWGQGTT VTVSS (SEQ ID NO: 349)
2B4	DIVMSQSPPSLAVSVGDKVTMSC TSSQSLFNSRSRKNYLAWYQQK SGQSPKLLISWASTRESGVPDRF TGSGSGTDFTLTISSVQAEDLAV YYCKQSYDLFTFGSGTKLEIK (SEQ ID NO: 350)	EVKLVESGGGLVQPGGSLRLSCA TFGFTFTDYYMTWVRQPPGKALE WVAFIRNRARGYTSDHNASVKGR FTISRDNSQNILYLQMNTLRAEDS ATYYCARDRPSYYVLDYWGQGTT VTVSS (SEQ ID NO: 351)
h2B4-	DIVMTQSPDSLAVSLGERATINCT SSQSLFNSRSRKNYLAWYQQKP	EVQLVESGGGLVQPGGSLRLSCA ASGFTFSDYYMTWVRQAPGKGLE

mAb	Light Chain	Heavy Chain
11	GQPPKLLIS**WASTRES**GVPDRFS GSGSGTDFTLTISSLQAEDVAVY YC**QQSYDTFT**FGSGTKLEIK (SEQ ID NO: 445)	WVA**FIRNRARGYT**SDHNASVKGR FTISRDNAKNSLYLQMNSLRAEDT AVYYCAR**DRPSYYVLDY**WGQGTT VTVSS (SEQ ID NO: 444)
1C10	DIVMSQSPSSLAVSAGEKVTMSC **KSSQSLLNSRTRKNY**LAWYQQK PGQSPKLLIY**WASTRES**GVPDRF TGSGSGTDFTLTIDSVQPEDLAV YYC**TQSFILRT**FGGGTKLEIK (SEQ ID NO: 352)	QVQLQQPGSELVRPGASVILSCKA S**GYTFTSY**WMHWVRQRPGQGLE WIG**NIYSGGDTI**NYDEKFKNKAILT VDTSSSTAYMHLSSLTSEDSAVYY CTR**DATSRYFFDY**WGQGTTVTVS S (SEQ ID NO: 354)
1A4	DIVMSQSPSSLAVSAGEKVTMSC **KSSQSLLNSRTRKNY**LAWYQQK PGQSPKLLIY**WASTRAS**GVPDRF TGSGSGTDFTLTISSVQAEDLAIY Y**CKQSFILRT**FGGGTKLEIK (SEQ ID NO: 355)	QVQLQQSGPDLVKPGASVEISCK AS**GYSFTTYYLH**WVRQRPGQGLE WIG**WIFPGSDN**TKYNEKFKGKATL TADTSSSTAYMQLSSLTSEDSAVY FCAR**NRDYYFDY**WGQGTTVTVSS (SEQ ID NO: 356)
7A3	DIVVSQSPSSLAVSAGEKVIMSC **KSSQSLLNSRTRKNY**LAWYQLK PGQSPKLLIY**SASTRES**GVPDRF TGSGSGTDFTLTISSVQTEDLAV YYC**MQSFTLRT**FGGGTKLEIK (SEQ ID NO: 443)	EVQLQQSGAELVRPGALVKLSCK GS**GFNIKDYYIH**WVKQRPEQGLE WIG**WIDPENGN**NKYDPKFQGKASI TADTSSNIAYLQLSSLTSEDTAVYY CAR**NDNYAFDY**WGQGTTVTVSS (SEQ ID NO: 442)
25A8	QAVVTQESALTTSPGEAVTLTC**R SSTGAVTTSNYAN**WVQEKPDHL FTGLIG**GTNTRAP**GVPARFSGSLI GDKAALTITGAQTEDEAIYFC**VL WYNNYWV**FGGGTKLTVL (SEQ ID NO: 377)	EVQLVESGGGLVRPEGSLRLSCA AS**GFTFNTYAMN**WVRQAPGKGLE WVGR**IRSKINNYAT**YYAESVKGRF TLSRDDSLSMVYLQMNSLKNEDT AMYYCVR**HETLRSGISWFAS**WGQ GTLVTVSS (SEQ ID NO: 378)
16G7	QAVVTQESALTTSPGETVTLTC**R SSTGAVTTSNYAN**WVQEKPDHL FTGLIG**GTNNRAP**GVPARFSGSL IGDKAALTITGAQTEDEAIYFC**AL WYSNHWV**FGGGTKLTVL (SEQ ID NO: 379)	EVQLVDSGGGLVQPKGSLKLSCA AS**GFTFNTYAMN**WVRQAPGKGLE WVA**RIRSKSNNYAT**YYADSVKDR FTISRDDSQSRLYLQMNNLKTEDT AMYYCVR**HETLRSGISWFAN**WG QGTLVTVSS (SEQ ID NO: 380)

mAb	Light Chain	Heavy Chain
h25A8-B5	QAVVTQEPSLTVSPGGTVTLTCR SSTGAVTTSNYANWVQQKPGQA PRGLIGGTNTRAPGTPARFSGSL LGGKAALTLSGAQPEDEAEYYCV LWYNNYWVFGGGTKLTVL (SEQ ID NO: 381)	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSTYAMNWVRQAPGKGLE WVGRIRSKINNYATYYAESVKGRF TISRDDSKNTLYLQMNSLKTEDTA VYYCVRHETLRSGISWFASWGQG TLVTVSS (SEQ ID NO: 382)
h25A8-B8	QAVVTQEPSLTVSPGGTVTLTCR SSTGAVTTSNYANWVQQKPGQA PRGLIGGTNTRAPGTPARFSGSL LGGKAALTLSGAQPEDEAEYYCV LWYNNHWVFGGGTKLTVL (SEQ ID NO: 383)	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSTYAMNWVRQAPGKGLE WVGRIRSKINNYATYYAESVKGRF TISRDDSKNTLYLQMNSLKTEDTA VYYCVRHETLRSGISWFASWGQG TLVTVSS (SEQ ID NO: 384)
h25A8-B12	QAVVTQEPSLTVSPGGTVTLTCR ASTGAVTTSNYANWVQQKPGQ APRGLIGGTNTRAPGTPARFSGS LLGGKAALTLSGAQPEDEAEYYC VLWYNNHWVFGGGTKLTVL (SEQ ID NO: 385)	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSTYAMNWVRQAPGKGLE WVGRIRSKINNYATYYAESVKGRF TISRDDSKNTLYLQMNSLKTEDTA VYYCVRHETLRSGISWFASWGQG TLVTVSS (SEQ ID NO: 386)
h25A8-B13	QAVVTQEPSLTVSPGGTVTLTCR TSTGAVTTSNYANWVQQKPGQA PRGLIGGTNTRAPGTPARFSGSL LGGKAALTLSGAQPEDEAEYYCV LWYNNHWVFGGGTKLTVL (SEQ ID NO: 387)	EVQLVESGGGLVKPGGSLRLSCA ASGFTFSTYAMNWVRQAPGKGLE WVGRIRSKINNYATYYAESVKGRF TISRDDSKNTLYLQMNSLKTEDTA VYYCVRHETLRSGISWFASWGQG TLVTVSS (SEQ ID NO: 388)
h25A8-C5	QAVVTQEPSLTVSPGGTVTLTCR SSTGAVTTSNYANWVQQKPGQA PRGLIGGTNTRAPGTPARFSGSL LGGKAALTLSGAQPEDEAEYYCV LWYNNYWVFGGGTKLTVL (SEQ ID NO: 389)	EVQLVESGGGLVKPGGSLRLSCA ASGFTFNTYAMNWVRQAPGKGLE WVGRIRSKINNYATYYAESVKGRF TISRDDSKNTLYLQMNSLKTEDTA VYYCVRHETLRSGISWFASWGQG TLVTVSS (SEQ ID NO: 390)
h25A8-C8	QAVVTQEPSLTVSPGGTVTLTCR SSTGAVTTSNYANWVQQKPGQA PRGLIGGTNTRAPGTPARFSGSL LGGKAALTLSGAQPEDEAEYYCV LWYNNHWVFGGGTKLTVL (SEQ ID NO: 391)	EVQLVESGGGLVKPGGSLRLSCA ASGFTFNTYAMNWVRQAPGKGLE WVGRIRSKINNYATYYAESVKGRF TISRDDSKNTLYLQMNSLKTEDTA VYYCVRHETLRSGISWFASWGQG TLVTVSS (SEQ ID NO: 392)
h25A8-	QAVVTQEPSLTVSPGGTVTLTCR	EVQLVESGGGLVKPGGSLRLSCA

mAb	Light Chain	Heavy Chain
D13	**TSTGAVTTSNYAN**WVQQKPGQA PRGLIG**GTNTRAP**GTPARFSGSL LGGKAALTLSGAQPEDEAEYYC**V LWYNNHWV**FGGGTKLTVL (SEQ ID NO: 393)	AS**GFTFSTY**AMNWVRQAPGKGLE WVGR**IRSHINNYA**TYYAESVKGRF TISRDDSKNTLYLQMNSLKTEDTA VYYCVR**HETLRSGISWFAS**WGQG TLVTVSS (SEQ ID NO: 394)
h25A8-E13	QAVVTQEPSLTVSPGGTVTLTC**R TSTGAVTTSNYAN**WVQQKPGQA PRGLIG**GTNTRAP**GTPARFSGSL LGGKAALTLSGAQPEDEAEYYC**V LWYNNHWV**FGGGTKLTVL (SEQ ID NO: 395)	EVQLVESGGGLVKPGGSLRLSCA AS**GFTFSTY**AMNWVRQAPGKGLE WVGR**IRSKYNNYA**TYYAESVKGR FTISRDDSKNTLYLQMNSLKTEDT AVYYCVR**HETLRSGISWFAS**WGQ GTLVTVSS (SEQ ID NO: 396)
h25A8-F13	QAVVTQEPSLTVSPGGTVTLTC**R TSTGAVTTSNYAN**WVQQKPGQA PRGLIG**GTNTRAP**GTPARFSGSL LGGKAALTLSGAQPEDEAEYYC**V LWYNNHWV**FGGGTKLTVL (SEQ ID NO: 397)	EVQLVESGGGLVKPGGSLRLSCA AS**GFTFSTY**AMNWVRQAPGKGLE WVGR**ERSKINNYA**TYYAESVKGR FTISRDDSKNTLYLQMNSLKTEDT AVYYCVR**HETLRSGISWFAS**WGQ GTLVTVSS (SEQ ID NO: 398)
h25A8-G13	QAVVTQEPSLTVSPGGTVTLTC**R TSTGAVTTSNYAN**WVQQKPGQA PRGLIG**GTNTRAP**GTPARFSGSL LGGKAALTLSGAQPEDEAEYYC**V LWYNNHWV**FGGGTKLTVL (SEQ ID NO: 399)	EVQLVESGGGLVKPGGSLRLSCA AS**GFTFSTY**AMNWVRQAPGKGLE WVGR**IRSKINNYK**TYYAESVKGRF TISRDDSKNTLYLQMNSLKTEDTA VYYCVR**HETLRSGISWFAS**WGQG TLVTVSS (SEQ ID NO: 400)

In Table 3, the underlined sequences are CDR sequences according to Kabat and in bold according to Chothia.

The invention also provides CDR portions of antibodies to CD3 (including Chothia, Kabat CDRs, and CDR contact regions). Determination of CDR regions is well within the skill of the art. It is understood that in some embodiments, CDRs can be a combination of the Kabat and Chothia CDR (also termed "combined CRs" or "extended CDRs"). In some embodiments, the CDRs are the Kabat CDRs. In other embodiments, the CDRs are the Chothia CDRs. In other words, in embodiments with more than one CDR, the CDRs may be any of Kabat, Chothia, combination CDRs, or combinations thereof. Table 4 provides examples of CDR sequences provided herein.

Table 4

Heavy Chain			
mAb	**CDRH1**	**CDRH2**	**CDRH3**
h2B4	DYYMT (SEQ ID NO: 331) (Kabat); GFTFSDY (SEQ ID NO: 332)(Chothia); GFTFSDYYMT (SEQ ID NO: 333) (Extended)	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDHNASVKG (SEQ ID NO: 334) (Chothia)	DRPSYYVLDY (SEQ ID NO: 335)
h2B4-VH-wt VL_TK	DYYMT (SEQ ID NO: 331) (Kabat); GFTFSDY (SEQ ID NO: 332)(Chothia); GFTFSDYYMT (SEQ ID NO: 333) (Extended)	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDHNASVKG (SEQ ID NO: 334) (Chothia)	DRPSYYVLDY (SEQ ID NO: 335)
h2B4-VH-hnps VL_TK	DYYMT (SEQ ID NO: 331) (Kabat); GFTFSDY (SEQ ID NO: 332)(Chothia); GFTFSDYYMT (SEQ ID NO: 333) (Extended)	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDHNPSVKG (SEQ ID NO: 336) (Chothia)	DRPSYYVLDY (SEQ ID NO: 335)
h2B4-VH-yaes VL_TK	DYYMT (SEQ ID NO: 331) (Kabat); GFTFSDY (SEQ ID NO: 332)(Chothia); GFTFSDYYMT (SEQ ID NO: 333) (Extended)	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDYAESVKG (SEQ ID NO: 337) (Chothia)	DRPSYYVLDY (SEQ ID NO: 335)

h2B4-VH-yadsVL_TK	DYYMT (SEQ ID NO: 331) (Kabat); GFTFSDY (SEQ ID NO: 332)(Chothia); GFTFSDYYMT (SEQ ID NO: 333) (Extended)	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDYADSVKG (SEQ ID NO: 338) (Chothia)	DRPSYYVLDY (SEQ ID NO: 335)
h2B4-VH-yapsVL_TK	DYYMT (SEQ ID NO: 331) (Kabat); GFTFSDY (SEQ ID NO: 332)(Chothia); GFTFSDYYMT (SEQ ID NO: 333) (Extended)	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDYAPSVKG (SEQ ID NO: 339) (Chothia)	DRPSYYVLDY (SEQ ID NO: 335)
h2B4-VH-hnpsVL_TK-S55Y	DYYMT (SEQ ID NO: 331) (Kabat); GFTFSDY (SEQ ID NO: 332)(Chothia); GFTFSDYYMT (SEQ ID NO: 333) (Extended)	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDHNPSVKG (SEQ ID NO: 336) (Chothia)	DRPSYYVLDY (SEQ ID NO: 335)
h2B4-VH-hnpsVL_TK-S105Q	DYYMT (SEQ ID NO: 331) (Kabat); GFTFSDY (SEQ ID NO: 332)(Chothia); GFTFSDYYMT (SEQ ID NO: 333) (Extended)	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDHNPSVKG (SEQ ID NO: 336) (Chothia)	DRPSYYVLDY (SEQ ID NO: 335)
h2B4-VH-hnpsVL_TK-	DYYMT (SEQ ID NO: 331) (Kabat); GFTFSDY (SEQ ID NO: 332)(Chothia);	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDHNPSVKG	DRPSYYVLDY (SEQ ID NO: 335)

S55Y/ S105Q	GFTFSDYYMT (SEQ ID NO: 333) (Extended)	(SEQ ID NO: 336) (Chothia)	
2B4	DYYMT (SEQ ID NO: 331) (Kabat); GFTFTDY (SEQ ID NO: 415)(Chothia); GFTFTDYYMT (SEQ ID NO: 416) (Extended)	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDHNASVKG (SEQ ID NO: 418) (Chothia)	DRPSYYVLDY (SEQ ID NO: 335)
h2B4-11	DYYMT (SEQ ID NO: 331) (Kabat); GFTFSDY (SEQ ID NO: 332)(Chothia); GFTFSDYYMT (SEQ ID NO: 333) (Extended)	RNRARGYT (SEQ ID NO: 417) (Kabat) FIRNRARGYTSDHNASVKG (SEQ ID NO: 418) (Chothia)	DRPSYYVLDY (SEQ ID NO: 335)
1C10	SYWMH (SEQ ID NO: 418) (Kabat) GYTFTSY (SEQ ID NO: 419) (Chothia) GYTFTSYWMH (SEQ ID NO: 420) (Extended)	YSGGDT (SEQ ID NO: 421) (Kabat) NIYSGGDTINYDEKFKN (SEQ ID NO: 422) (Chothia)	DATSRYFFDY (SEQ ID NO: 423)
1A4	TYYLH (SEQ ID NO: 424) (Kabat) GYSFTTYY (SEQ ID NO: 425) (Chothia) GYSFTTYYLH (SEQ ID NO: 426) (Extended)	FPGSDN (SEQ ID NO: 427) (Kabat) WIFPGSDNTKYNEKFKG (SEQ ID NO: 428) (Chothia)	NRDYYFDY (SEQ ID NO: 429)
7A3	DYYIH (SEQ ID NO: 446) (Kabat) GFNIKDY(SEQ ID	DPENGN (SEQ ID NO: 449) (Kabat)	NDNYAFDY (SEQ ID NO: 451)

	NO: 447) (Chothia) GFNIKDYYIH (SEQ ID NO: 448) (Extended)	WIDPENGNNKYDPKFQG (SEQ ID NO: 450) (Chothia)	
25A8	TYAMN (SEQ ID NO: 401) (Kabat); GFTFNTY (SEQ ID NO: 402)(Chothia); GFTFNTYAMN (SEQ ID NO: 403) (Extended)	RSKINNYA (SEQ ID NO: 404) (Kabat) RIRSKINNYATYYAESVKG (SEQ ID NO: 405) (Chothia)	HETLRSGISWFAS (SEQ ID NO: 406)
16G7	TYAMN (SEQ ID NO: 401) (Kabat); GFTFNTY (SEQ ID NO: 402)(Chothia); GFTFNTYAMN (SEQ ID NO: 403) (Extended)	RSKSNNYA (SEQ ID NO: 404) (Kabat) RIRSKSNNYATYYADSVKD (SEQ ID NO: 405) (Chothia)	HETLRSGISWFAN (SEQ ID NO: 406)
h25A8-B5	TYAMN (SEQ ID NO: 401) (Kabat); GFTFSTY (SEQ ID NO: 407)(Chothia); GFTFSTYAMN (SEQ ID NO: 408) (Extended)	RSKINNYA (SEQ ID NO: 404) (Kabat) RIRSKINNYATYYAESVKG (SEQ ID NO: 405) (Chothia)	HETLRSGISWFAS (SEQ ID NO: 406)
h25A8-B8	TYAMN (SEQ ID NO: 401) (Kabat); GFTFSTY (SEQ ID NO: 407)(Chothia); GFTFSTYAMN (SEQ ID NO: 408) (Extended)	RSKINNYA (SEQ ID NO: 404) (Kabat) RIRSKINNYATYYAESVKG (SEQ ID NO: 405) (Chothia)	HETLRSGISWFAS (SEQ ID NO: 406)
h25A8-	TYAMN (SEQ ID NO:	RSKINNYA (SEQ ID NO:	HETLRSGISWFA

B12	401) (Kabat); GFTFSTY (SEQ ID NO: 407)(Chothia); GFTFSTYAMN (SEQ ID NO: 408) (Extended)	404) (Kabat) RIRSKINNYATYYAESVKG (SEQ ID NO: 405) (Chothia)	S (SEQ ID NO: 406)
h25A8-B13	TYAMN (SEQ ID NO: 401) (Kabat); GFTFSTY (SEQ ID NO: 407)(Chothia); GFTFSTYAMN (SEQ ID NO: 408) (Extended)	RSKINNYA (SEQ ID NO: 404) (Kabat) RIRSKINNYATYYAESVKG (SEQ ID NO: 405) (Chothia)	HETLRSGISWFAS (SEQ ID NO: 406)
h25A8-C5	TYAMN (SEQ ID NO: 401) (Kabat); GFTFNTY (SEQ ID NO: 402)(Chothia); GFTFNTYAMN (SEQ ID NO: 403) (Extended)	RSKINNYA (SEQ ID NO: 404) (Kabat) RIRSKINNYATYYAESVKG (SEQ ID NO: 405) (Chothia)	HETLRSGISWFAS (SEQ ID NO: 406)
h25A8-C8	TYAMN (SEQ ID NO: 401) (Kabat); GFTFNTY (SEQ ID NO: 402)(Chothia); GFTFNTYAMN (SEQ ID NO: 403)	RSKINNYA (SEQ ID NO: 404) (Kabat) RIRSKINNYATYYAESVKG (SEQ ID NO: 405) (Chothia)	HETLRSGISWFAS (SEQ ID NO: 406)
h25A8-D13	TYAMN (SEQ ID NO: 401) (Kabat); GFTFSTY (SEQ ID NO: 407)(Chothia); GFTFSTYAMN (SEQ	RSHINNYA (SEQ ID NO: 409) (Kabat) RIRSHINNYATYYAESVKG (SEQ ID NO: 410) (Chothia)	HETLRSGISWFAS (SEQ ID NO: 406)

	ID NO: 408) (Extended)		
h25A8-E13	TYAMN (SEQ ID NO: 401) (Kabat); GFTFSTY (SEQ ID NO: 407)(Chothia); GFTFSTYAMN (SEQ ID NO: 408) (Extended)	RSKYNNYA (SEQ ID NO: 411) (Kabat) RIRSKYNNYATYYAESVKG (SEQ ID NO: 412) (Chothia)	HETLRSGISWFAS (SEQ ID NO: 406)
h25A8-F13	TYAMN (SEQ ID NO: 401) (Kabat); GFTFSTY (SEQ ID NO: 407)(Chothia); GFTFSTYAMN (SEQ ID NO: 408) (Extended)	RSKINNYA (SEQ ID NO: 404) (Kabat) RERSKINNYATYYAESVKG (SEQ ID NO: 413) (Chothia)	HETLRSGISWFAS (SEQ ID NO: 406)
h25A8-G13	TYAMN (SEQ ID NO: 401) (Kabat); GFTFSTY (SEQ ID NO: 407)(Chothia); GFTFSTYAMN (SEQ ID NO: 408) (Extended)	RSKINNYA (SEQ ID NO: 404) (Kabat) RIRSKINNYKTYYAESVKG (SEQ ID NO: 414) (Chothia)	HETLRSGISWFAS (SEQ ID NO: 406)
Light Chain			
mAb	**CDRH1**	**CDRH2**	**CDRH3**
h2B4	TSSQSLFNVRSRKNYLA (SEQ ID NO: 340)	WASTRES (SEQ ID NO: 341)	KQSYDLFT (SEQ ID NO: 342)
h2B4-VH-wt VL_TK	KSSQSLFNVRSRKNYLA (SEQ ID NO: 343)	WASTRES (SEQ ID NO: 341)	KQSYDLFT (SEQ ID NO: 342)

h2B4-VH-hnps VL_TK	KSSQSLFNVRSRKNYLA (SEQ ID NO: 343)	WASTRES (SEQ ID NO: 341)	KQSYDLFT (SEQ ID NO: 342)
h2B4-VH-yaes VL_TK	KSSQSLFNVRSRKNYLA (SEQ ID NO: 343)	WASTRES (SEQ ID NO: 341)	KQSYDLFT (SEQ ID NO: 342)
h2B4-VH-yads VL_TK	KSSQSLFNVRSRKNYLA (SEQ ID NO: 343)	WASTRES (SEQ ID NO: 341)	KQSYDLFT (SEQ ID NO: 342)
h2B4-VH-yaps VL_TK	KSSQSLFNVRSRKNYLA (SEQ ID NO: 343)	WASTRES (SEQ ID NO: 341)	KQSYDLFT (SEQ ID NO: 342)
2B4	TSSQSLFNSRSRKNYLA (SEQ ID NO: 430)	WASTRES (SEQ ID NO: 341)	KQSYDLFT (SEQ ID NO: 342)
h2B4-11	TSSQSLFNSRSRKNYLA (SEQ ID NO: 430)	WASTRES (SEQ ID NO: 341)	QQSYDTFT (SEQ ID NO: 446)
1C10	KSSQSLLNSRTRKNY (SEQ ID NO: 431)	WASTRES (SEQ ID NO: 341)	TQSFILRT (SEQ ID NO: 432)
1A4	KSSQSLLNSRTRKNY (SEQ ID NO: 431)	WASTRAS (SEQ ID NO: 433)	KQSFILRT (SEQ ID NO: 434)
7A3	KSSQSLLNSRTRKNY (SEQ ID NO: 431)	SASTRES (SEQ ID NO: 452)	MQSFTLRT (SEQ ID NO: 453)
h2B4-VH-hnps VL_TK - S55Y	KSSQSLFNVRSRKNYLA (SEQ ID NO: 343)	WASTRES (SEQ ID NO: 341)	KQSYDLFT (SEQ ID NO: 342)

h2B4-VH-hnps VL_TK - S105Q	KSSQSLFNVRSRKNYLA (SEQ ID NO: 343)	WASTRES (SEQ ID NO: 341)	KQSYDLFT (SEQ ID NO: 342)
h2B4-VH-hnps VL_TK - S55Y/ S105Q	KSSQSLFNVRSRKNYLA (SEQ ID NO: 343)	WASTRES (SEQ ID NO: 341)	KQSYDLFT (SEQ ID NO: 342)
25A8	RSSTGAVTTSNYAN (SEQ ID NO: 435)	GTNTRAP (SEQ ID NO: 436)	VLWYNNYWV (SEQ ID NO: 437)
16G7	RSSTGAVTTSNYAN (SEQ ID NO: 435)	GTNTRAP (SEQ ID NO: 436)	ALWYSNHWV (SEQ ID NO: 438)
h25A8-B5	RSSTGAVTTSNYAN (SEQ ID NO: 435)	GTNTRAP (SEQ ID NO: 436)	VLWYNNYWV (SEQ ID NO: 437)
h25A8-B8	RSSTGAVTTSNYAN (SEQ ID NO: 435)	GTNTRAP (SEQ ID NO: 436)	VLWYNNHWV (SEQ ID NO: 439)
h25A8-B12	RASTGAVTTSNYAN (SEQ ID NO: 440)	GTNTRAP (SEQ ID NO: 436)	VLWYNNHWV (SEQ ID NO: 439)
h25A8-B13	RTSTGAVTTSNYAN (SEQ ID NO: 441)	GTNTRAP (SEQ ID NO: 436)	VLWYNNHWV (SEQ ID NO: 439)
h25A8-C5	RSSTGAVTTSNYAN (SEQ ID NO: 435)	GTNTRAP (SEQ ID NO: 436)	VLWYNNYWV (SEQ ID NO: 437)
h25A8-C8	RSSTGAVTTSNYAN (SEQ ID NO: 435)	GTNTRAP (SEQ ID NO: 436)	VLWYNNHWV (SEQ ID NO: 439)
h25A8-D13	RTSTGAVTTSNYAN (SEQ ID NO: 441)	GTNTRAP (SEQ ID NO: 436)	VLWYNNHWV (SEQ ID NO: 439)
h25A8-E13	RTSTGAVTTSNYAN (SEQ ID NO: 441)	GTNTRAP (SEQ ID NO: 436)	VLWYNNHWV (SEQ ID NO: 439)
h25A8-	RTSTGAVTTSNYAN	GTNTRAP (SEQ ID NO:	VLWYNNHWV

F13	(SEQ ID NO: 441)	436)	(SEQ ID NO: 439)
h25A8-G13	RTSTGAVTTSNYAN (SEQ ID NO: 441)	GTNTRAP (SEQ ID NO: 436)	VLWYNNHWV (SEQ ID NO: 439)

The invention also provides isolated polynucleotides encoding the antibodies of the invention, and vectors and host cells comprising the polynucleotide.

In one embodiment, a polynucleotide comprises a sequence encoding the heavy chain and/or the light chain variable regions of antibody h2B4, h2B4-VH-wt VL_TK, h2B4-VH-hnps VL_TK, h2B4-VH-yaes VL_TK, h2B4-VH-yads VL_TK, h2B4-VH-yaps VL_TK, h2B4-VH-hnps VL_TK-S55Y, h2B4-VH-hnps VL_TK-S105Q, h2B4—vH-hnps VL_TK-S55Y/S105Q, 2B4, h2B4-11, 1C10, 1A4, 7A3, 25A8, 16G7, h25A8-B5, h25A8-B8, h25A8-B12, h25A8-B13, h25A8-C5, h25A8-C8, h25A8-D13, h25A8-E13, h25A8-F13, or h25A8-G13. The sequence encoding the antibody of interest may be maintained in a vector in a host cell and the host cell can then be expanded and frozen for future use. Vectors (including expression vectors) and host cells are further described herein.

The invention also encompasses fusion proteins comprising one or more fragments or regions from the antibodies of this invention. In one embodiment, a fusion polypeptide is provided that comprises at least 10 contiguous amino acids of the variable light chain region shown in SEQ ID NOs: 319, 321, 323, 325, 327, 329, 344, 346, 348, 350, 445, 352, 355, 443, 377, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, or 399, and/or at least 10 amino acids of the variable heavy chain region shown in SEQ ID NOs: 320, 322, 324, 326, 328, 330, 345, 347, 349, 351, 354, 356, 444, 442, 378, 380, 382, 384, 386, 388, 390, 392, 394, 396, 398, or 400. In other embodiments, a fusion polypeptide is provided that comprises at least about 10, at least about 15, at least about 20, at least about 25, or at least about 30 contiguous amino acids of the variable light chain region and/or at least about 10, at least about 15, at least about 20, at least about 25, or at least about 30 contiguous amino acids of the variable heavy chain region. In another embodiment, the fusion polypeptide comprises a light chain variable region and/or a heavy chain variable region, as shown in any of the sequence pairs selected from among SEQ ID NOs: 319 and 320, 321 and 322, 323 and 324, 325 and 326, 327 and 328, 329 and 330, 344 and 345,

346 and 347, 348 and 349, 350 and 351, 445 and 444, 352 and 354, 355 and 356, 443 and 442, 377 and 378, 379 and 380, 381 and 382, 383 and 384, 385 and 386, 387 and 388, 389 and 390, 391 and 392, 393 and 394, 395 and 396, 397 and 398, or 399 and 400. In another embodiment, the fusion polypeptide comprises one or more CDR(s). In still other embodiments, the fusion polypeptide comprises CDR H3 (VH CDR3) and/or CDR L3 (VL CDR3). For purposes of this invention, a fusion protein contains one or more antibodies and another amino acid sequence to which it is not attached in the native molecule, for example, a heterologous sequence or a homologous sequence from another region. Exemplary heterologous sequences include, but are not limited to a "tag" such as a FLAG tag or a 6His tag. Tags are well known in the art.

A fusion polypeptide can be created by methods known in the art, for example, synthetically or recombinantly. Typically, the fusion proteins of this invention are made by preparing an expressing a polynucleotide encoding them using recombinant methods described herein, although they may also be prepared by other means known in the art, including, for example, chemical synthesis.

Representative materials of the CD3 antibody in the present invention were deposited in the American Type Culture Collection (ATCC) on September 11, 2015. Vector having ATCC Accession No. PTA-122513 is a polynucleotide encoding the heavy chain variable region of humanized CD3 antibody h2B4-VH-hnps VL_TK, and vector having ATCC Accession No. PTA-122512 is a polynucleotide encoding the light chain variable region of humanized CD3 antibodyh2B4-VH-hnps VL_TK . The deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposit will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Pfizer, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U.S. patent or upon laying open to the public of any U.S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U.S. Commissioner of Patents and Trademarks to be entitled thereto according to 35 U.S.C. Section 122 and the

Commissioner's rules pursuant thereto (including 37 C.F.R. Section 1.14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

Bispecific Antibodies and Methods of Making

Bispecific antibodies, monoclonal antibodies that have binding specificities for at least two different antigens, can be prepared using the antibodies disclosed herein. Methods for making bispecific antibodies are known in the art (see, e.g., Suresh et al., Methods in Enzymology 121:210, 1986). Traditionally, the recombinant production of bispecific antibodies was based on the coexpression of two immunoglobulin heavy chain-light chain pairs, with the two heavy chains having different specificities (Millstein and Cuello, Nature 305, 537-539, 1983).

According to one approach to making bispecific antibodies, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant region sequences. The fusion preferably is with an immunoglobulin heavy chain constant region, comprising at least part of the hinge, CH2 and CH3 regions. It is preferred to have the first heavy chain constant region (CH1), containing the site necessary for light chain binding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are cotransfected into a suitable host organism. This provides for great flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yields. It is, however, possible to insert the coding sequences for two or all three polypeptide

chains in one expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios are of no particular significance.

In one approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. This asymmetric structure, with an immunoglobulin light chain in only one half of the bispecific molecule, facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations. This approach is described in PCT Publication No. WO 94/04690.

In another approach, the bispecific antibodies are composed of amino acid modification in the first hinge region in one arm, and the substituted/replaced amino acid in the first hinge region has an opposite charge to the corresponding amino acid in the second hinge region in another arm. This approach is described in International Patent Application No. PCT/US2011/036419 (WO2011/143545).

In another approach, the formation of a desired heteromultimeric or heterodimeric protein (e.g., bispecific antibody) is enhanced by altering or engineering an interface between a first and a second immunoglobulin-like Fc region (e.g., a hinge region and/or a CH3 region). In this approach, the bispecific antibodies may be composed of a CH3 region, wherein the CH3 region comprises a first CH3 polypeptide and a second CH3 polypeptide which interact together to form a CH3 interface, wherein one or more amino acids within the CH3 interface destabilize homodimer formation and are not electrostatically unfavorable to homodimer formation. This approach is described in International Patent Application No. PCT/US2011/036419 (WO2011/143545).

In another approach, the bispecific antibodies can be generated using a glutamine-containing peptide tag engineered to the antibody directed to an epitope (e.g., BCMA) in one arm and another peptide tag (e.g., a Lys-containing peptide tag or a reactive endogenous Lys) engineered to a second antibody directed to a second epitope in another arm in the presence of transglutaminase. This approach is described in International Patent Application No. PCT/IB2011/054899 (WO2012/059882).

In another aspect of the invention, the heterodimeric protein (e.g., bispecific antibody) as described herein comprises a full-length human antibody, wherein a first

antibody variable domain of the heterodimeric protein is capable of recruiting the activity of a human immune effector cell by specifically binding to an effector antigen located on the human immune effector cell, and wherein a second antibody variable domain of the heterodimeric protein is capable of specifically binding to a target antigen. In some embodiments, the human antibody has an IgG1, IgG2, IgG3, or IgG4 isotype. In some embodiments, the heterodimeric protein comprises an immunologically inert Fc region.

The human immune effector cell can be any of a variety of immune effector cells known in the art. For example, the immune effector cell can be a member of the human lymphoid cell lineage, including, but not limited to, a T cell (e.g., a cytotoxic T cell), a B cell, and a natural killer (NK) cell. The immune effector cell can also be, for example without limitation, a member of the human myeloid lineage, including, but not limited to, a monocyte, a neutrophilic granulocyte, and a dendritic cell. Such immune effector cells may have either a cytotoxic or an apoptotic effect on a target cell or other desired effect upon activation by binding of an effector antigen.

The effector antigen is an antigen (e.g., a protein or a polypeptide) that is expressed on the human immune effector cell. Examples of effector antigens that can be bound by the heterodimeric protein (e.g., a heterodimeric antibody or a bispecific antibody) include, but are not limited to, human CD3 (or CD3 (Cluster of Differentiation) complex), CD16, NKG2D, NKp46, CD2, CD28, CD25, CD64, and CD89.

The target cell can be a cell that is native or foreign to humans. In a native target cell, the cell may have been transformed to be a malignant cell or pathologically modified (e.g., a native target cell infected with a virus, a plasmodium, or a bacterium). In a foreign target cell, the cell is an invading pathogen, such as a bacterium, a plasmodium, or a virus.

The target antigen is expressed on a target cell, and is not effector antigen. Examples of the target antigens include, but are not limited to, BCMA, EpCAM (Epithelial Cell Adhesion Molecule), CCR5 (Chemokine Receptor type 5), CD19, HER (Human Epidermal Growth Factor Receptor)-2/neu, HER-3, HER-4, EGFR (Epidermal Growth Factor Receptor), PSMA, CEA, MUC-1 (Mucin), MUC2, MUC3, MUC4, MUC5AC, MUC5B, MUC7, ClhCG, Lewis-Y, CD20, CD33, CD30, ganglioside GD3, 9-O-Acetyl-GD3, GM2, Globo H, fucosyl GM1, Poly SA, GD2, Carboanhydrase IX (MN/CA IX), CD44v6, Shh (Sonic Hedgehog), Wue-1, Plasma Cell Antigen, (membrane-bound) IgE, MCSP

(Melanoma Chondroitin Sulfate Proteoglycan), CCR8, TNF-alpha precursor, STEAP, mesothelin, A33 Antigen, PSCA (Prostate Stem Cell Antigen), Ly-6; desmoglein 4, E-cadherin neoepitope, Fetal Acetylcholine Receptor, CD25, CA19-9 marker, CA-125 marker and MIS (Muellerian Inhibitory Substance) Receptor type II, sTn (sialylated Tn antigen; TAG-72), FAP (fibroblast activation antigen), endosialin, EGFRvIII, LG, SAS and CD63.

In some embodiments, the heterodimeric protein (e.g., bispecific antibody) as described herein comprises a full-length human antibody, wherein a first antibody variable domain of the heterodimeric protein is capable of recruiting the activity of a human immune effector cell by specifically binding to an effector antigen (e.g., CD3 antigen) located on the human immune effector cell, wherein a second antibody variable domain of the heterodimeric protein is capable of specifically binding to a target antigen (e.g., CD20 antigen or EpCAM), wherein the first and second antibody variable domain of the heterodimeric protein comprise amino acid modifications at positions 223, 225, and 228 (e.g., (C223E or C223R), (E225R), and (P228E or P228R)) in the hinge region and at position 409 or 368 (e.g., K409R or L368E (EU numbering scheme)) in the CH3 region of human IgG2 (SEQ ID NO: 493).

In some embodiments, the first and second antibody variable domains of the heterodimeric protein comprise amino acid modifications at positions 221 and 228 (e.g., (D221R or D221E) and (P228R or P228E)) in the hinge region and at position 409 or 368 (e.g., K409R or L368E (EU numbering scheme)) in the CH3 region of human IgG1 (SEQ ID NO: 494).

In some embodiments, the first and second antibody variable domains of the heterodimeric protein comprise amino acid modifications at positions 228 (e.g., (P228E or P228R)) in the hinge region and at position 409 or 368 (e.g., R409 or L368E (EU numbering scheme)) in the CH3 region of human IgG4 (SEQ ID NO: 495).

In another embodiment, the first antibody variable domain of the heterodimeric protein comprises a VH region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 320, 322, 324, 326, 328, 330, 345, 347, 349, 351, 444, 354, 356, 378, 442, 380, 382, 384 386, 388, 390, 392, 394, 396, 398, or 400; and/or a light chain variable (VL) region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 319, 321, 323, 325, 327, 329, 344, 346, 348, 350, 352,

355, 377, 443, 445, 379, 381, 383, 385, 387, 389, 391, 393, 395, 397, or 399, and the second antibody variable domain of the heterodimeric protein comprises VH region comprising the VH sequence shown in SEQ ID NO: 2, 3, 7, 8, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 37, 39, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 83, 87, 92, 95, 97, 99, 101, 104, 106, 110, 112, 114, 118, 120, 122, 125, 127, 313, 314, 363, or 365; and/or a VL region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 1, 4, 5, 6, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 34, 36, 38, 40, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 317, 81, 82, 84, 85, 86, 88, 89, 90, 91, 93, 94, 96, 98, 100, 102, 103, 105, 107, 108, 109, 111, 113, 115, 116, 117, 119, 121, 123, 124, 126, 128, 315, or 364.

In another embodiment, the first antibody variable domain comprises a heavy chain variable (VH) region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 324 or 388; and/or a light chain variable (VL) region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 323 or 387; and the second antibody variable domain comprises a heavy chain variable (VH) region comprising a VH CDR1, VH CDR2, and VH CDR3 of the VH sequence shown in SEQ ID NO: 112; and/or a light chain variable (VL) region comprising VL CDR1, VL CDR2, and VL CDR3 of the VL sequence shown in SEQ ID NO: 38.

In another embodiment, the first antibody variable domain comprises a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 331 (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 417; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; and a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 343; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a heavy chain VH region comprising a heavy chain variable (VH) region comprising (i) a VH CDR1 comprising the sequence shown in SEQ ID NO: 156; (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 159; and (iii) a VH CDR3 comprising SEQ ID NO: 155; and a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence

shown in SEQ ID NO: 209; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 225. The VH CDR1 of the first antibody variable domain may further comprise the sequence of S, FS, TFS, FTFS or GFTFS immediately preceding the sequence shown in SEQ ID NO: 331. For example, the VH CDR1 of the first antibody variable domain may comprise the sequence shown in SEQ ID NO: 333. The VH CDR2 of the first antibody variable domain may further comprise the sequence of F or FI immediately preceding the sequence shown in SEQ ID NO: 417 and/or the sequence of S, SD, SDH, SDHN, SDHNP, SDHNPS, SDHNPSV, SDHNPSVK, or SDHNPSVKG immediately following the sequence shown in SEQ ID NO: 417. For example, the VH CDR2 of the frist antibody variable domain may comprise the sequence shown in SEQ ID NO: 336. The VH CDR1 of the second antibody variable domain may further comprise the sequence of S, FS, TFS, FTFS or GFTFS immediately preceding the sequence shown in SEQ ID NO: 156. For example, the VH CDR1 of the second antibody variable domain may comprise the sequence shown in SEQ ID NO: 157. The VH CDR2 of the second antibody variable domain may further comprise the sequence of A or AI immediately preceding the sequence shown in SEQ ID NO: 159 and/or the sequence of L, LP, LPY, LPYA, LPYAD, LPYADS, LPYADSV, LPYADSVK, or LPYADSVKG immediately following the sequence shown in SEQ ID NO: 159. For example, the VH CDR2 of the second antibody variable domain may comprise the sequence shown in SEQ ID NO: 158.

In another embodiment, the first antibody variable domain comprises a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 332 (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 336; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; and a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 343; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a heavy chain VH region comprising a heavy chain variable (VH) region comprising (i) a VH CDR1 comprising the sequence shown in SEQ ID NO: 151; (ii) a VH CDR2 comprising the

sequence shown in SEQ ID NO: 158; and (iii) a VH CDR3 comprising SEQ ID NO: 155; and a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 225. The VH CDR1 of the first antibody variable domain may further comprise the sequence of Y, YM or YMT immediatelly follwing the sequence shown in SEQ ID NO: 332. For example, the VH CDR1 of the first antibody variable domain may comprise the sequence shown in SEQ ID NO: 333. The VH CDR1 of the second antibody variable domain may further comprise the sequence P, PM, or PMS immediately following the sequence shown in SEQ ID NO: 151. For example, the VH CDR1 of the second antibody variable domain may comprise the sequence shown in SEQ ID NO: 157.

In another embodiment, the first antibody variable domain comprises a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 401 (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 404; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 406; and a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 441; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 436; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 439; and the second antibody variable domain comprises a heavy chain VH region comprising a heavy chain variable (VH) region comprising (i) a VH CDR1 comprising the sequence shown in SEQ ID NO: 156; (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 159; and (iii) a VH CDR3 comprising SEQ ID NO: 155; and a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 225. The VH CDR1 of the first antibody variable domain may further comprise the sequence of S, FS, TFS, FTFS or GFTFS immediately preceding the sequence shown in SEQ ID NO: 401. For example, the VH CDR1 of the first antibody variable domain comprises the sequence shown in SEQ ID NO: 408. The VH CDR2 of the first antibody variable domain may further comprise the sequence of R or RI immediately preceding the sequence shown in SEQ ID

NO: 404 and/or the sequence of T, TY, TYY, TYYA, TYYAE, TYYAES, TYYAESV, TYYAESVK, or TYYAESVKG immediately following the sequence shown in SEQ ID NO: 404. For example, the bispecific antibody of claim 49, wherein the VH CDR2 of the frist antibody variable domain comprises the sequence shown in SEQ ID NO: 405. The VH CDR1 of the second antibody variable domain may further comprise the sequence of S, FS, TFS, FTFS or GFTFS immediately preceding the sequence shown in SEQ ID NO: 156. For example, the VH CDR1 of the second antibody variable domain comprises the sequence shown in SEQ ID NO: 157. The VH CDR2 of the second antibody variable domain may further comprise the sequence of A or AI immediately preceding the sequence shown in SEQ ID NO: 159 and/or the sequence of L, LP, LPY, LPYA, LPYAD, LPYADS, LPYADSV, LPYADSVK, or LPYADSVKG immediately following the sequence shown in SEQ ID NO: 159. For example, the VH CDR2 of the second antibody variable domain may comprise the sequence shown in SEQ ID NO: 158.

In another embodiment, the first antibody variable domain comprises a heavy chain variable (VH) region comprising (i) a VH complementarity determining region one (CDR1) comprising the sequence shown in SEQ ID NO: 407 (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 405; and iii) a VH CDR3 comprising the sequence shown in SEQ ID NO: 406; and a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 441; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 436; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 439; and the second antibody variable domain comprises a heavy chain VH region comprising a heavy chain variable (VH) region comprising (i) a VH CDR1 comprising the sequence shown in SEQ ID NO: 151; (ii) a VH CDR2 comprising the sequence shown in SEQ ID NO: 158; and (iii) a VH CDR3 comprising SEQ ID NO: 155; and a light chain variable (VL) region comprising (i) a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; (ii) a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and (iii) a VL CDR3 comprising the sequence shown in SEQ ID NO: 225. The VH CDR1 of the first antibody variable domain may further comprise the sequence of A, AM or AMN immediately follwing the sequence shown in SEQ ID NO: 407. For example, the VH CDR1 of the first antibody variable domain may comprise the sequence shown in SEQ ID

NO: 408. The VH CDR1 of the second antibody variable domain may further comprise the sequence P, PM, or PMS immediately following the sequence shown in SEQ ID NO: 151. For example, the VH CDR1 of the second antibody variable domain may comprise the sequence shown in SEQ ID NO: 157.

The antibodies useful in the present invention can encompass monoclonal antibodies, polyclonal antibodies, antibody fragments (e.g., Fab, Fab', F(ab')2, Fv, Fc, etc.), chimeric antibodies, bispecific antibodies, heteroconjugate antibodies, single chain (ScFv), mutants thereof, fusion proteins comprising an antibody portion (e.g., a domain antibody), humanized antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity, including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and covalently modified antibodies. The antibodies may be murine, rat, human, or any other origin (including chimeric or humanized antibodies).

In some embodiments, the BCMA or CD3 antibody as described herein is a monoclonal antibody. For example, the BCMA or CD3 antibody is a humanized monoclonal antibody or a chimeric monoclonal antibody.

In some embodiments, the antibody comprises a modified constant region, such as, for example without limitation, a constant region that has increased potential for provoking an immune response. For example, the constant region may be modified to have increased affinity to an Fc gamma receptor such as, e.g., FcγRI, FcγRIIA, or FcγIII.

In some embodiments, the antibody comprises a modified constant region, such as a constant region that is immunologically inert, that is, having a reduced potential for provoking an immune response. In some embodiments, the constant region is modified as described in Eur. J. Immunol., 29:2613-2624, 1999; PCT Application No. PCT/GB99/01441; and/or UK Patent Application No. 98099518. The Fc can be human IgG1, human IgG2, human IgG3, or human IgG4. The Fc can be human IgG2 containing the mutation A330P331 to S330S331 (IgG2Δa), in which the amino acid residues are numbered with reference to the wild type IgG2 sequence. Eur. J. Immunol., 29:2613-2624, 1999. In some embodiments, the antibody comprises a constant region of IgG_4 comprising the following mutations (Armour et al., Molecular Immunology 40 585-593, 2003):

E233F234L235 to P233V234A235 (IgG4Δc), in which the numbering is with reference to wild type IgG4. In yet another embodiment, the Fc is human IgG4 E233F234L235 to P233V234A235 with deletion G236 (IgG4Δb). In another embodiment, the Fc is any human IgG4 Fc (IgG4, IgG4Δb or IgG4Δc) containing hinge stabilizing mutation S228 to P228 (Aalberse et al., Immunology 105, 9-19, 2002). In another embodiment, the Fc can be aglycosylated Fc.

In some embodiments, the constant region is aglycosylated by mutating the oligosaccharide attachment residue (such as Asn297) and/or flanking residues that are part of the glycosylation recognition sequence in the constant region. In some embodiments, the constant region is aglycosylated for N-linked glycosylation enzymatically. The constant region may be aglycosylated for N-linked glycosylation enzymatically or by expression in a glycosylation deficient host cell.

In some embodiments, the constant region has a modified constant region that removes or reduces Fc gamma receptor binding. For example, the Fc can be human IgG2 containing the mutation D265, in which the amino acid residues are numbered with reference to the wild type IgG2 sequence (SEQ ID NO: 493). Accordingly, in some embodiments, the constant region has a modified constant region having the sequence shown in SEQ ID NO: 496:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCRVRCPRCPAPPVAGPSV
FLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTF
RVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKTKGQPREPQVYTLPPSREEMTK
NQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSRLTVDKSRWQQ
GNVFSCSVMHEALHNHYTQKSLSLSPGK.

In some embodiments, the constant region has a modified constant region having the sequence shown in SEQ ID NO: 497:

ASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSS
GLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCEVECPECPAPPVAGPSV
FLFPPKPKDTLMISRTPEVTCVVVAVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTF
RVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKTKGQPREPQVYTLPPSREEMTK

NQVSLTCEVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQ GNVFSCSVMHEALHNHYTQKSLSLSPGK.

One way of determining binding affinity of antibodies to BCMA or CD3 is by measuring binding affinity of monofunctional Fab fragments of the antibody. To obtain monofunctional Fab fragments, an antibody (for example, IgG) can be cleaved with papain or expressed recombinantly. The affinity of a BCMA Fab fragment of an antibody can be determined by surface plasmon resonance (Biacore™3000™ surface plasmon resonance (SPR) system, Biacore™, INC, Piscataway NJ) equipped with pre-immobilized streptavidin sensor chips (SA) or anti-mouse Fc or anti-human Fc using HBS-EP running buffer (0.01M HEPES, pH 7.4, 0.15 NaCl, 3 mM EDTA, 0.005% v/v Surfactant P20). Biotinylated or Fc fusion human BCMA can be diluted into HBS-EP buffer to a concentration of less than 0.5 µg/mL and injected across the individual chip channels using variable contact times, to achieve two ranges of antigen density, either 50-200 response units (RU) for detailed kinetic studies or 800-1,000 RU for screening assays. Regeneration studies have shown that 25 mM NaOH in 25% v/v ethanol effectively removes the bound Fab while keeping the activity of BCMA on the chip for over 200 injections. Typically, serial dilutions (spanning concentrations of 0.1-10x estimated K_D) of purified Fab samples are injected for 1 min at 100 µL/minute and dissociation times of up to 2 hours are allowed. The concentrations of the Fab proteins are determined by ELISA and/or SDS-PAGE electrophoresis using a Fab of known concentration (as determined by amino acid analysis) as a standard. Kinetic association rates (k_{on}) and dissociation rates (k_{off}) are obtained simultaneously by fitting the data globally to a 1:1 Langmuir binding model (Karlsson, R. Roos, H. Fagerstam, L. Petersson, B. (1994). Methods Enzymology 6. 99-110) using the BIAevaluation program. Equilibrium dissociation constant (K_D) values are calculated as k_{off}/k_{on}. This protocol is suitable for use in determining binding affinity of an antibody to any BCMA, including human BCMA, BCMA of another mammal (such as mouse BCMA, rat BCMA, or primate BCMA), as well as different forms of BCMA (e.g., glycosylated BCMA). Binding affinity of an antibody is generally measured at 25°C, but can also be measured at 37°C.

The antibodies as described herein may be made by any method known in the art. For the production of hybridoma cell lines, the route and schedule of immunization of the host animal are generally in keeping with established and conventional techniques for

antibody stimulation and production, as further described herein. General techniques for production of human and mouse antibodies are known in the art and/or are described herein.

It is contemplated that any mammalian subject including humans or antibody producing cells therefrom can be manipulated to serve as the basis for production of mammalian, including human and hybridoma cell lines. Typically, the host animal is inoculated intraperitoneally, intramuscularly, orally, subcutaneously, intraplantar, and/or intradermally with an amount of immunogen, including as described herein.

Hybridomas can be prepared from the lymphocytes and immortalized myeloma cells using the general somatic cell hybridization technique of Kohler, B. and Milstein, C., Nature 256:495-497, 1975 or as modified by Buck, D. W., et al., In Vitro, 18:377-381, 1982. Available myeloma lines, including but not limited to X63-Ag8.653 and those from the Salk Institute, Cell Distribution Center, San Diego, Calif., USA, may be used in the hybridization. Generally, the technique involves fusing myeloma cells and lymphoid cells using a fusogen such as polyethylene glycol, or by electrical means well known to those skilled in the art. After the fusion, the cells are separated from the fusion medium and grown in a selective growth medium, such as hypoxanthine-aminopterin-thymidine (HAT) medium, to eliminate unhybridized parent cells. Any of the media described herein, supplemented with or without serum, can be used for culturing hybridomas that secrete monoclonal antibodies. As another alternative to the cell fusion technique, EBV immortalized B cells may be used to produce the monoclonal antibodies of the subject invention. The hybridomas are expanded and subcloned, if desired, and supernatants are assayed for anti-immunogen activity by conventional immunoassay procedures (e.g., radioimmunoassay, enzyme immunoassay, or fluorescence immunoassay).

Hybridomas that may be used as source of antibodies encompass all derivatives, progeny cells of the parent hybridomas that produce monoclonal antibodies specific for BCMA, CD3, or portions thereof.

Hybridomas that produce such antibodies may be grown *in vitro* or *in vivo* using known procedures. The monoclonal antibodies may be isolated from the culture media or body fluids, by conventional immunoglobulin purification procedures such as ammonium sulfate precipitation, gel electrophoresis, dialysis, chromatography, and ultrafiltration, if

desired. Undesired activity, if present, can be removed, for example, by running the preparation over adsorbents made of the immunogen attached to a solid phase and eluting or releasing the desired antibodies off the immunogen. Immunization of a host animal with a human BCMA or CD3, or a fragment containing the target amino acid sequence conjugated to a protein that is immunogenic in the species to be immunized, e.g., keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor using a bifunctional or derivatizing agent, for example, maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, $SOCl_2$, or $R^1N=C=NR$, where R and R^1 are different alkyl groups, can yield a population of antibodies (e.g., monoclonal antibodies).

If desired, the antibody (monoclonal or polyclonal) of interest may be sequenced and the polynucleotide sequence may then be cloned into a vector for expression or propagation. The sequence encoding the antibody of interest may be maintained in vector in a host cell and the host cell can then be expanded and frozen for future use. Production of recombinant monoclonal antibodies in cell culture can be carried out through cloning of antibody genes from B cells by means known in the art. See, e.g. Tiller et al., J. Immunol. Methods 329, 112, 2008; U.S. Pat. No. 7,314,622.

In an alternative, the polynucleotide sequence may be used for genetic manipulation to "humanize" the antibody or to improve the affinity, or other characteristics of the antibody. For example, the constant region may be engineered to more nearly resemble human constant regions. It may be desirable to genetically manipulate the antibody sequence to obtain greater affinity to BCMA or CD3 and greater efficacy in inhibiting BCMA.

There are four general steps to humanize a monoclonal antibody. These are: (1) determining the nucleotide and predicted amino acid sequence of the starting antibody light and heavy variable domains (2) designing the humanized antibody, i.e., deciding which antibody framework region to use during the humanizing process (3) the actual humanizing methodologies/techniques and (4) the transfection and expression of the humanized antibody. See, for example, U.S. Pat. Nos. 4,816,567; 5,807,715; 5,866,692; 6,331,415; 5,530,101; 5,693,761; 5,693,762; 5,585,089; and 6,180,370.

A number of "humanized" antibody molecules comprising an antigen binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent or modified rodent V regions and their associated CDRs fused to human constant regions. See, for example, Winter et al. Nature 349:293-299, 1991, Lobuglio et al. Proc. Nat. Acad. Sci. USA 86:4220-4224, 1989, Shaw et al. J Immunol. 138:4534-4538, 1987, and Brown et al. Cancer Res. 47:3577-3583, 1987. Other references describe rodent CDRs grafted into a human supporting framework region (FR) prior to fusion with an appropriate human antibody constant region. See, for example, Riechmann et al. Nature 332:323-327, 1988, Verhoeyen et al. Science 239:1534-1536, 1988, and Jones et al. Nature 321:522-525, 1986. Another reference describes rodent CDRs supported by recombinantly engineered rodent framework regions. See, for example, European Patent Publication No. 0519596. These "humanized" molecules are designed to minimize unwanted immunological response toward rodent anti-human antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients. For example, the antibody constant region can be engineered such that it is immunologically inert (e.g., does not trigger complement lysis). See, e.g. PCT Publication No. PCT/GB99/01441; UK Patent Application No. 9809951.8. Other methods of humanizing antibodies that may also be utilized are disclosed by Daugherty et al., Nucl. Acids Res. 19:2471-2476, 1991, and in U.S. Pat. Nos. 6,180,377; 6,054,297; 5,997,867; 5,866,692; 6,210,671; and 6,350,861; and in PCT Publication No. WO 01/27160.

The general principles related to humanized antibodies discussed above are also applicable to customizing antibodies for use, for example, in dogs, cats, primate, equines and bovines. Further, one or more aspects of humanizing an antibody described herein may be combined, e.g., CDR grafting, framework mutation and CDR mutation.

In one variation, fully human antibodies may be obtained by using commercially available mice that have been engineered to express specific human immunoglobulin proteins. Transgenic animals that are designed to produce a more desirable (e.g., fully human antibodies) or more robust immune response may also be used for generation of humanized or human antibodies. Examples of such technology are Xenomouse™ from

Abgenix, Inc. (Fremont, CA) and HuMAb-Mouse® and TC Mouse™ from Medarex, Inc. (Princeton, NJ).

In an alternative, antibodies may be made recombinantly and expressed using any method known in the art. In another alternative, antibodies may be made recombinantly by phage display technology. See, for example, U.S. Pat. Nos. 5,565,332; 5,580,717; 5,733,743; and 6,265,150; and Winter et al., Annu. Rev. Immunol. 12:433-455, 1994. Alternatively, the phage display technology (McCafferty et al., Nature 348:552-553, 1990) can be used to produce human antibodies and antibody fragments *in vitro*, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B cell. Phage display can be performed in a variety of formats; for review see, e.g., Johnson, Kevin S. and Chiswell, David J., Current Opinion in Structural Biology 3:564-571, 1993. Several sources of V-gene segments can be used for phage display. Clackson et al., Nature 352:624-628, 1991, isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Mark et al., J. Mol. Biol. 222:581-597, 1991, or Griffith et al., EMBO J. 12:725-734, 1993. In a natural immune response, antibody genes accumulate mutations at a high rate (somatic hypermutation). Some of the changes introduced will confer higher affinity, and B cells displaying high-affinity surface immunoglobulin are preferentially replicated and differentiated during subsequent antigen challenge. This natural process can be mimicked by employing the technique known as "chain shuffling." (Marks et al., Bio/Technol. 10:779-783, 1992). In this method, the affinity of "primary" human antibodies obtained by phage display can be improved by sequentially replacing the heavy and light chain V region genes with

repertoires of naturally occurring variants (repertoires) of V domain genes obtained from unimmunized donors. This technique allows the production of antibodies and antibody fragments with affinities in the pM-nM range. A strategy for making very large phage antibody repertoires (also known as "the mother-of-all libraries") has been described by Waterhouse et al., Nucl. Acids Res. 21:2265-2266, 1993. Gene shuffling can also be used to derive human antibodies from rodent antibodies, where the human antibody has similar affinities and specificities to the starting rodent antibody. According to this method, which is also referred to as "epitope imprinting", the heavy or light chain V domain gene of rodent antibodies obtained by phage display technique is replaced with a repertoire of human V domain genes, creating rodent-human chimeras. Selection on antigen results in isolation of human variable regions capable of restoring a functional antigen binding site, i.e., the epitope governs (imprints) the choice of partner. When the process is repeated in order to replace the remaining rodent V domain, a human antibody is obtained (see PCT Publication No. WO 93/06213). Unlike traditional humanization of rodent antibodies by CDR grafting, this technique provides completely human antibodies, which have no framework or CDR residues of rodent origin.

Antibodies may be made recombinantly by first isolating the antibodies and antibody producing cells from host animals, obtaining the gene sequence, and using the gene sequence to express the antibody recombinantly in host cells (e.g., CHO cells). Another method which may be employed is to express the antibody sequence in plants (e.g., tobacco) or transgenic milk. Methods for expressing antibodies recombinantly in plants or milk have been disclosed. See, for example, Peeters, et al. Vaccine 19:2756, 2001; Lonberg, N. and D. Huszar Int. Rev. Immunol 13:65, 1995; and Pollock, et al., J Immunol Methods 231:147, 1999. Methods for making derivatives of antibodies, e.g., humanized, single chain, etc. are known in the art.

Immunoassays and flow cytometry sorting techniques such as fluorescence activated cell sorting (FACS) can also be employed to isolate antibodies that are specific for BCMA, CD3, or tumor antigens of interest.

The antibodies as described herein can be bound to many different carriers. Carriers can be active and/or inert. Examples of well-known carriers include polypropylene, polystyrene, polyethylene, dextran, nylon, amylases, glass, natural and

modified celluloses, polyacrylamides, agaroses, and magnetite. The nature of the carrier can be either soluble or insoluble for purposes of the invention. Those skilled in the art will know of other suitable carriers for binding antibodies, or will be able to ascertain such, using routine experimentation. In some embodiments, the carrier comprises a moiety that targets the myocardium.

DNA encoding the monoclonal antibodies is 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 monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors (such as expression vectors disclosed in PCT Publication No. WO 87/04462), which are then transfected into host cells such as E. coli cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. See, e.g., PCT Publication No. WO 87/04462. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant regions in place of the homologous murine sequences, Morrison et al., Proc. Nat. Acad. Sci. 81:6851, 1984, or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. In that manner, "chimeric" or "hybrid" antibodies are prepared that have the binding specificity of a monoclonal antibody herein.

The BCMA or tumor antigen of interest antibodies as described herein can be identified or characterized using methods known in the art, whereby reduction of BCMA or other tumor antigen expression levels are detected and/or measured. In some embodiments, a BCMA antibody is identified by incubating a candidate agent with BCMA and monitoring binding and/or attendant reduction of BCMA expression levels. The binding assay may be performed with purified BCMA polypeptide(s), or with cells naturally expressing, or transfected to express, BCMA polypeptide(s). In one embodiment, the binding assay is a competitive binding assay, where the ability of a candidate antibody to compete with a known BCMA antibody for BCMA binding is evaluated. The assay may be performed in various formats, including the ELISA format.

Following initial identification, the activity of a candidate BCMA, CD3, or other tumor antigen antibody can be further confirmed and refined by bioassays, known to test the targeted biological activities. Alternatively, bioassays can be used to screen candidates directly. Some of the methods for identifying and characterizing antibodies are described in detail in the Examples.

BCMA, CD3, or other tumor antigen antibodies may be characterized using methods well known in the art. For example, one method is to identify the epitope to which it binds, or "epitope mapping." There are many methods known in the art for mapping and characterizing the location of epitopes on proteins, including solving the crystal structure of an antibody-antigen complex, competition assays, gene fragment expression assays, and synthetic peptide-based assays, as described, for example, in Chapter 11 of Harlow and Lane, Using Antibodies, a Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1999. In an additional example, epitope mapping can be used to determine the sequence to which an antibody binds. Epitope mapping is commercially available from various sources, for example, Pepscan Systems (Edelhertweg 15, 8219 PH Lelystad, The Netherlands). The epitope can be a linear epitope, i.e., contained in a single stretch of amino acids, or a conformational epitope formed by a three-dimensional interaction of amino acids that may not necessarily be contained in a single stretch. Peptides of varying lengths (e.g., at least 4-6 amino acids long) can be isolated or synthesized (e.g., recombinantly) and used for binding assays with a BCMA, CD3, or other tumor antigen antibody. In another example, the epitope to which the BCMA, CD3, or other tumor antigen antibody binds can be determined in a systematic screening by using overlapping peptides derived from the BCMA, CD3, or other tumor antigen sequence and determining binding by the BCMA, CD3, or other tumor antigen antibody. According to the gene fragment expression assays, the open reading frame encoding BCMA, CD3, or other tumor antigen is fragmented either randomly or by specific genetic constructions and the reactivity of the expressed fragments of BCMA, CD3, or other tumor antigen with the antibody to be tested is determined. The gene fragments may, for example, be produced by PCR and then transcribed and translated into protein in vitro, in the presence of radioactive amino acids. The binding of the antibody to the radioactively labeled BCMA, CD3, or other tumor antigen fragments is then determined by immunoprecipitation and gel

electrophoresis. Certain epitopes can also be identified by using large libraries of random peptide sequences displayed on the surface of phage particles (phage libraries). Alternatively, a defined library of overlapping peptide fragments can be tested for binding to the test antibody in simple binding assays. In an additional example, mutagenesis of an antigen binding domain, domain swapping experiments and alanine scanning mutagenesis can be performed to identify residues required, sufficient, and/or necessary for epitope binding. For example, domain swapping experiments can be performed using a mutant BCMA, CD3, or other tumor antigen in which various fragments of the BCMA, CD3, or other tumor antigen protein have been replaced (swapped) with sequences from BCMA from another species (e.g., mouse), or a closely related, but antigenically distinct protein (e.g., Trop-1). By assessing binding of the antibody to the mutant BCMA, CD3, or other tumor antigen, the importance of the particular BCMA, CD3, or other tumor antigen fragment to antibody binding can be assessed.

Yet another method which can be used to characterize a BCMA, CD3, or other tumor antigen antibody is to use competition assays with other antibodies known to bind to the same antigen, i.e., various fragments on BCMA, CD3, or other tumor antigen, to determine if the BCMA, CD3, or other tumor antigen antibody binds to the same epitope as other antibodies. Competition assays are well known to those of skill in the art.

An expression vector can be used to direct expression of a BCMA, CD3, or other tumor antigen antibody. One skilled in the art is familiar with use of expression vectors to obtain expression of an exogenous protein in vivo. See, e.g., U.S. Pat. Nos. 6,436,908; 6,413,942; and 6,376,471.

In some embodiments, the invention encompasses compositions, including pharmaceutical compositions, comprising antibodies described herein or made by the methods and having the characteristics described herein. As used herein, compositions comprise one or more antibodies that bind to CD3 and a tumor antigen (e.g BCMA), and/or one or more polynucleotides comprising sequences encoding one or more these antibodies. These compositions may further comprise suitable excipients, such as pharmaceutically acceptable excipients including buffers, which are well known in the art.

The invention also provides methods of making any of these antibodies. The antibodies of this invention can be made by procedures known in the art. The polypeptides can be produced by proteolytic or other degradation of the antibodies, by recombinant methods (i.e., single or fusion polypeptides) as described above or by chemical synthesis. Polypeptides of the antibodies, especially shorter polypeptides up to about 50 amino acids, are conveniently made by chemical synthesis. Methods of chemical synthesis are known in the art and are commercially available. For example, an antibody could be produced by an automated polypeptide synthesizer employing the solid phase method. See also, U.S. Pat. Nos. 5,807,715; 4,816,567; and 6,331,415.

Heteroconjugate antibodies, comprising two covalently joined antibodies, are also within the scope of the invention. Such antibodies have been used to target immune system cells to unwanted cells (U.S. Pat. No. 4,676,980). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents and techniques are well known in the art, and are described in U.S. Pat. No. 4,676,980.

Chimeric or hybrid antibodies also may be prepared *in vitro* using known methods of synthetic protein chemistry, including those involving cross-linking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate.

In the recombinant humanized antibodies, the Fcγ portion can be modified to avoid interaction with Fcγ receptor and the complement and immune systems. The techniques for preparation of such antibodies are described in WO 99/58572. For example, the constant region may be engineered to more resemble human constant regions to avoid immune response. See, for example, U.S. Pat. Nos. 5,997,867 and 5,866,692.

The invention encompasses modifications to the antibodies and polypeptides of the invention variants as described herein, including functionally equivalent antibodies which do not significantly affect their properties and variants which have enhanced or decreased activity and/or affinity. For example, the amino acid sequence may be mutated to obtain an antibody with the desired binding affinity to BCMA and/or CD3. Modification of polypeptides is routine practice in the art and need not be described in detail herein. Examples of modified polypeptides include polypeptides with conservative substitutions of

amino acid residues, one or more deletions or additions of amino acids which do not significantly deleteriously change the functional activity, or which mature (enhance) the affinity of the polypeptide for its ligand, or use of chemical analogs.

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 or the antibody fused to an epitope tag. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody of an enzyme or a polypeptide which increases the half-life of the antibody in the blood circulation.

Substitution variants have at least one amino acid residue in the antibody molecule removed and a different residue inserted in its place. The sites of greatest interest for substitutional mutagenesis include the hypervariable regions, but FR alterations are also contemplated. Conservative substitutions are shown in Table 5 under the heading of "conservative substitutions." If such substitutions result in a change in biological activity, then more substantial changes, denominated "exemplary substitutions" in Table 5, or as further described below in reference to amino acid classes, may be introduced and the products screened.

Table 5: Amino Acid Substitutions

Original Residue (naturally occurring amino acid)	Conservative Substitutions	Exemplary Substitutions
Ala (A)	Val	Val; Leu; Ile
Arg (R)	Lys	Lys; Gln; Asn
Asn (N)	Gln	Gln; His; Asp, Lys; Arg
Asp (D)	Glu	Glu; Asn
Cys (C)	Ser	Ser; Ala
Gln (Q)	Asn	Asn; Glu
Glu (E)	Asp	Asp; Gln
Gly (G)	Ala	Ala

Original Residue (naturally occurring amino acid)	Conservative Substitutions	Exemplary Substitutions
His (H)	Arg	Asn; Gln; Lys; Arg
Ile (I)	Leu	Leu; Val; Met; Ala; Phe; Norleucine
Leu (L)	Ile	Norleucine; Ile; Val; Met; Ala; Phe
Lys (K)	Arg	Arg; Gln; Asn
Met (M)	Leu	Leu; Phe; Ile
Phe (F)	Tyr	Leu; Val; Ile; Ala; Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr
Thr (T)	Ser	Ser
Trp (W)	Tyr	Tyr; Phe
Tyr (Y)	Phe	Trp; Phe; Thr; Ser
Val (V)	Leu	Ile; Leu; Met; Phe; Ala; Norleucine

Substantial modifications in the biological properties of the antibody are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring amino acid residues are divided into groups based on common side-chain properties:

(1) Non-polar: Norleucine, Met, Ala, Val, Leu, Ile;

(2) Polar without charge: Cys, Ser, Thr, Asn, Gln;

(3) Acidic (negatively charged): Asp, Glu;

(4) Basic (positively charged): Lys, Arg;

(5) Residues that influence chain orientation: Gly, Pro; and

(6) Aromatic: Trp, Tyr, Phe, His.

Non-conservative substitutions are made by exchanging a member of one of these classes for another class.

Any cysteine residue not involved in maintaining the proper conformation of the antibody also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant cross-linking. Conversely, cysteine bond(s) may be added to the antibody to improve its stability, particularly where the antibody is an antibody fragment such as an Fv fragment.

Amino acid modifications can range from changing or modifying one or more amino acids to complete redesign of a region, such as the variable region. Changes in the variable region can alter binding affinity and/or specificity. In some embodiments, no more than one to five conservative amino acid substitutions are made within a CDR domain. In other embodiments, no more than one to three conservative amino acid substitutions are made within a CDR domain. In still other embodiments, the CDR domain is CDR H3 and/or CDR L3.

Modifications also include glycosylated and nonglycosylated polypeptides, as well as polypeptides with other post-translational modifications, such as, for example, glycosylation with different sugars, acetylation, and phosphorylation. Antibodies are glycosylated at conserved positions in their constant regions (Jefferis and Lund, Chem. Immunol. 65:111-128, 1997; Wright and Morrison, TibTECH 15:26-32, 1997). The oligosaccharide side chains of the immunoglobulins affect the protein's function (Boyd et al., Mol. Immunol. 32:1311-1318, 1996; Wittwe and Howard, Biochem. 29:4175-4180, 1990) and the intramolecular interaction between portions of the glycoprotein, which can affect the conformation and presented three-dimensional surface of the glycoprotein (Jefferis and Lund, supra; Wyss and Wagner, Current Opin. Biotech. 7:409-416, 1996). Oligosaccharides may also serve to target a given glycoprotein to certain molecules based upon specific recognition structures. Glycosylation of antibodies has also been reported to affect antibody-dependent cellular cytotoxicity (ADCC). In particular, CHO cells with tetracycline-regulated expression of β(1,4)-N-acetylglucosaminyltransferase III (GnTIII), a glycosyltransferase catalyzing formation of bisecting GlcNAc, was reported to have improved ADCC activity (Umana et al., Mature Biotech. 17:176-180, 1999).

Glycosylation of antibodies is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine, asparagine-X-threonine, and asparagine-X-

cysteine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

Addition of glycosylation sites to the antibody is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original antibody (for O-linked glycosylation sites).

The glycosylation pattern of antibodies may also be altered without altering the underlying nucleotide sequence. Glycosylation largely depends on the host cell used to express the antibody. Since the cell type used for expression of recombinant glycoproteins, e.g. antibodies, as potential therapeutics is rarely the native cell, variations in the glycosylation pattern of the antibodies can be expected (see, e.g. Hse et al., J. Biol. Chem. 272:9062-9070, 1997).

In addition to the choice of host cells, factors that affect glycosylation during recombinant production of antibodies include growth mode, media formulation, culture density, oxygenation, pH, purification schemes and the like. Various methods have been proposed to alter the glycosylation pattern achieved in a particular host organism including introducing or overexpressing certain enzymes involved in oligosaccharide production (U.S. Pat. Nos. 5,047,335; 5,510,261 and 5,278,299). Glycosylation, or certain types of glycosylation, can be enzymatically removed from the glycoprotein, for example, using endoglycosidase H (Endo H), N-glycosidase F, endoglycosidase F1, endoglycosidase F2, endoglycosidase F3. In addition, the recombinant host cell can be genetically engineered to be defective in processing certain types of polysaccharides. These and similar techniques are well known in the art.

Other methods of modification include using coupling techniques known in the art, including, but not limited to, enzymatic means, oxidative substitution and chelation. Modifications can be used, for example, for attachment of labels for immunoassay.

Modified polypeptides are made using established procedures in the art and can be screened using standard assays known in the art, some of which are described below and in the Examples.

In some embodiments of the invention, the antibody comprises a modified constant region, such as a constant region that has increased affinity to a human Fc gamma receptor, is immunologically inert or partially inert, e.g., does not trigger complement mediated lysis, does not stimulate antibody-dependent cell mediated cytotoxicity (ADCC), or does not activate macrophages; or has reduced activities (compared to the unmodified antibody) in any one or more of the following: triggering complement mediated lysis, stimulating antibody-dependent cell mediated cytotoxicity (ADCC), or activating microglia. Different modifications of the constant region may be used to achieve optimal level and/or combination of effector functions. See, for example, Morgan et al., Immunology 86:319-324, 1995; Lund et al., J. Immunology 157:4963-9 157:4963-4969, 1996; Idusogie et al., J. Immunology 164:4178-4184, 2000; Tao et al., J. Immunology 143: 2595-2601, 1989; and Jefferis et al., Immunological Reviews 163:59-76, 1998. In some embodiments, the constant region is modified as described in Eur. J. Immunol., 1999, 29:2613-2624; PCT Application No. PCT/GB99/01441; and/or UK Patent Application No. 9809951.8. In other embodiments, the antibody comprises a human heavy chain IgG2 constant region comprising the following mutations: A330P331 to S330S331 (amino acid numbering with reference to the wild type IgG2 sequence). Eur. J. Immunol., 1999, 29:2613-2624. In still other embodiments, the constant region is aglycosylated for N-linked glycosylation. In some embodiments, the constant region is aglycosylated for N-linked glycosylation by mutating the glycosylated amino acid residue or flanking residues that are part of the N-glycosylation recognition sequence in the constant region. For example, N-glycosylation site N297 may be mutated to A, Q, K, or H. See, Tao et al., J. Immunology 143: 2595-2601, 1989; and Jefferis et al., Immunological Reviews 163:59-76, 1998. In some embodiments, the constant region is aglycosylated for N-linked glycosylation. The constant region may be aglycosylated for N-linked glycosylation enzymatically (such as removing carbohydrate by enzyme PNGase), or by expression in a glycosylation deficient host cell.

Other antibody modifications include antibodies that have been modified as described in PCT Publication No. WO 99/58572. These antibodies comprise, in addition to a binding domain directed at the target molecule, an effector domain having an amino acid sequence substantially homologous to all or part of a constant region of a human immunoglobulin heavy chain. These antibodies are capable of binding the target molecule without triggering significant complement dependent lysis, or cell-mediated destruction of the target. In some embodiments, the effector domain is capable of specifically binding FcRn and/or FcγRIIb. These are typically based on chimeric domains derived from two or more human immunoglobulin heavy chain C_H2 domains.

The invention includes affinity matured embodiments. For example, affinity matured antibodies can be produced by procedures known in the art (Marks et al., Bio/Technology, 10:779-783, 1992; Barbas et al., Proc Nat. Acad. Sci, USA 91:3809-3813, 1994; Schier et al., Gene, 169:147-155, 1995; Yelton et al., J. Immunol., 155:1994-2004, 1995; Jackson et al., J. Immunol., 154(7):3310-9, 1995, Hawkins et al., J. Mol. Biol., 226:889-896, 1992; and PCT Publication No. WO2004/058184).

The following methods may be used for adjusting the affinity of an antibody and for characterizing a CDR. One way of characterizing a CDR of an antibody and/or altering (such as improving) the binding affinity of a polypeptide, such as an antibody, termed "library scanning mutagenesis". Generally, library scanning mutagenesis works as follows. One or more amino acid positions in the CDR are replaced with two or more (such as 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20) amino acids using art recognized methods. This generates small libraries of clones (in some embodiments, one for every amino acid position that is analyzed), each with a complexity of two or more members (if two or more amino acids are substituted at every position). Generally, the library also includes a clone comprising the native (unsubstituted) amino acid. A small number of clones, e.g., about 20-80 clones (depending on the complexity of the library), from each library are screened for binding affinity to the target polypeptide (or other binding target), and candidates with increased, the same, decreased, or no binding are identified. Methods for determining binding affinity are well-known in the art. Binding affinity may be determined using Biacore™ surface plasmon resonance analysis, which detects differences in binding affinity of about 2-fold or greater. Biacore™ is particularly useful

when the starting antibody already binds with a relatively high affinity, for example a K_D of about 10 nM or lower. Screening using Biacore™ surface plasmon resonance is described in the Examples, herein.

Binding affinity may be determined using Kinexa Biocensor, scintillation proximity assays, ELISA, ORIGEN immunoassay (IGEN), fluorescence quenching, fluorescence transfer, and/or yeast display. Binding affinity may also be screened using a suitable bioassay.

In some embodiments, every amino acid position in a CDR is replaced (in some embodiments, one at a time) with all 20 natural amino acids using art recognized mutagenesis methods (some of which are described herein). This generates small libraries of clones (in some embodiments, one for every amino acid position that is analyzed), each with a complexity of 20 members (if all 20 amino acids are substituted at every position).

In some embodiments, the library to be screened comprises substitutions in two or more positions, which may be in the same CDR or in two or more CDRs. Thus, the library may comprise substitutions in two or more positions in one CDR. The library may comprise substitution in two or more positions in two or more CDRs. The library may comprise substitution in 3, 4, 5, or more positions, said positions found in two, three, four, five or six CDRs. The substitution may be prepared using low redundancy codons. See, e.g., Table 2 of Balint et al., Gene 137(1):109-18, 1993.

The CDR may be CDRH3 and/or CDRL3. The CDR may be one or more of CDRL1, CDRL2, CDRL3, CDRH1, CDRH2, and/or CDRH3. The CDR may be a Kabat CDR, a Chothia CDR, or an extended CDR.

Candidates with improved binding may be sequenced, thereby identifying a CDR substitution mutant which results in improved affinity (also termed an "improved" substitution). Candidates that bind may also be sequenced, thereby identifying a CDR substitution which retains binding.

Multiple rounds of screening may be conducted. For example, candidates (each comprising an amino acid substitution at one or more position of one or more CDR) with improved binding are also useful for the design of a second library containing at least the original and substituted amino acid at each improved CDR position (i.e., amino acid

position in the CDR at which a substitution mutant showed improved binding). Preparation, and screening or selection of this library is discussed further below.

Library scanning mutagenesis also provides a means for characterizing a CDR, in so far as the frequency of clones with improved binding, the same binding, decreased binding or no binding also provide information relating to the importance of each amino acid position for the stability of the antibody-antigen complex. For example, if a position of the CDR retains binding when changed to all 20 amino acids, that position is identified as a position that is unlikely to be required for antigen binding. Conversely, if a position of CDR retains binding in only a small percentage of substitutions, that position is identified as a position that is important to CDR function. Thus, the library scanning mutagenesis methods generate information regarding positions in the CDRs that can be changed to many different amino acids (including all 20 amino acids), and positions in the CDRs which cannot be changed or which can only be changed to a few amino acids.

Candidates with improved affinity may be combined in a second library, which includes the improved amino acid, the original amino acid at that position, and may further include additional substitutions at that position, depending on the complexity of the library that is desired, or permitted using the desired screening or selection method. In addition, if desired, adjacent amino acid position can be randomized to at least two or more amino acids. Randomization of adjacent amino acids may permit additional conformational flexibility in the mutant CDR, which may in turn, permit or facilitate the introduction of a larger number of improving mutations. The library may also comprise substitution at positions that did not show improved affinity in the first round of screening.

The second library is screened or selected for library members with improved and/or altered binding affinity using any method known in the art, including screening using Biacore™ surface plasmon resonance analysis, and selection using any method known in the art for selection, including phage display, yeast display, and ribosome display.

This invention also provides compositions comprising antibodies conjugated (for example, linked) to an agent that facilitate coupling to a solid support (such as biotin or avidin). For simplicity, reference will be made generally to antibodies with the understanding that these methods apply to any of the BCMA antibody embodiments described herein. Conjugation generally refers to linking these components as described

herein. The linking (which is generally fixing these components in proximate association at least for administration) can be achieved in any number of ways. For example, a direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

In another aspect, the invention provides a method of making any of the polynucleotides described herein.

Polynucleotides complementarity to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes an antibody or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants contain one or more substitutions, additions, deletions and/or insertions such that the immunoreactivity of the encoded polypeptide is not diminished, relative to a native immunoreactive molecule. The effect on the immunoreactivity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably, at least about 80% identity, yet more preferably, at least about 90% identity, and most preferably, at least about 95% identity to a polynucleotide sequence that encodes a native antibody or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and

compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, or 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O., 1978, A model of evolutionary change in proteins - Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J., 1990, Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M., 1989, CABIOS 5:151-153; Myers, E.W. and Muller W., 1988, CABIOS 4:11-17; Robinson, E.D., 1971, Comb. Theor. 11:105; Santou, N., Nes, M., 1987, Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R., 1973, Numerical Taxonomy the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J., 1983, Proc. Natl. Acad. Sci. USA 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e., gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing

under moderately stringent conditions to a naturally occurring DNA sequence encoding a native antibody (or a complementarity sequence).

Suitable "moderately stringent conditions" include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1 % SDS.

As used herein, "highly stringent conditions" or "high stringency conditions" are those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50 mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) employ 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with washes at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) and 50% formamide at 55°C, followed by a high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C. The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

The polynucleotides of this invention can be obtained using chemical synthesis, recombinant methods, or PCR. Methods of chemical polynucleotide synthesis are well known in the art and need not be described in detail herein. One of skill in the art can use the sequences provided herein and a commercial DNA synthesizer to produce a desired DNA sequence.

For preparing polynucleotides using recombinant methods, a polynucleotide comprising a desired sequence can be inserted into a suitable vector, and the vector in turn can be introduced into a suitable host cell for replication and amplification, as further discussed herein. Polynucleotides may be inserted into host cells by any means known in the art. Cells are transformed by introducing an exogenous polynucleotide by direct uptake, endocytosis, transfection, F-mating or electroporation. Once introduced, the exogenous polynucleotide can be maintained within the cell as a non-integrated vector (such as a plasmid) or integrated into the host cell genome. The polynucleotide so amplified can be isolated from the host cell by methods well known within the art. See, e.g., Sambrook et al., 1989.

Alternatively, PCR allows reproduction of DNA sequences. PCR technology is well known in the art and is described in U.S. Patent Nos. 4,683,195, 4,800,159, 4,754,065 and 4,683,202, as well as PCR: The Polymerase Chain Reaction, Mullis et al. eds., Birkauswer Press, Boston, 1994.

RNA can be obtained by using the isolated DNA in an appropriate vector and inserting it into a suitable host cell. When the cell replicates and the DNA is transcribed into RNA, the RNA can then be isolated using methods well known to those of skill in the art, as set forth in Sambrook et al., 1989, supra, for example.

Suitable cloning vectors may be constructed according to standard techniques, or may be selected from a large number of cloning vectors available in the art. While the cloning vector selected may vary according to the host cell intended to be used, useful cloning vectors will generally have the ability to self-replicate, may possess a single target for a particular restriction endonuclease, and/or may carry genes for a marker that can be used in selecting clones containing the vector. Suitable examples include plasmids and bacterial viruses, e.g., pUC18, pUC19, Bluescript (e.g., pBS SK+) and its derivatives, mp18, mp19, pBR322, pMB9, ColE1, pCR1, RP4, phage DNAs, and shuttle vectors such

as pSA3 and pAT28. These and many other cloning vectors are available from commercial vendors such as BioRad, Strategene, and Invitrogen.

Expression vectors generally are replicable polynucleotide constructs that contain a polynucleotide according to the invention. It is implied that an expression vector must be replicable in the host cells either as episomes or as an integral part of the chromosomal DNA. Suitable expression vectors include but are not limited to plasmids, viral vectors, including adenoviruses, adeno-associated viruses, retroviruses, cosmids, and expression vector(s) disclosed in PCT Publication No. WO 87/04462. Vector components may generally include, but are not limited to, one or more of the following: a signal sequence; an origin of replication; one or more marker genes; suitable transcriptional controlling elements (such as promoters, enhancers and terminator). For expression (i.e., translation), one or more translational controlling elements are also usually required, such as ribosome binding sites, translation initiation sites, and stop codons.

The vectors containing the polynucleotides of interest can be introduced into the host cell by any of a number of appropriate means, including electroporation, transfection employing calcium chloride, rubidium chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (e.g., where the vector is an infectious agent such as vaccinia virus). The choice of introducing vectors or polynucleotides will often depend on features of the host cell.

The invention also provides host cells comprising any of the polynucleotides described herein. Any host cells capable of over-expressing heterologous DNAs can be used for the purpose of isolating the genes encoding the antibody, polypeptide or protein of interest. Non-limiting examples of mammalian host cells include but not limited to COS, HeLa, and CHO cells. See also PCT Publication No. WO 87/04462. Suitable non-mammalian host cells include prokaryotes (such as *E. coli* or *B. subtillis*) and yeast (such as *S. cerevisae*, *S. pombe*; or *K. lactis*). Preferably, the host cells express the cDNAs at a level of about 5 fold higher, more preferably, 10 fold higher, even more preferably, 20 fold higher than that of the corresponding endogenous antibody or protein of interest, if present, in the host cells. Screening the host cells for a specific binding to BCMA or an BCMA domain (e.g., domains 1-4) is effected by an immunoassay or FACS. A cell overexpressing the antibody or protein of interest can be identified.

The BCMA antibody conjugates and CD3-BCMA bispecific antibodies encompassed within the scope of the invention are candidates which may be potentially useful for the treatment of multiple myeloma.

Formulations

The antibodies (e.g., BCMA or CD3-BCMA bispecific) or the BCMA antibody conjugates may be formulated for potential administration to a subject via any suitable route. It should be understood by persons skilled in the art that the examples described herein are not intended to be limiting but to be illustrative of the techniques available. Accordingly, in some embodiments, the antibody (e.g., BCMA or CD3-BCMA bispecific) or the BCMA antibody conjugate may be formulated for potential intravenous administration, e.g., as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, intracranial, transdermal, subcutaneous, intra-articular, sublingually, intrasynovial, via insufflation, intrathecal, oral, inhalation or topical routes.

In some embodiments, the antibody (e.g., BCMA or CD3-BCMA bispecific) or the BCMA antibody conjugate and a pharmaceutically acceptable excipient may be in various formulations. Pharmaceutically acceptable excipients are known in the art, and are relatively inert substances that facilitate administration of a pharmacologically effective substance. For example, an excipient can give form or consistency, or act as a diluent. Suitable excipients may include but are not limited to stabilizing agents, wetting and emulsifying agents, salts for varying osmolarity, encapsulating agents, buffers, and skin penetration enhancers. Excipients as well as formulations for parenteral and nonparenteral delivery are set forth in Remington, The Science and Practice of Pharmacy 21st Ed. Mack Publishing, 2005.

The antibodies (e.g., BCMA or CD3-BCMA bispecific) or the BCMA antibody conjugates as described herein may be formulated for potential administration using any suitable method, including by injection (e.g., intraperitoneally, intravenously, subcutaneously, intramuscularly, etc.). Accordingly, pharmaceutically acceptable vehicles

such as saline, Ringer's solution, dextrose solution, and the like may be included in formulations for injection.

In some embodiments, more than one antibody (e.g., BCMA or CD3-BCMA bispecific) or BCMA antibody conjugate may be present. At least one, at least two, at least three, at least four, at least five different or more antibody (e.g., BCMA or CD3-BCMA bispecific) or BCMA antibody conjugate may be present. Generally, those antibodies (e.g., BCMA or CD3-BCMA bispecific) or BCMA antibody conjugates may have complementary activities that do not adversely affect each other. For example, one or more of the following antibody may be used: a first BCMA or CD3 antibody directed to one epitope on BCMA or CD3 and a second BCMA or CD3 antibody directed to a different epitope on BCMA or CD3.

Formulations of the antibody (e.g., BCMA or CD3-BCMA bispecific) or the BCMA antibody conjugate used in accordance with the present invention may be prepared for storage by mixing an antibody having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (Remington, The Science and Practice of Pharmacy 21st Ed. Mack Publishing, 2005), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and may comprise buffers such as phosphate, citrate, and other organic acids; salts such as sodium chloride; 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 TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

Liposomes containing the antibody (e.g., BCMA or CD3-BCMA bispecific) or the BCMA antibody conjugate may be prepared by methods known in the art, such as described in Epstein, et al., Proc. Natl. Acad. Sci. USA 82:3688, 1985; Hwang, et al., Proc. Natl Acad. Sci. USA 77:4030, 1980; and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Pat. No. 5,013,556. Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington, The Science and Practice of Pharmacy 21st Ed. Mack Publishing, 2005.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations may include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g. films, or microcapsules. Examples of sustained-release matrices may include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or 'poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and 7 ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT ™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), sucrose acetate isobutyrate, and poly-D-(-)-3-hydroxybutyric acid.

The formulations for potential use *in vivo* must be sterile. This is readily accomplished by, for example, filtration through sterile filtration membranes. Antibody (e.g., BCMA or CD3-BCMA bispecific) or BCMA antibody conjugate compositions may be placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions may contain up to 20% oil, for example, between 5 and 20%. The fat emulsion may comprise fat droplets between 0.1 and 1.0 μm, particularly 0.1 and 0.5 μm, and have a pH in the range of 5.5 to 8.0.

The emulsion compositions may be those prepared by mixing an antibody (e.g., BCMA or CD3-BCMA bispecific) or a BCMA antibody conjugate with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions

In some embodiments, the composition comprises one or more antibodies (e.g., BCMA or CD3-BCMA bispecific) or BCMA antibody conjugates. For example, BCMA antibody or CD3-BCMA bispecific antibody recognizes human BCMA or CD3-BCMA. In some embodiments, the BCMA or CD3-BCMA antibody is a human antibody, a humanized antibody, or a chimeric antibody. In some embodiments, the BCMA antibody or CD3-BCMA antibody comprises a constant region that is capable of triggering a desired immune response, such as antibody-mediated lysis or ADCC. In other embodiments, the BCMA antibody or CD3-BCMA antibody comprises a constant region that does not trigger an unwanted or undesirable immune response, such as antibody-mediated lysis or ADCC.

It is understood that the compositions can comprise more than one antibody (e.g., BCMA or CD3-BCMA bispecific) or BCMA antibody conjugate (e.g., a mixture of BCMA antibodies or CD3-BCMA bispecific antibodies that recognize different epitopes of BCMA or CD3 and BCMA). Other exemplary compositions comprise more than one BCMA antibody, CD3-BCMA antibody, or BCMA antibody conjugate that recognize the same epitope(s), or different species of BCMA antibodies, CD3-BCMA bispecific antibodies, or

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NOM DU FICHIER / FILE NAME :

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CLAIMS:

1. A bispecific antibody comprising a first antibody variable domain and a second antibody variable domain, wherein the first antibody variable domain specifically binds to Cluster of Differentiation 3 (CD3), the second antibody variable domain specifically binds to B-Cell Maturation Antigen (BCMA), and wherein

(a) the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 333; a VH CDR2 comprising the sequence shown in SEQ ID NO: 417; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 157; a VH CDR2 comprising the sequence shown in SEQ ID NO: 159; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225;

(b) the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 331; a VH CDR2 comprising the sequence shown in SEQ ID NO: 336; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL_CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 156; a VH CDR2 comprising the sequence shown in SEQ ID NO: 158; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225;

(c) the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 332; a VH CDR2 comprising the sequence shown in SEQ ID NO: 417; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 151; a VH CDR2 comprising the sequence shown in SEQ ID NO:159; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225; or

(d) the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 333; a VH CDR2 comprising the sequence shown in SEQ ID NO: 336; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 157; a VH CDR2 comprising the sequence shown in SEQ ID NO:158; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225.

2. The bispecific antibody of claim 1, wherein the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 333; a VH CDR2 comprising the sequence shown in SEQ ID NO: 417; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335;

a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 157; a VH CDR2 comprising the sequence shown in SEQ ID NO: 159; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225.

3. The bispecific antibody of claim 1, wherein the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 331; a VH CDR2 comprising the sequence shown in SEQ ID NO: 336; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 156; a VH CDR2 comprising the sequence shown in SEQ ID NO:158; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225.

4. The bispecific antibody of claim 1, wherein the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 332; a VH CDR2 comprising the sequence shown in SEQ ID NO: 417; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 151;

a VH CDR2 comprising the sequence shown in SEQ ID NO: 159; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225.

5. The bispecific antibody of claim 1, wherein the first antibody variable domain comprises a heavy chain variable region complementarity determining region one (VH CDR1) comprising the sequence shown in SEQ ID NO: 333; a VH CDR2 comprising the sequence shown in SEQ ID NO: 336; a VH CDR3 comprising the sequence shown in SEQ ID NO: 335; a light chain variable region CDR1 (VL CDR1) comprising the sequence shown in SEQ ID NO: 343; a VL CDR2 comprising the sequence shown in SEQ ID NO: 341; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 342; and the second antibody variable domain comprises a VH CDR1 comprising the sequence shown in SEQ ID NO: 157; a VH CDR2 comprising the sequence shown in SEQ ID NO: 158; a VH CDR3 comprising the sequence shown in SEQ ID NO: 155; a VL CDR1 comprising the sequence shown in SEQ ID NO: 209; a VL CDR2 comprising the sequence shown in SEQ ID NO: 221; and a VL CDR3 comprising the sequence shown in SEQ ID NO: 225.

6. The bispecific antibody of claim 1, wherein the second antibody variable domain comprises a VH CDR2 comprising the sequence shown in SEQ ID NO: 159.

7. The bispecific antibody of any one of claims 1 to 6, wherein the bispecific antibody further comprises a human IgG2 heavy chain constant region.

8. The bispecific antibody of claim 7, wherein the human IgG2 heavy chain constant region is a modified human IgG2 heavy chain constant region, as compared to a wildtype human IgG2 heavy chain constant region.

9. The bispecific antibody of claim 7, wherein the bispecific antibody comprises two human IgG2 heavy chain constant regions, wherein one heavy chain constant region comprises the sequence shown in SEQ ID NO: 496 and the other heavy chain constant region comprises the sequence shown in SEQ ID NO: 497.

10. The bispecific antibody of any one of claims 1 to 6, further comprising two heavy chain constant regions, wherein one heavy chain constant region comprises the sequence shown in SEQ ID NO: 496.

11. The bispecific antibody of any one of claims 1 to 6, further comprising two heavy chain constant regions, wherein one heavy chain constant region comprises the sequence shown in SEQ ID NO: 497.

12. The bispecific antibody of claim 1, wherein the first antibody variable domain comprises a heavy chain variable region comprising the sequence shown in SEQ ID NO: 324, and a light chain variable region comprising the sequence shown in SEQ ID NO: 323; and

the second antibody variable domain comprises a heavy chain variable region comprising the sequence shown in SEQ ID NO: 112, and a light chain variable region comprising the sequence shown in SEQ ID NO: 38.

13. The bispecific antibody of claim 1, wherein the first antibody variable domain comprises a heavy chain variable region comprising the sequence shown in SEQ ID NO: 324, and a light chain variable region comprising the sequence shown in SEQ ID NO: 323; and

the second antibody variable domain comprises a heavy chain variable region encoded by the polynucleotide sequence shown in SEQ ID NO: 486, and a light chain variable region encoded by the polynucleotide sequence shown in SEQ ID NO: 485.

14. The bispecific antibody of claim 13, further comprising two heavy chain constant regions, wherein one heavy chain constant region comprises the sequence shown in SEQ ID NO: 496 and the other heavy chain constant region comprises the sequence shown in SEQ ID NO: 497.

15. The bispecific antibody of claim 1, wherein the first antibody variable domain comprises a heavy chain variable region comprising the sequence shown in SEQ ID NO: 324, and a light chain variable region comprising the sequence shown in SEQ ID NO: 323; and

the second antibody variable domain comprises a heavy chain variable region encoded by the polynucleotide having ATCC Accession No. PTA-122094, and a light chain variable region encoded by the polynucleotide having ATCC Accession No. PTA-122093.

16. The bispecific antibody of claim 15, further comprising two heavy chain constant regions, wherein one heavy chain constant region comprises the sequence shown in SEQ ID NO: 496 and the other heavy chain constant region comprises the sequence shown in SEQ ID NO: 497.

17. A bispecific antibody comprising a first antibody variable domain and a second antibody variable domain, wherein

the first antibody variable domain comprises a heavy chain variable region comprising the sequence shown in SEQ ID NO: 324, and a light chain variable region comprising the sequence shown in SEQ ID NO: 323; and

the second antibody variable domain comprises a heavy chain variable region comprising the sequence shown in SEQ ID NO: 112, and a light chain variable region comprising the sequence shown in SEQ ID NO: 38.

18. A bispecific antibody comprising a first antibody variable domain and a second antibody variable domain, wherein

the first antibody variable domain comprises a heavy chain variable region comprising the sequence shown in SEQ ID NO: 324, and a light chain variable region comprising the sequence shown in SEQ ID NO: 323; and

the second antibody variable domain comprises a heavy chain variable region encoded by the polynucleotide sequence shown in SEQ ID NO: 486, and a light chain variable region encoded by the polynucleotide sequence shown in SEQ ID NO: 485.

19. A pharmaceutical composition comprising the bispecific antibody of any one of claims 1 to 18 and a pharmaceutically acceptable carrier.

20. An isolated polynucleotide comprising a nucleotide sequence encoding the bispecific antibody of any one of claims 1-18.

21. A vector comprising the polynucleotide of claim 20.

22. A host cell comprising the vector of claim 21.

Figure 1A

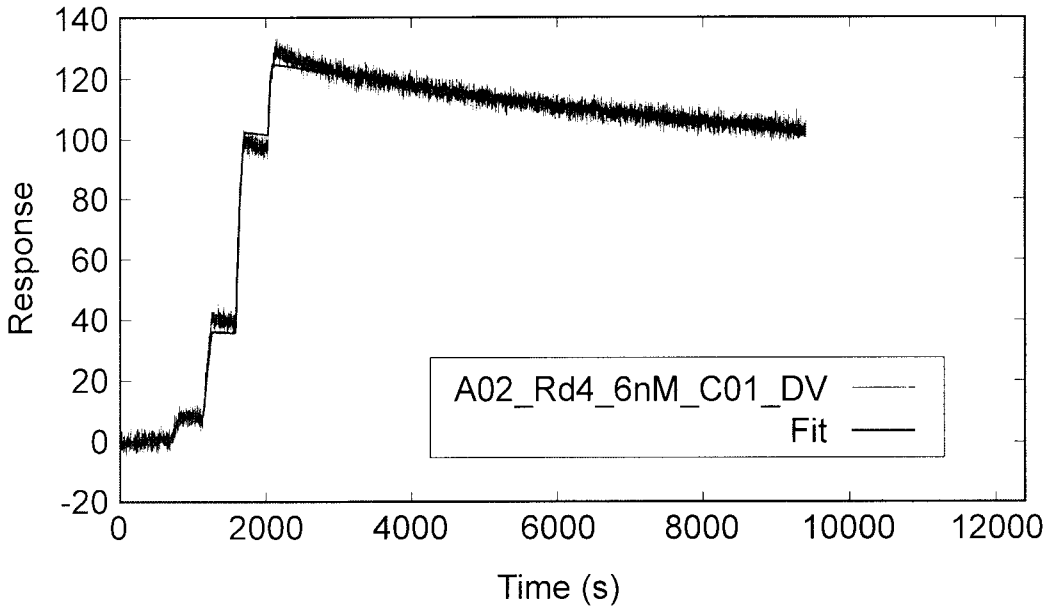


Figure 1B

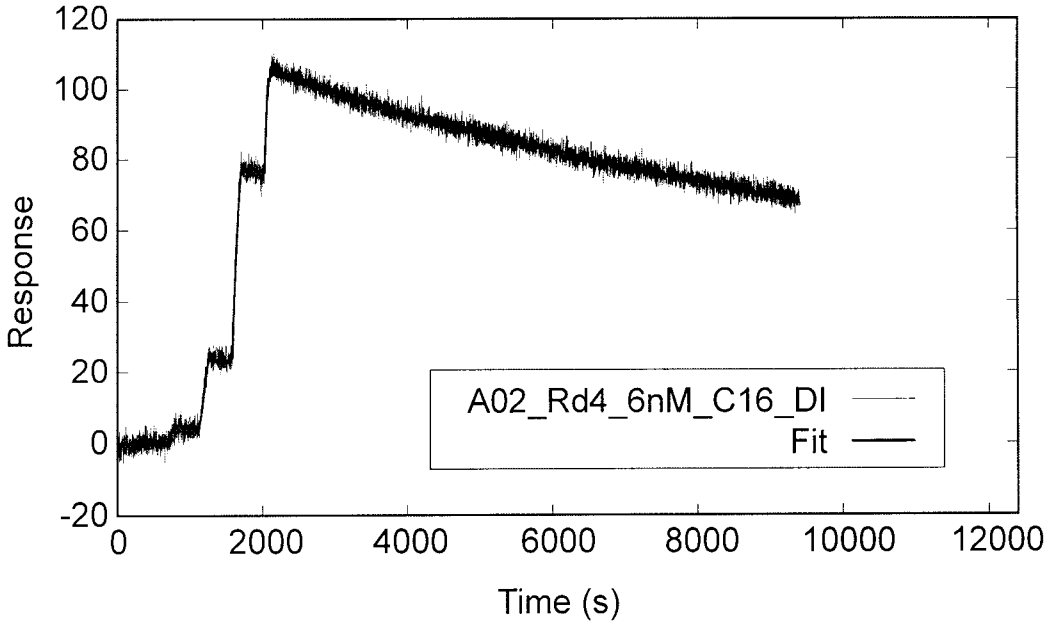


Figure 1C

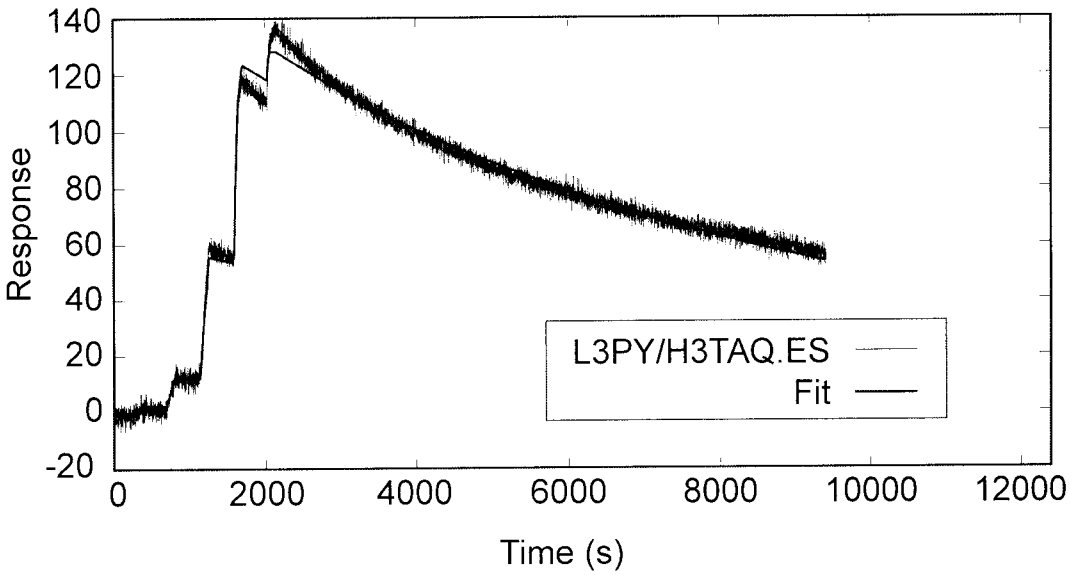


Figure 1D

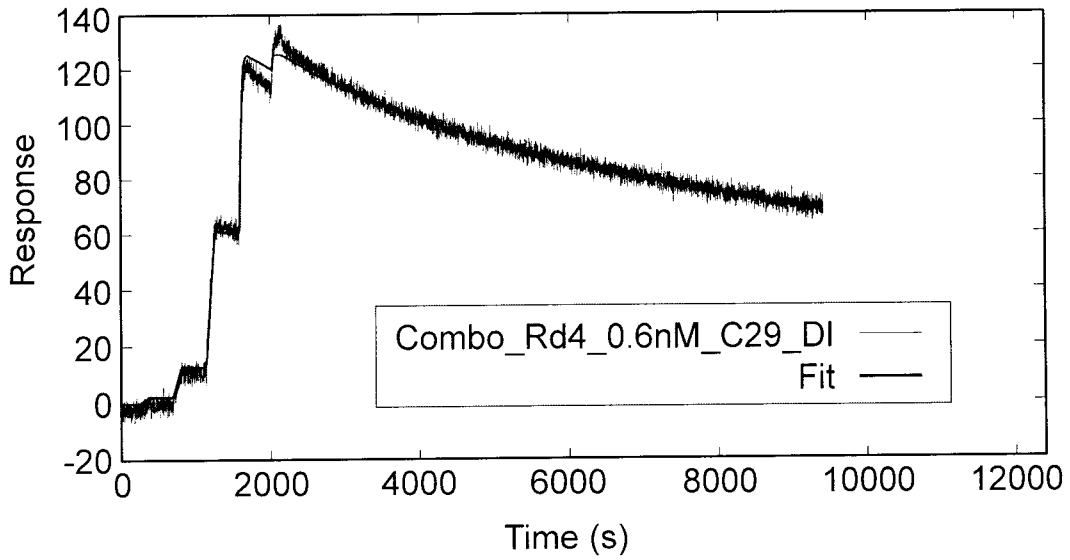


Figure 2

MM1S

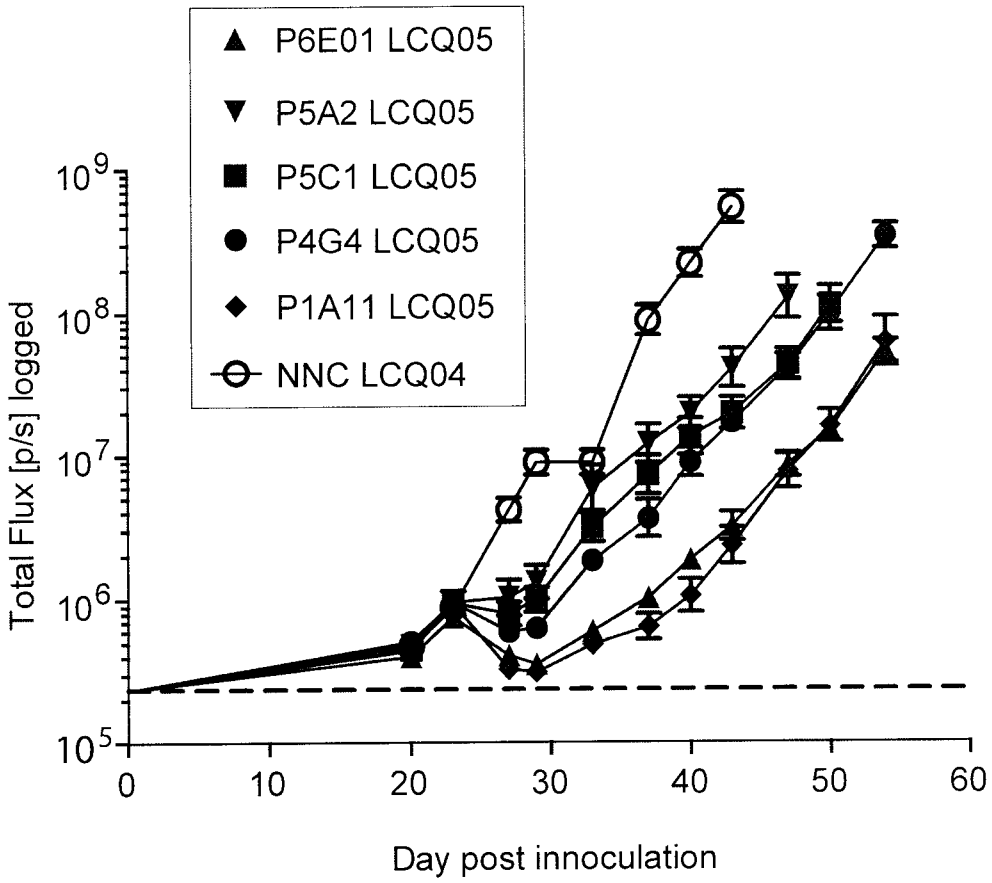


Figure 3

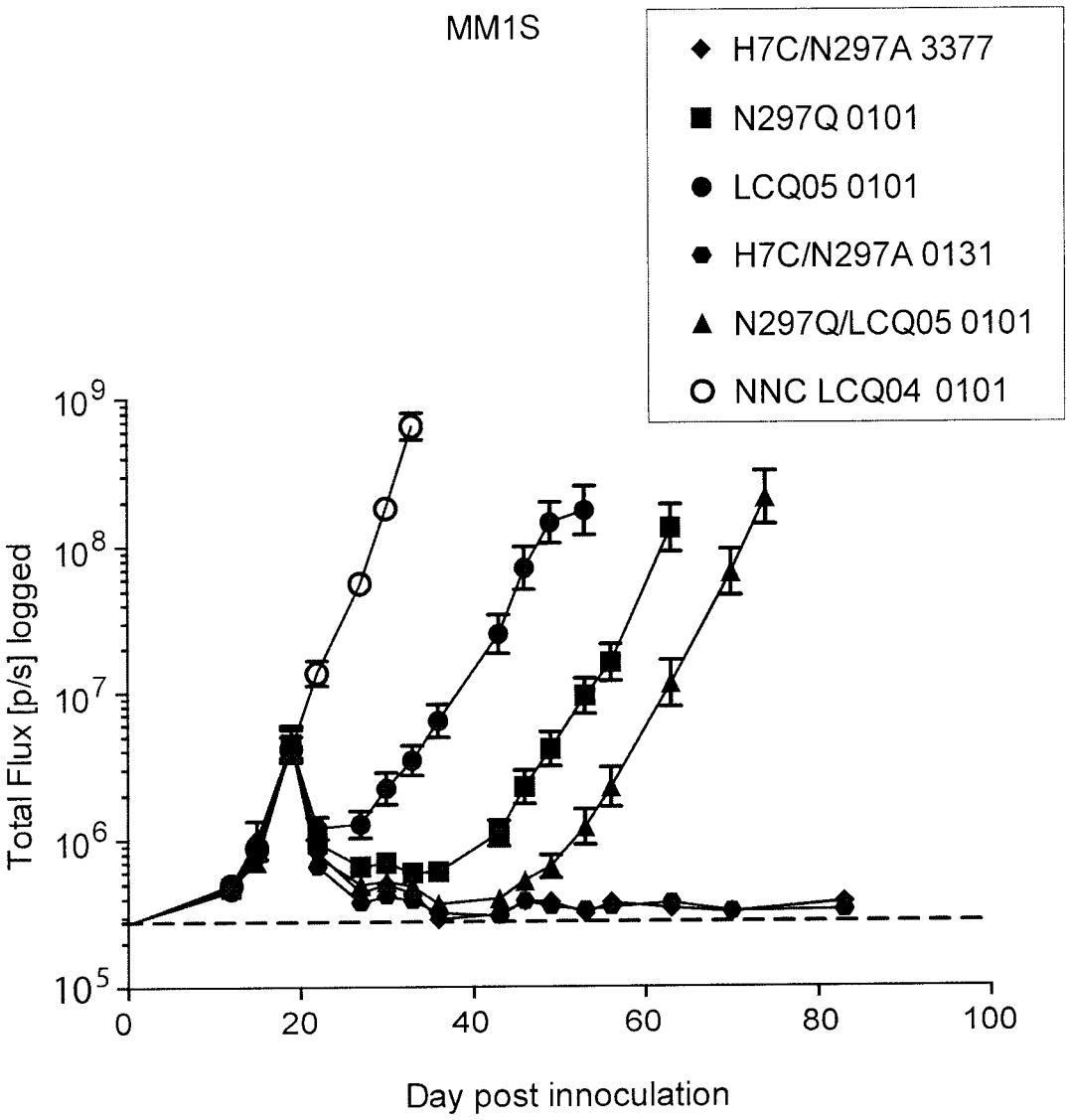

MM1S
H7C/N297A 3377
N297Q 0101
LCQ05 0101
H7C/N297A 0131
N297Q/LCQ05 0101
NNC LCQ04 0101
Total Flux [p/s] logged
10^9
10^8
10^7
10^6
10^5
0
20
40
60
80
100
Day post innoculation

Figure 4

KMS12BM

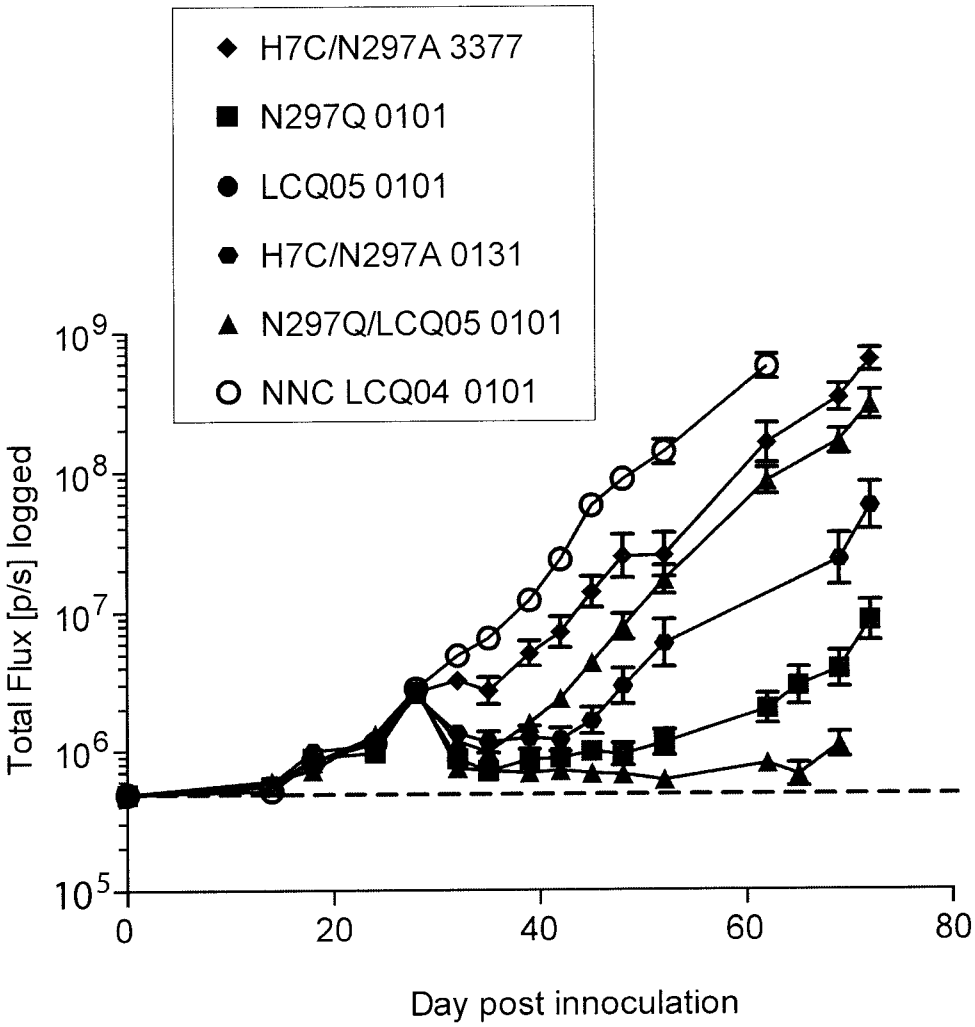


Figure 5

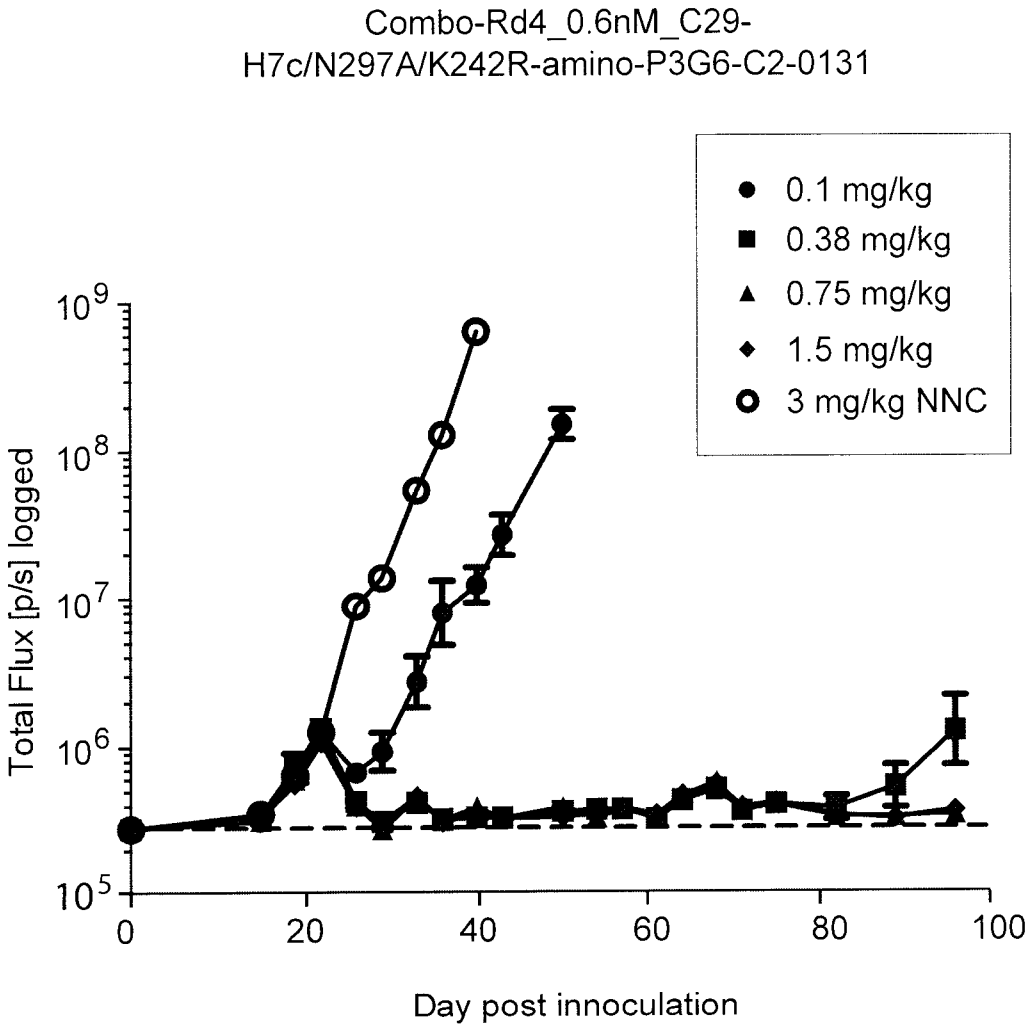

Combo-Rd4_0.6nM_C29-
H7c/N297A/K242R-amino-P3G6-C2-0131
0.1 mg/kg
0.38 mg/kg
0.75 mg/kg
1.5 mg/kg
3 mg/kg NNC
Total Flux [p/s] logged
10^9
10^8
10^7
10^6
10^5
0
20
40
60
80
100
Day post innoculation

Figure 6A

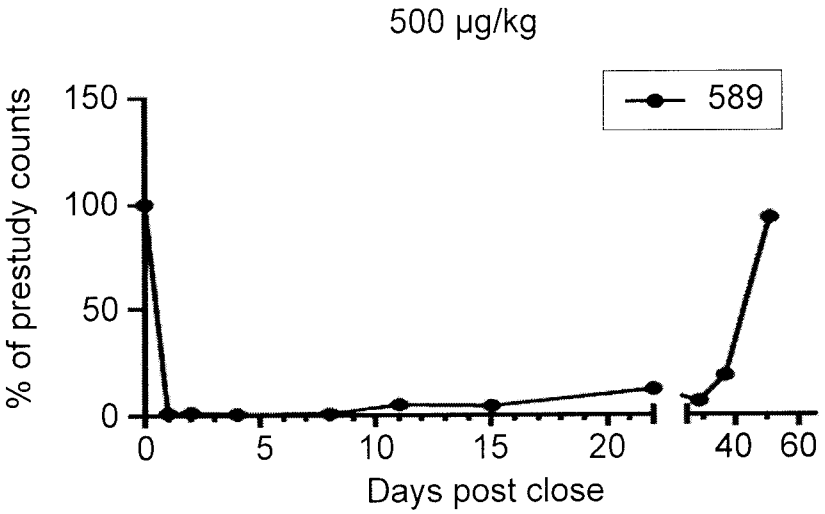


Figure 6B

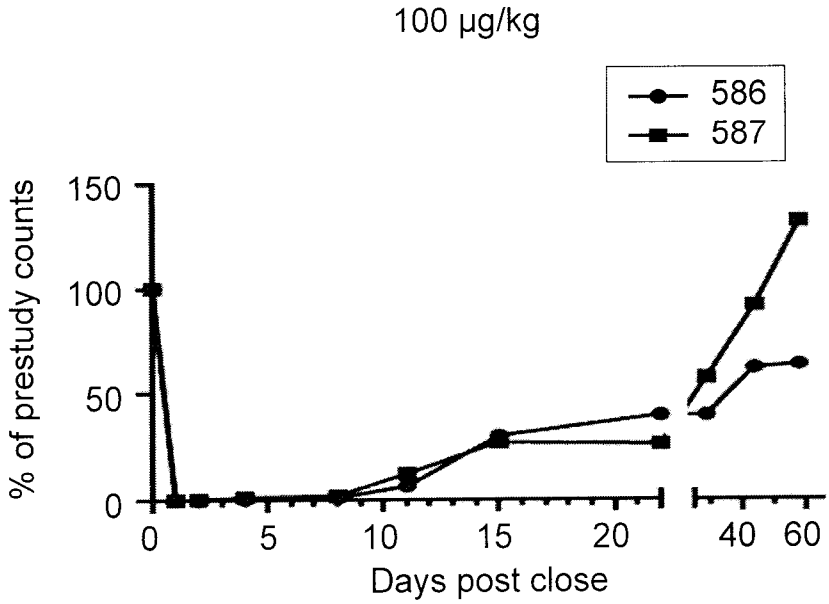


Figure 6C

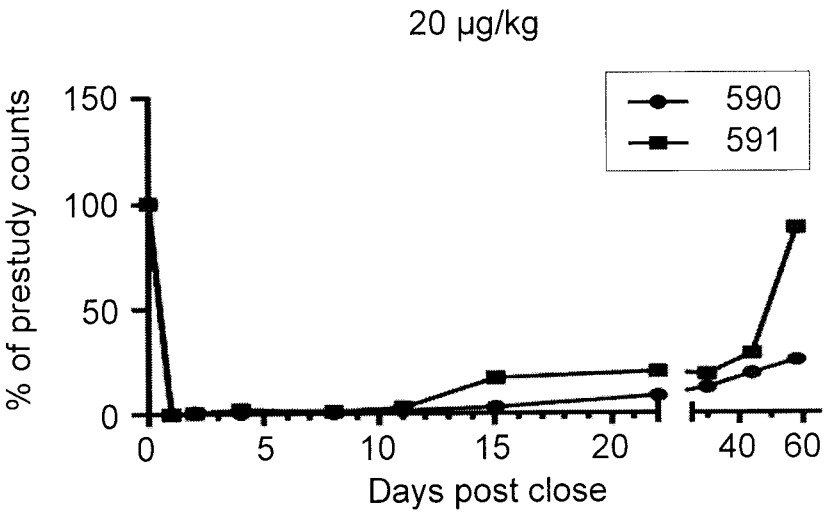


Figure 6D

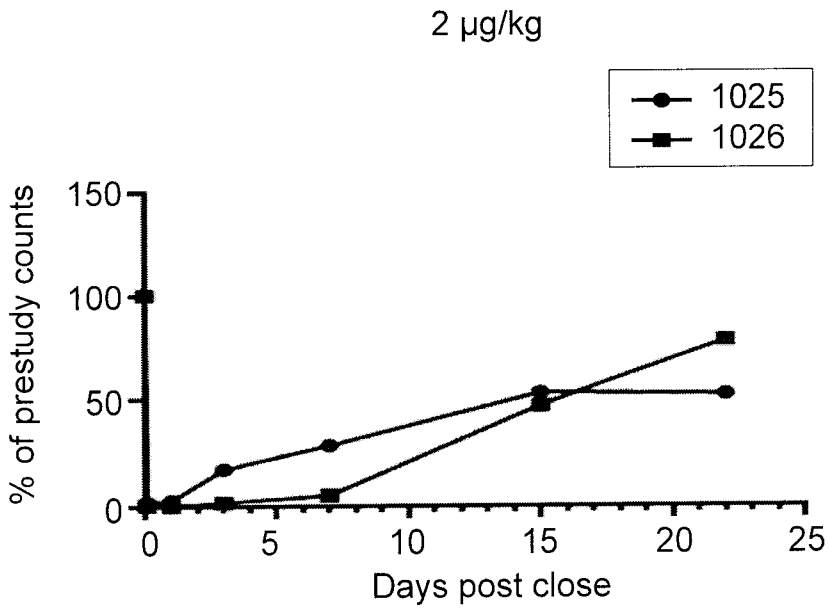


Figure 6E

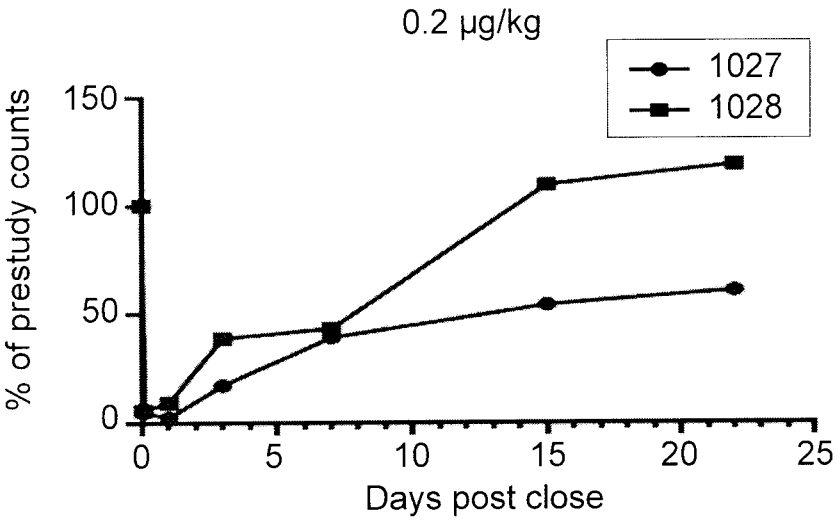


Figure 6F

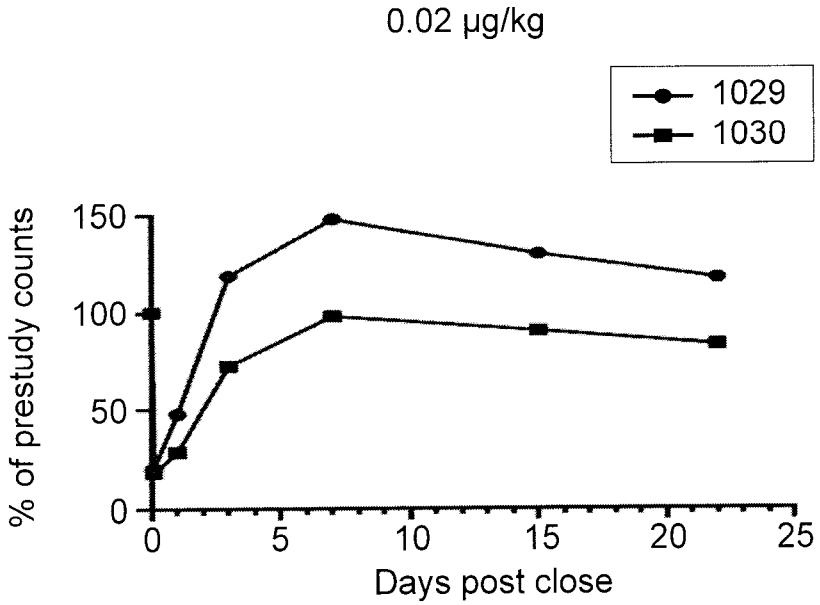


Figure 7A

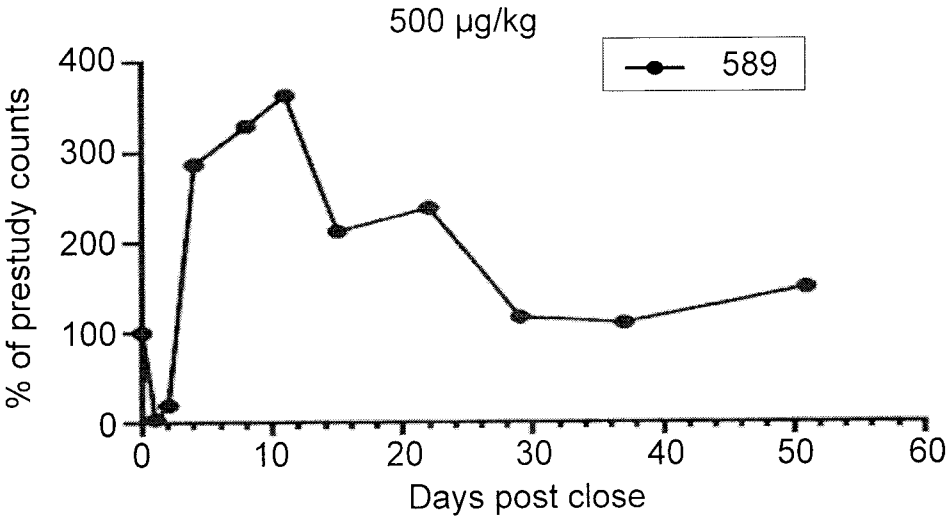


Figure 7B

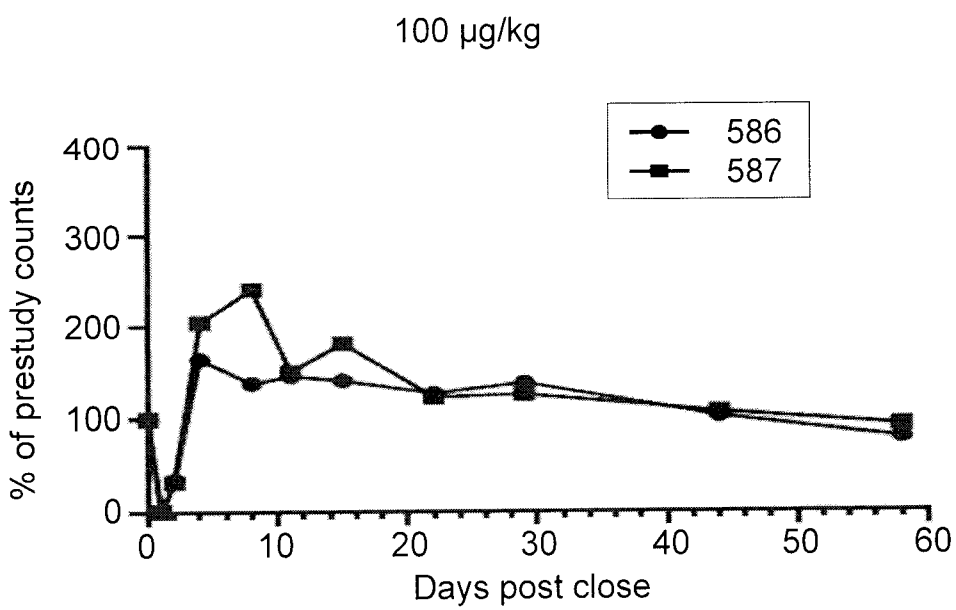


Figure 7C

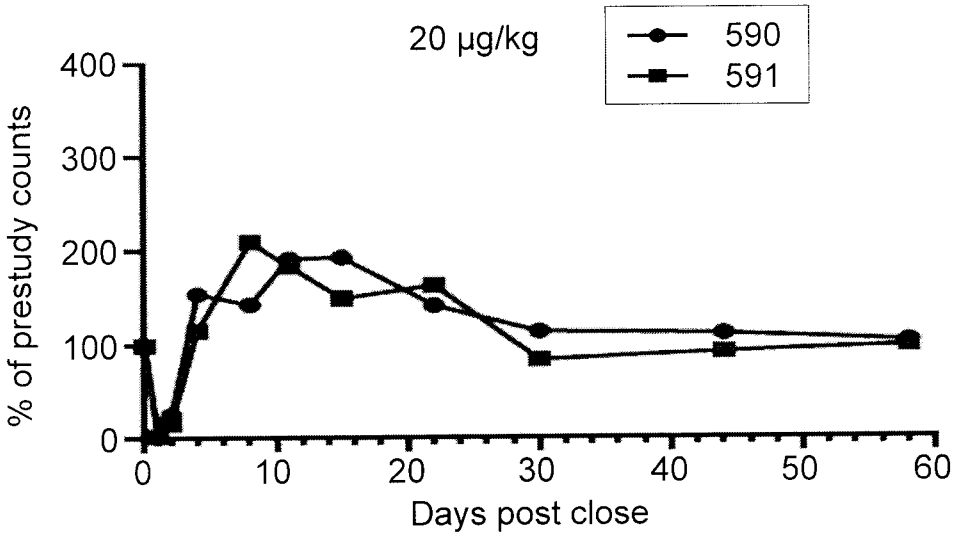


Figure 7D

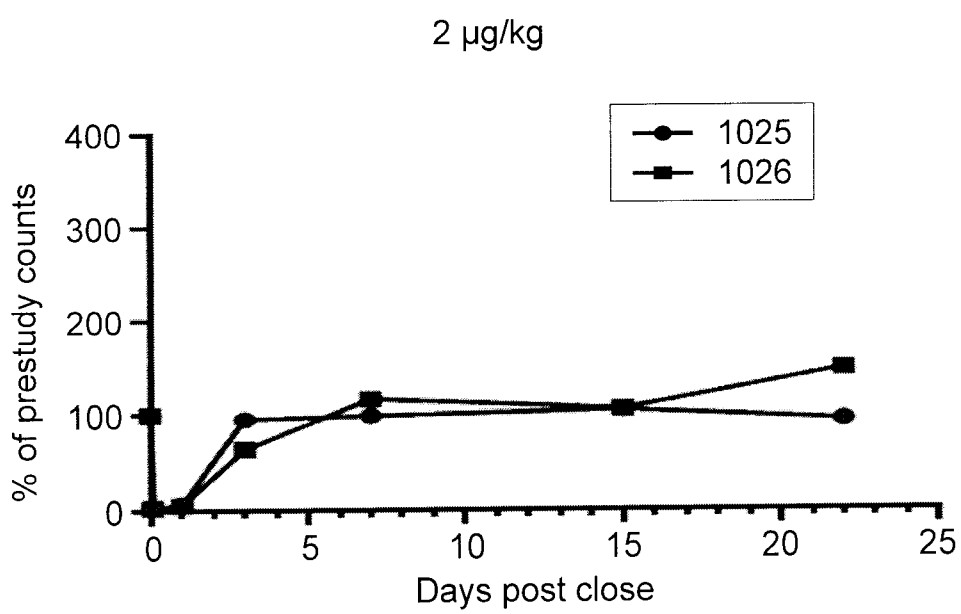


Figure 7E

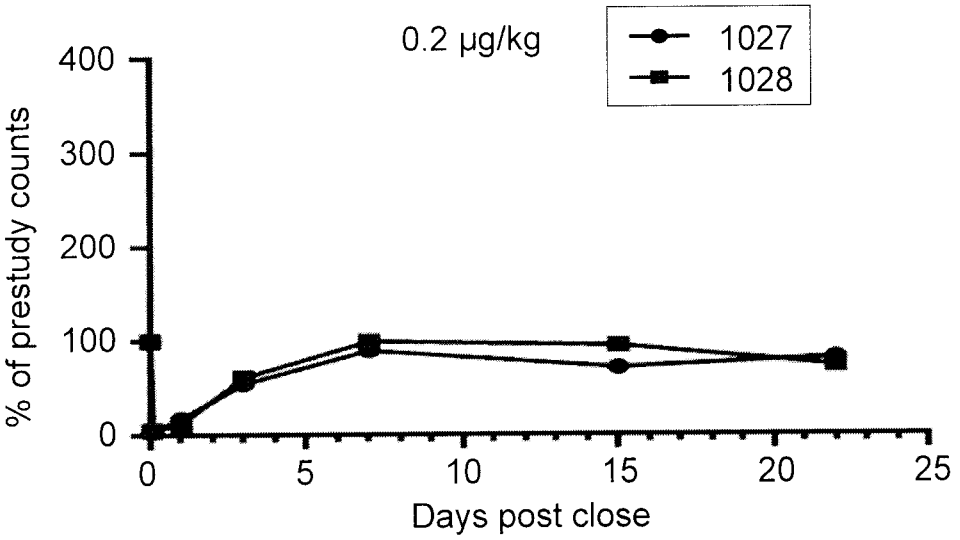


Figure 7F

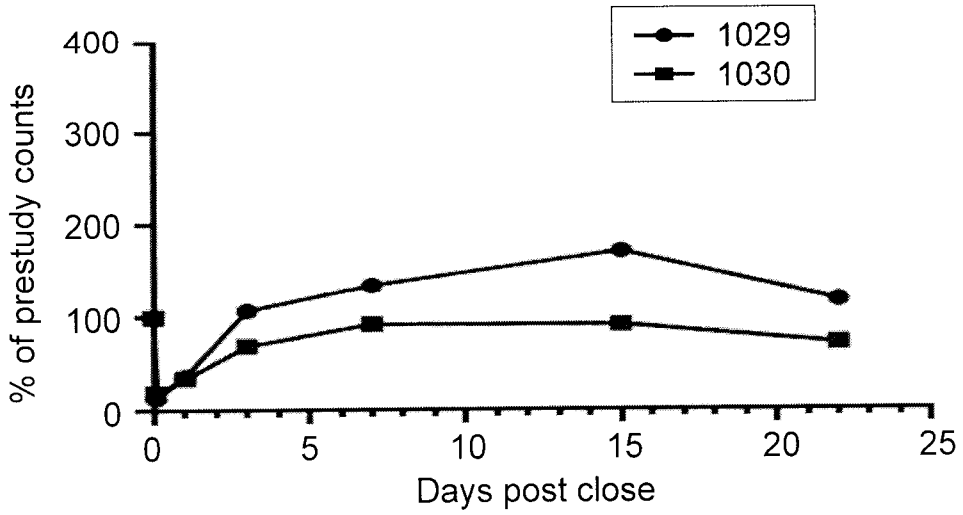


Figure 8A

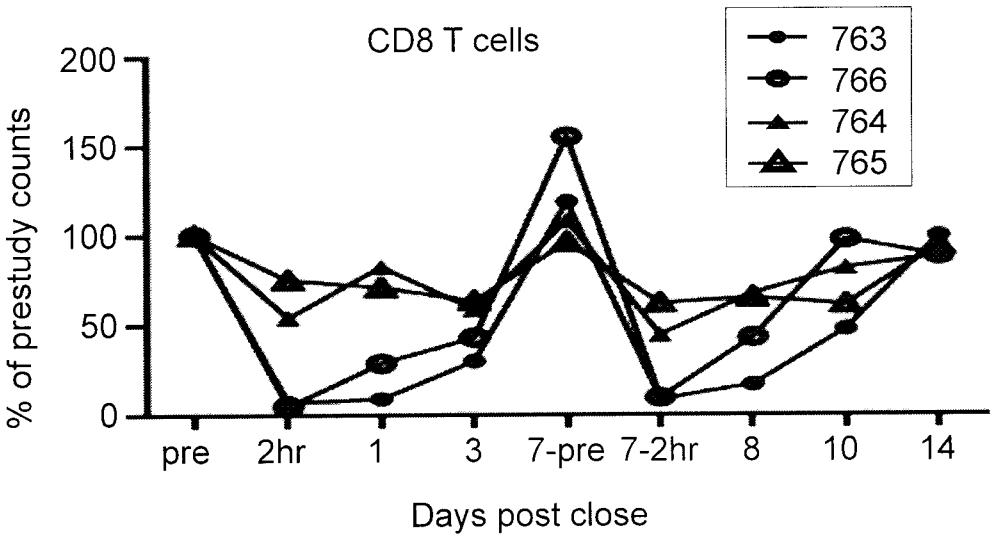


Figure 8B

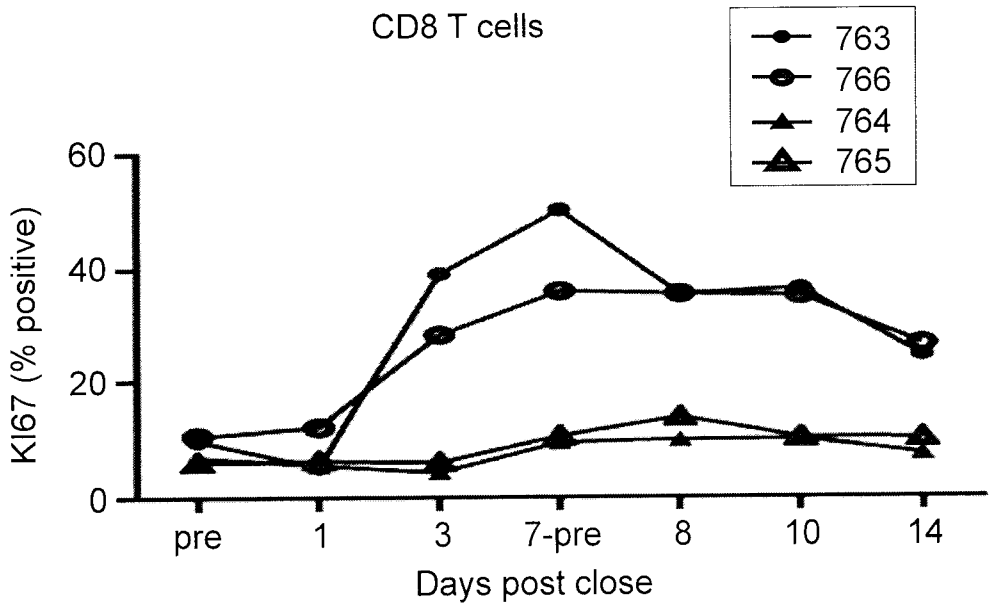


Figure 9A

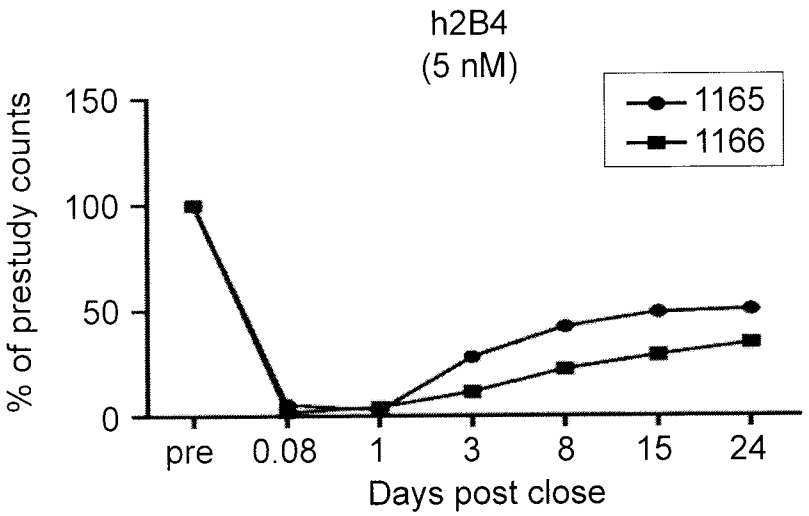


Figure 9B

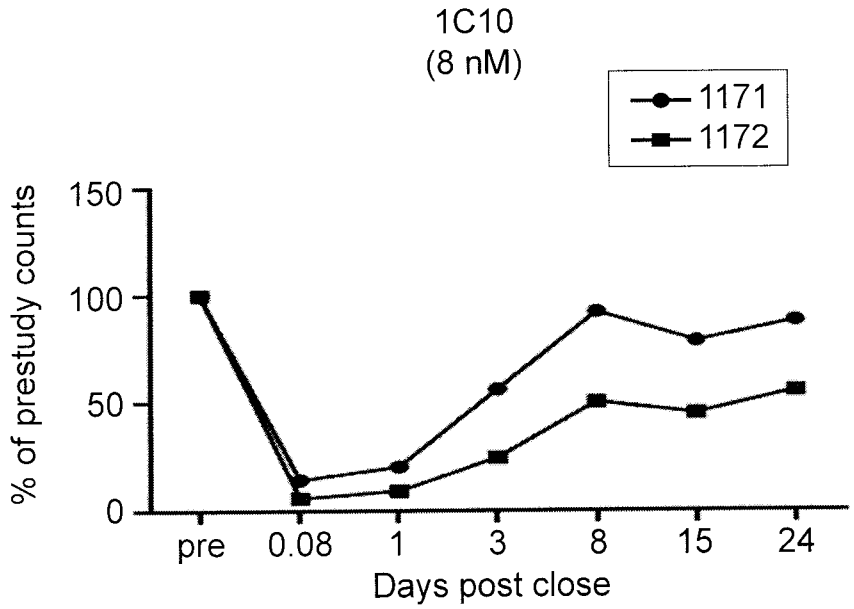


Figure 9C

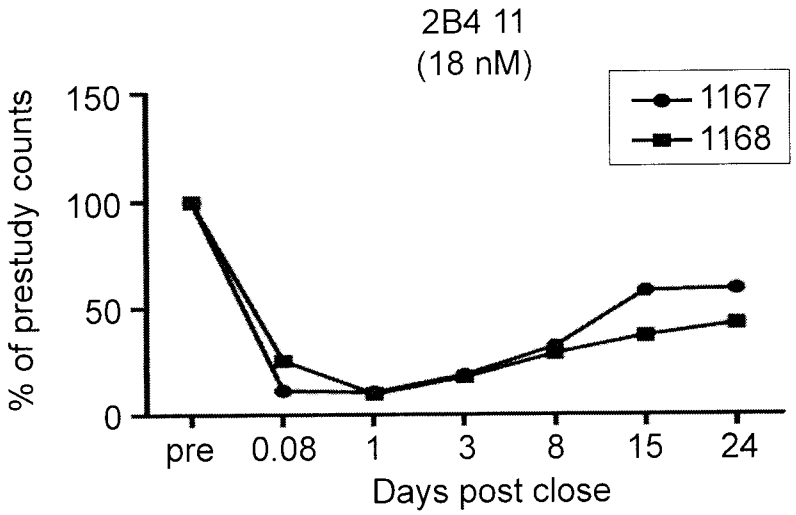


Figure 9D

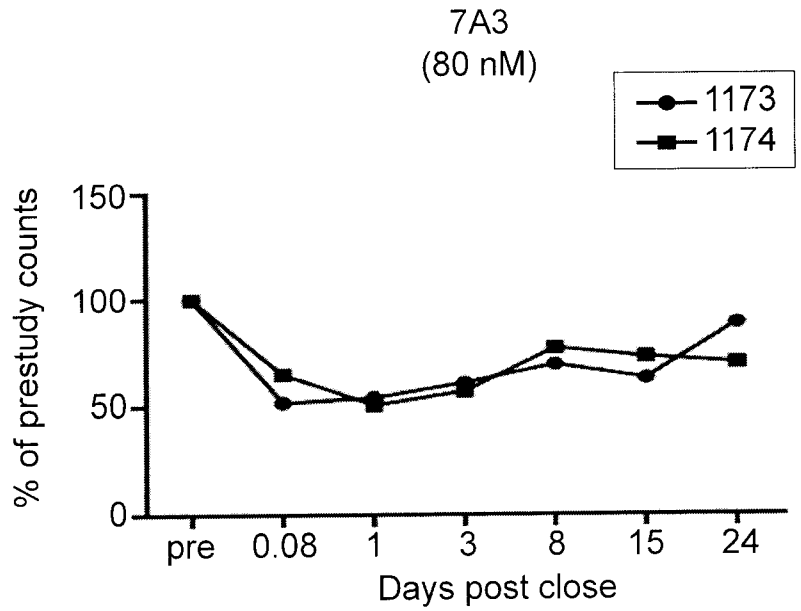


Figure 10A

T cell Activation/Proliferation Quantified by
^{3}H incorporation in human PBMC: **48 hr later**

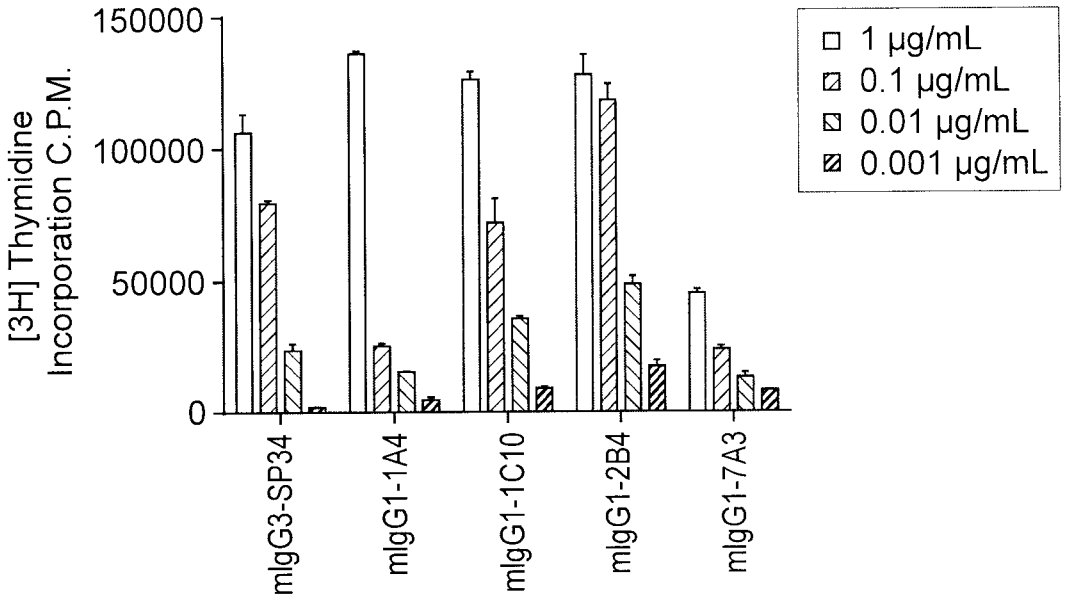


Figure 10B

T cell Activation/Proliferation Quantified by
^{3}H incorporation in cynomolgus PBMC: **48 hr later**

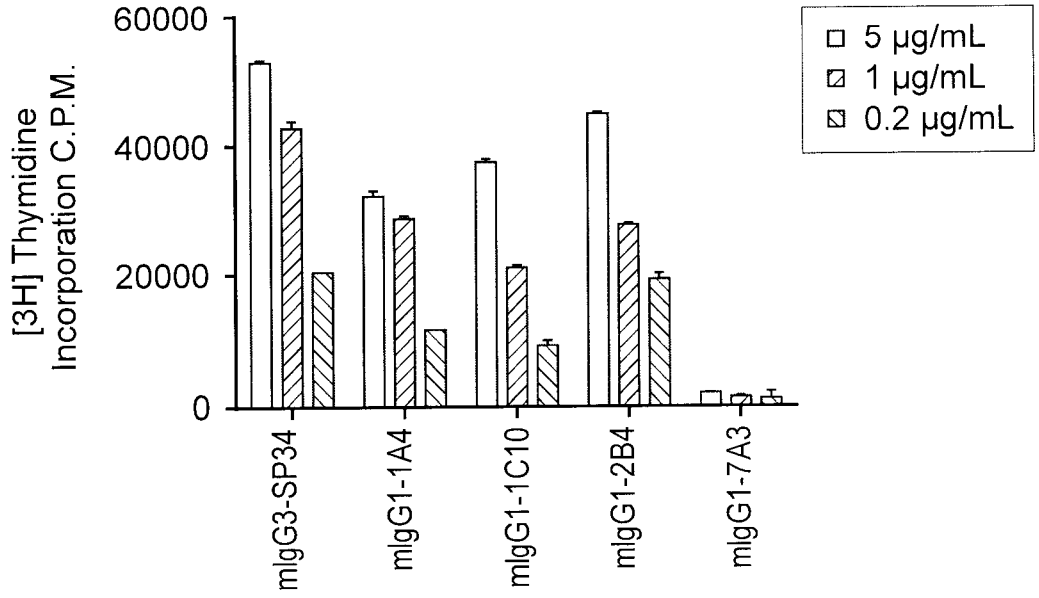


Figure 11A

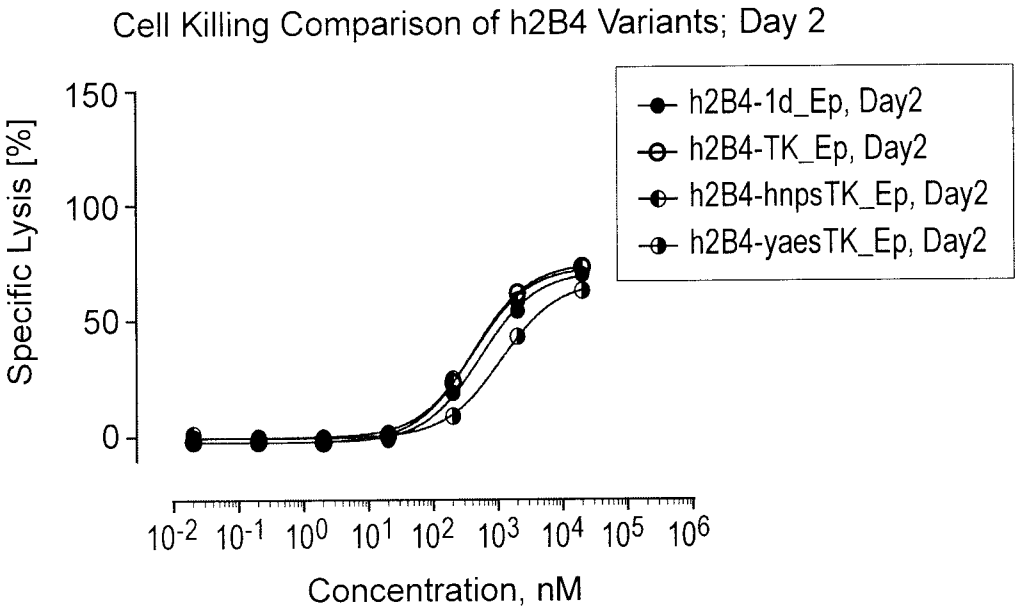


Figure 11B

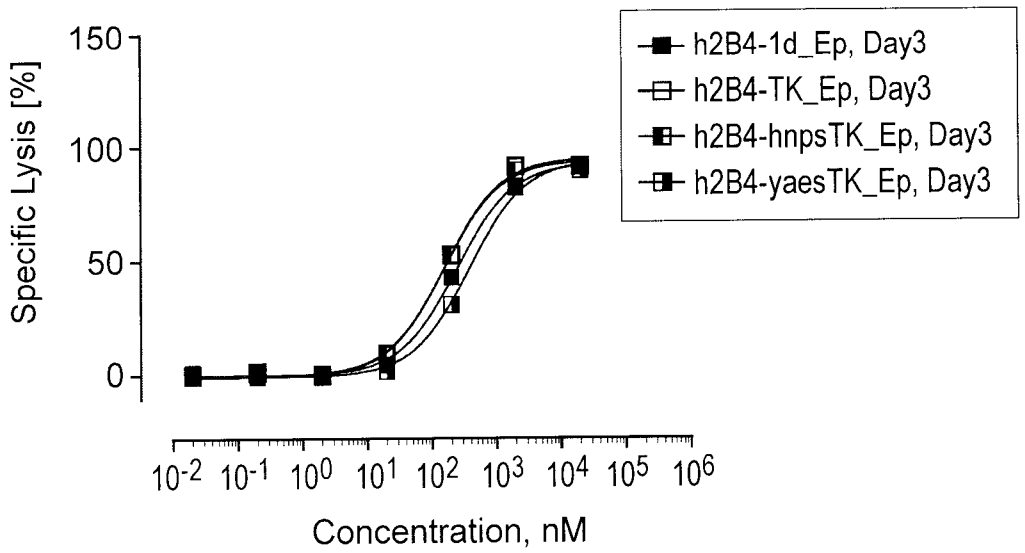


Figure 11C

CD3: h2B4 *vs.* 25A8 Variants; Day 2
PanT as Effector/ SW480 as Target

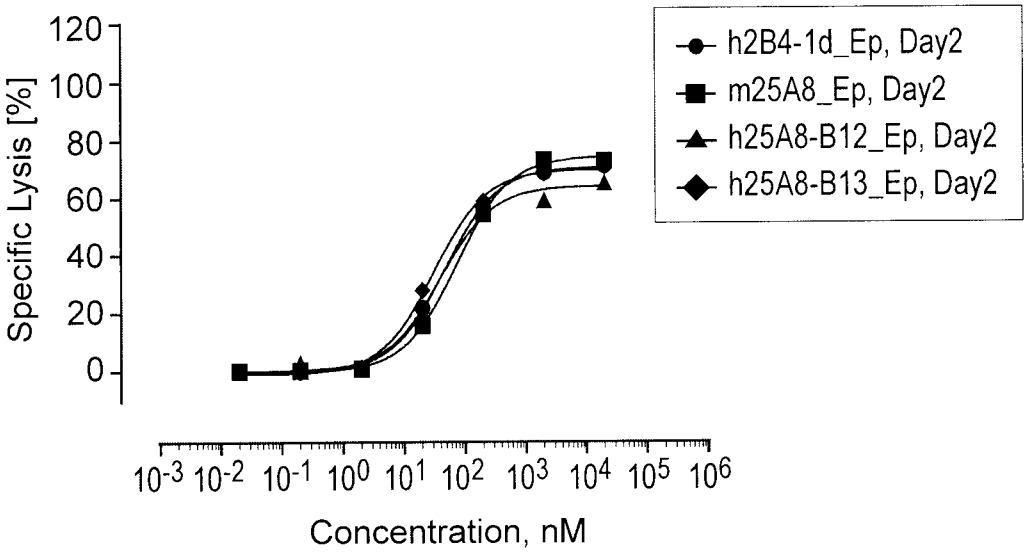


Figure 11D

CD3: h2B4 *vs.* 25A8 Variants; Day 3
PanT as Effector/ SW480 as Target

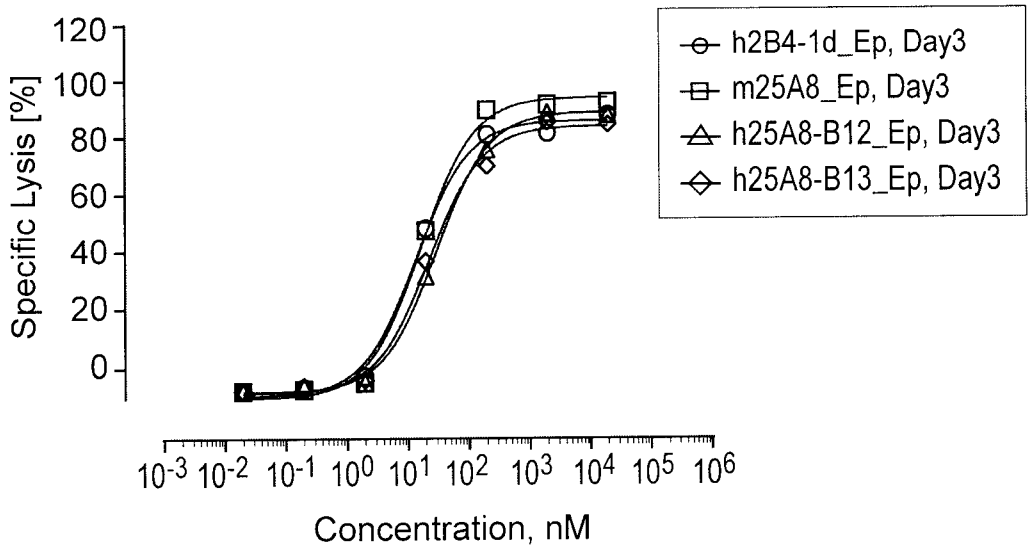


Figure 12

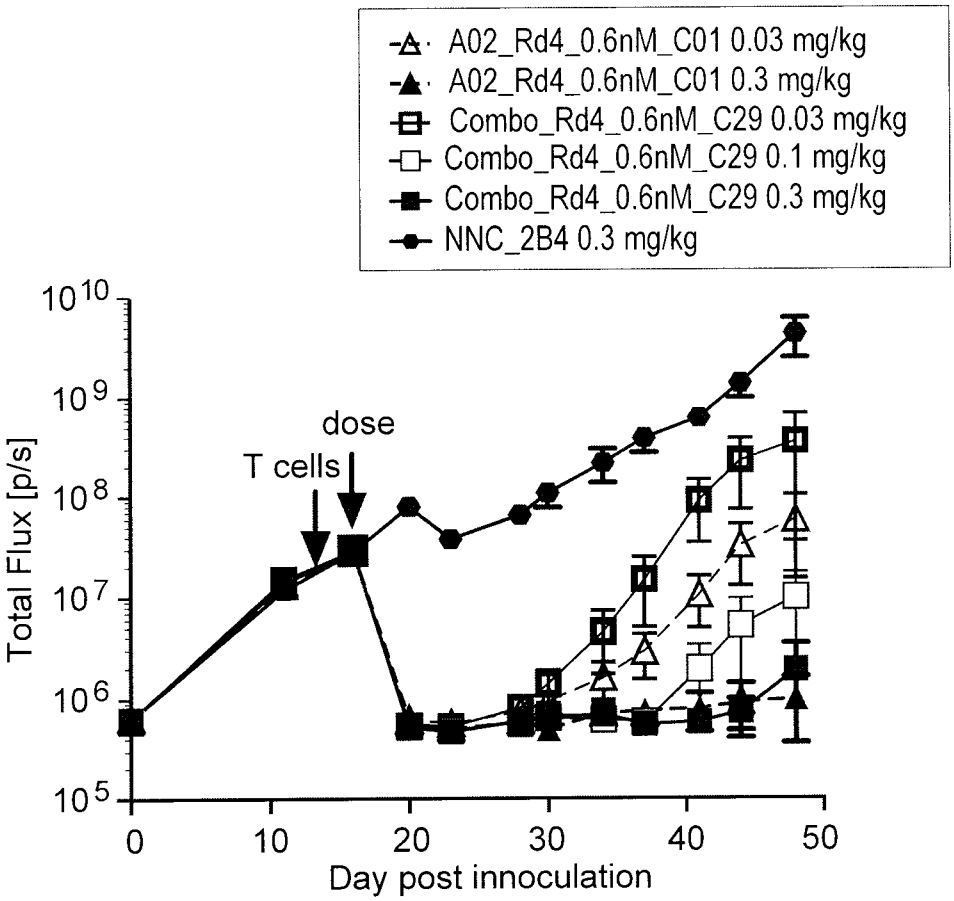

A02_Rd4_0.6nM_C01 0.03 mg/kg
A02_Rd4_0.6nM_C01 0.3 mg/kg
Combo_Rd4_0.6nM_C29 0.03 mg/kg
Combo_Rd4_0.6nM_C29 0.1 mg/kg
Combo_Rd4_0.6nM_C29 0.3 mg/kg
NNC_2B4 0.3 mg/kg
Total Flux [p/s]
10^{10}
10^{9}
10^{8}
10^{7}
10^{6}
10^{5}
dose
T cells
0
10
20
30
40
50
Day post innoculation

Figure 13

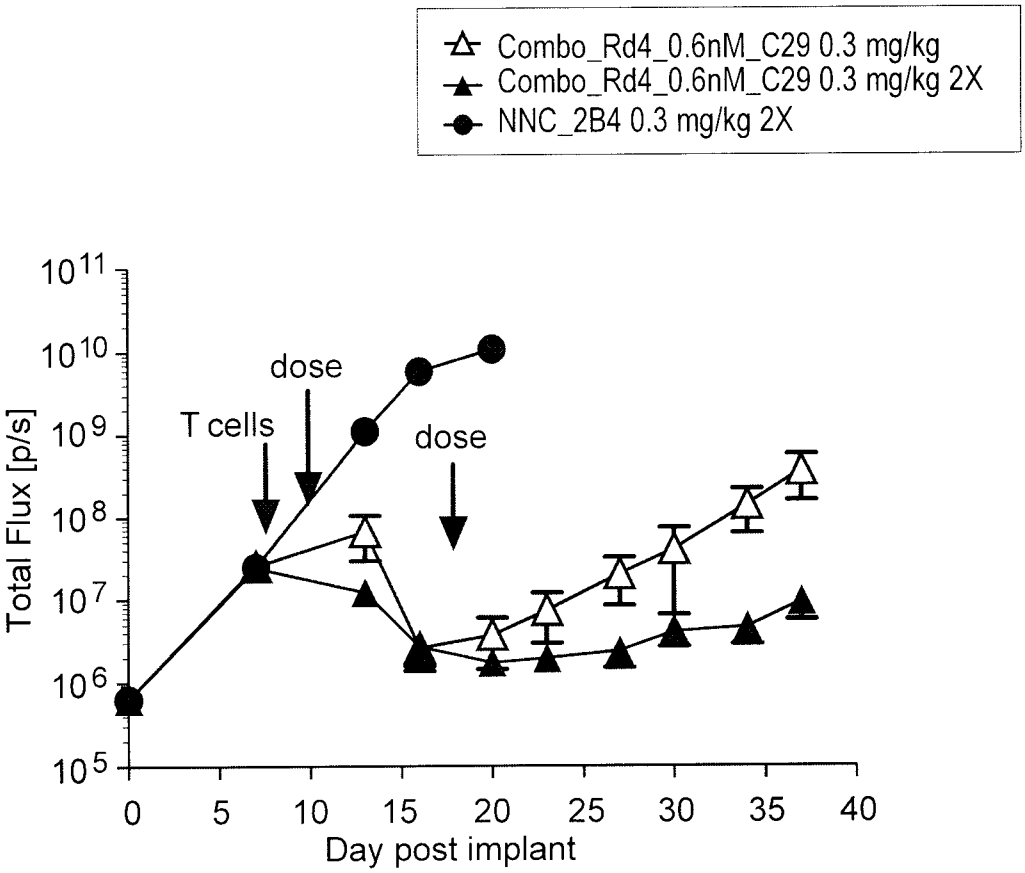

Combo_Rd4_0.6nM_C29 0.3 mg/kg
Combo_Rd4_0.6nM_C29 0.3 mg/kg 2X
NNC_2B4 0.3 mg/kg 2X
Total Flux [p/s]
10^{11}
10^{10}
10^{9}
10^{8}
10^{7}
10^{6}
10^{5}
T cells
dose
dose
0
5
10
15
20
25
30
35
40
Day post implant

Figure 14

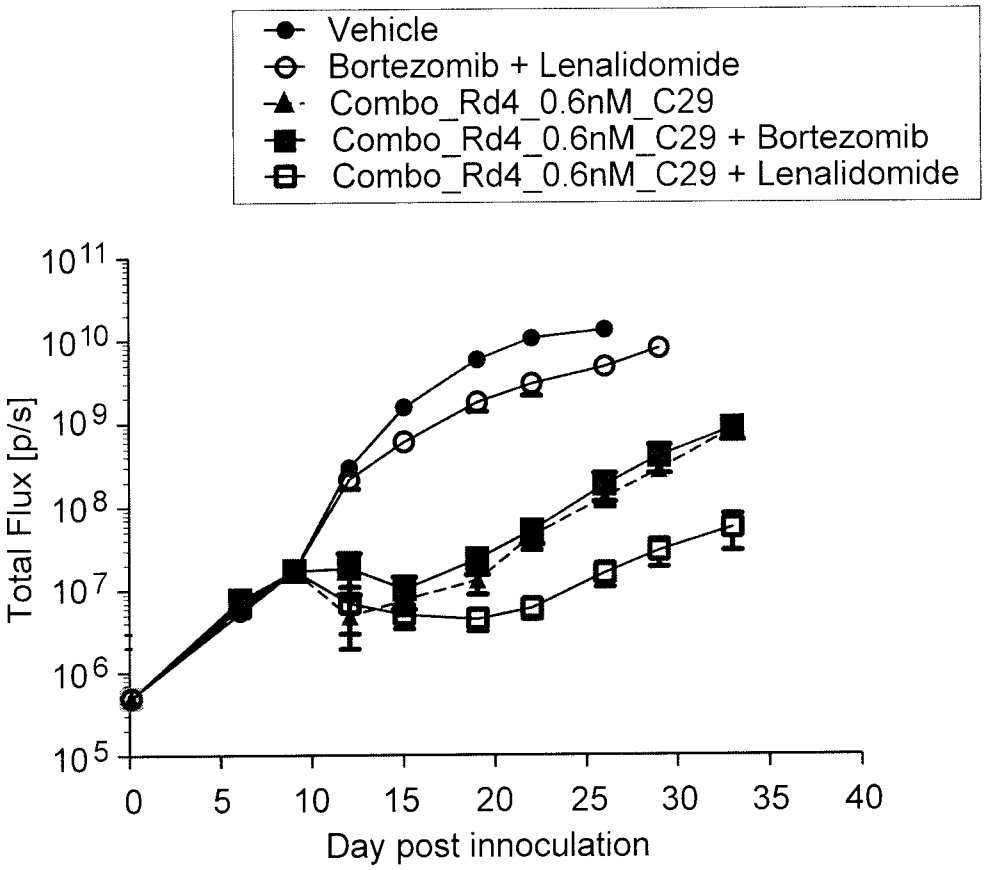

Vehicle
Bortezomib + Lenalidomide
Combo_Rd4_0.6nM_C29
Combo_Rd4_0.6nM_C29 + Bortezomib
Combo_Rd4_0.6nM_C29 + Lenalidomide
Total Flux [p/s]
10^11
10^10
10^9
10^8
10^7
10^6
10^5
0
5
10
15
20
25
30
35
40
Day post innoculation

Figure 15A

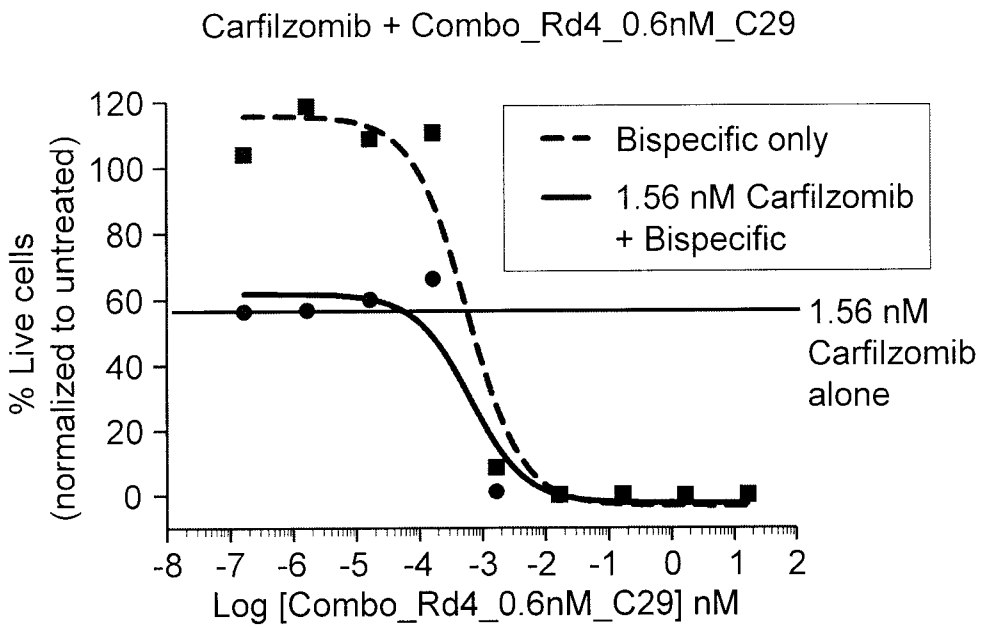


Figure 15B

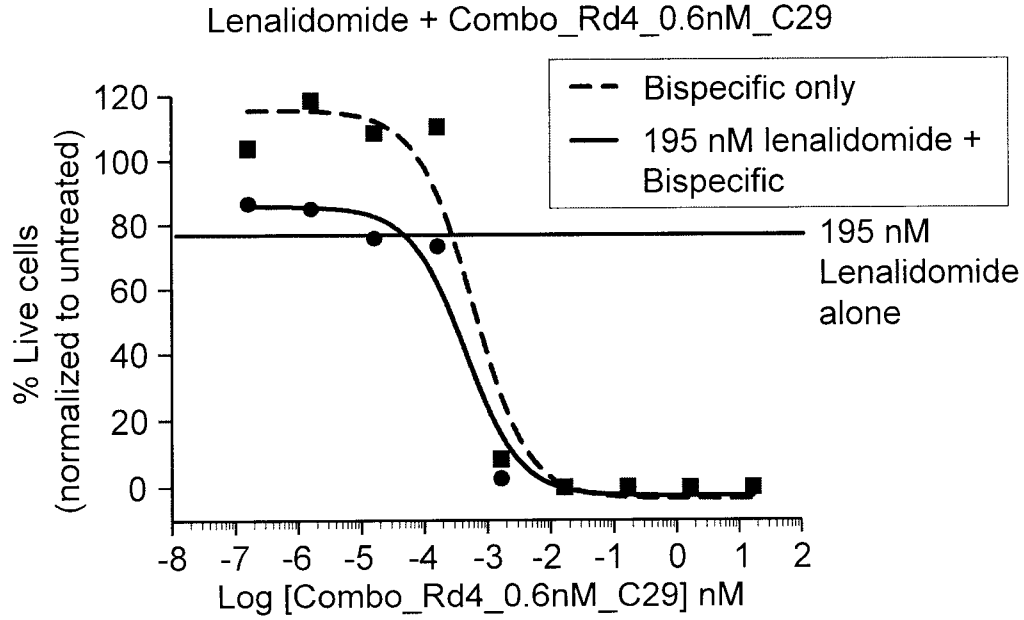


Figure 15C

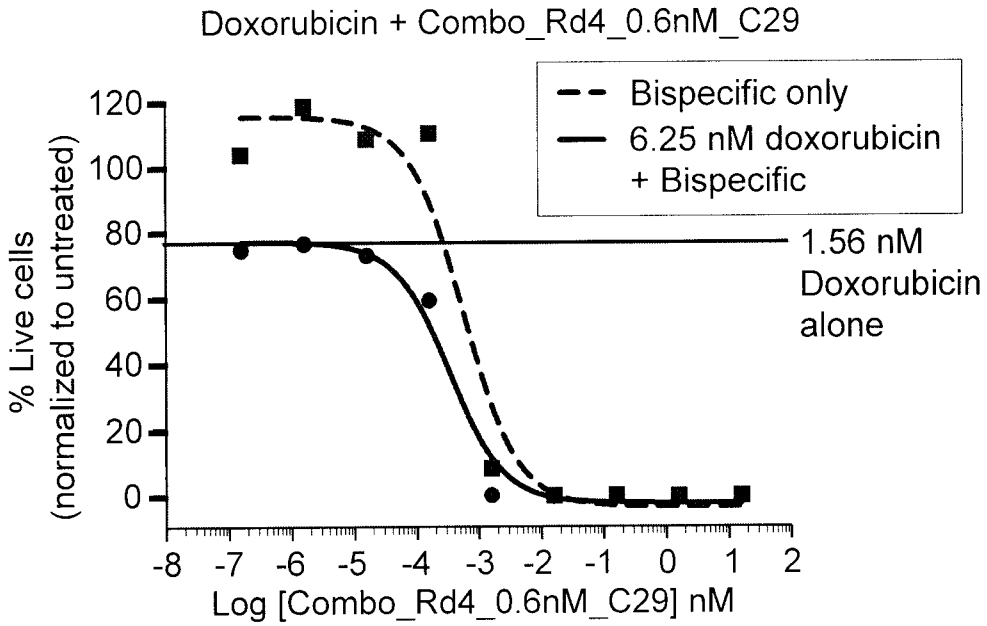
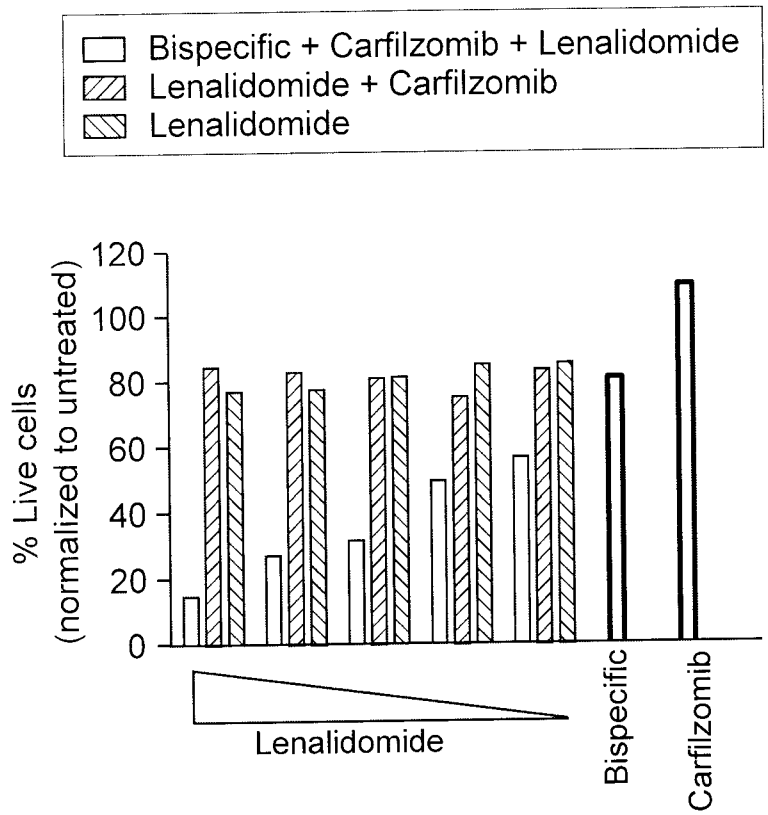
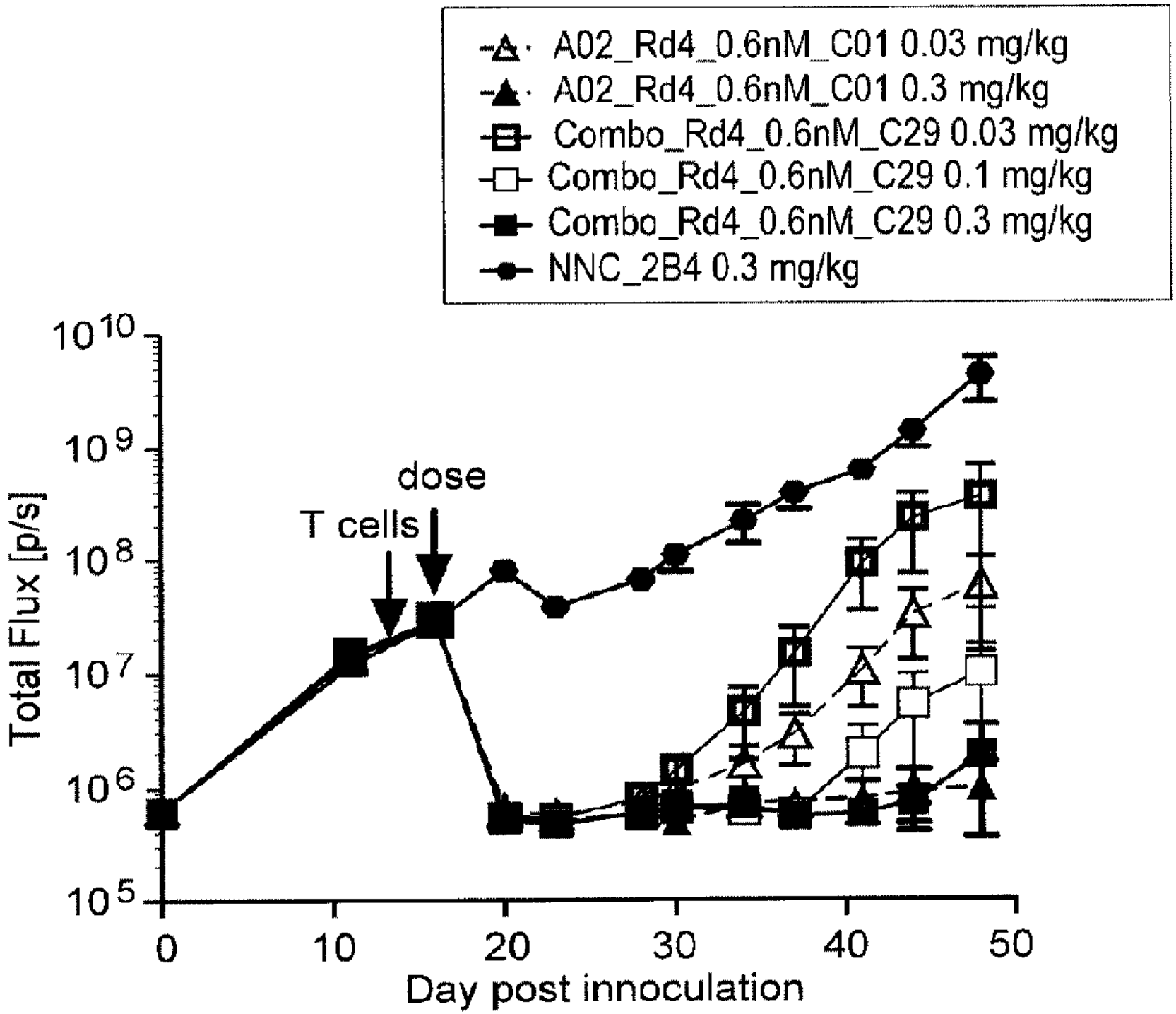

Doxorubicin + Combo_Rd4_0.6nM_C29
Bispecific only
6.25 nM doxorubicin + Bispecific
1.56 nM Doxorubicin alone
% Live cells (normalized to untreated)
120
100
80
60
40
20
0
-8 -7 -6 -5 -4 -3 -2 -1 0 1 2
Log [Combo_Rd4_0.6nM_C29] nM

Figure 16

KMS12BM




A02_Rd4_0.6nM_C01 0.03 mg/kg
A02_Rd4_0.6nM_C01 0.3 mg/kg
Combo_Rd4_0.6nM_C29 0.03 mg/kg
Combo_Rd4_0.6nM_C29 0.1 mg/kg
Combo_Rd4_0.6nM_C29 0.3 mg/kg
NNC_2B4 0.3 mg/kg
Total Flux [p/s]
10^10
10^9
10^8
10^7
10^6
10^5
dose
T cells
0
10
20
30
40
50
Day post innoculation