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(71) Applicant: **DANA-FARBER CANCER INSTITUTE, INC.** [US/US]; 450 Brookline Avenue, Boston, Massachusetts 02215 (US).

(72) Inventors: **MARASCO, Wayne A.**; 43 Rice Street, Wellesley, Massachusetts 02481 (US). **CHANG, Matthew**; 35 Vernon St, Brookline, Massachusetts 02135 (US).

(74) Agent: **ESTRADA DE MARTIN, Paula**; 201 St. Charles Avenue, Suite 3600, New Orleans, Louisiana 70170 (US).

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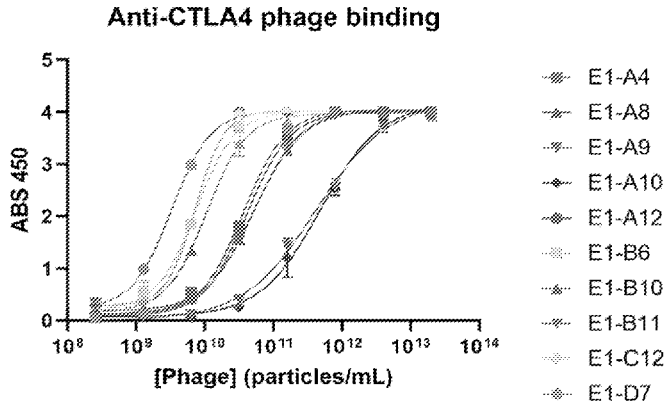

E1-D7 is positive control phage identified in first set of soluble protein panning

FIG. 1

(57) Abstract: The present invention is directed to antibodies against human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) and methods of use thereof.

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ANTIBODIES AGAINST CTLA-4 AND METHODS OF USE THEREOF

[0001] This application claims priority to U.S. Provisional Application No. 63/282,887, filed on November 24, 2021, the entire contents of which are incorporated herein by reference.

[0002] All patents, patent applications and publications cited herein are hereby incorporated by reference in their entirety. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein.

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SEQUENCE LISTING

[0004] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on [ ], is named [ ] and is [ ] bytes in size.

FIELD OF THE INVENTION

[0005] This invention is directed to antibodies against human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) and methods of use thereof.

BACKGROUND

[0006] CTLA-4 is an inhibitory receptor acting as a major negative regulator of T-cell responses. The affinity of CTLA4 for its natural B7 family ligands, CD80 and CD86, is stronger that the affinity of their cognate stimulatory coreceptor CD28.

SUMMARY OF THE INVENTION

[0007] The invention provides for human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) and methods of use thereof.

[0008] Embodiments are drawn to an isolated antibody or fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising (a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 61, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 62, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 63; or (b) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 29, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 30, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 65, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 66; or (c) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 32, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 33, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 67, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 68, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 69; or (d) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 35, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 36, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 70, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 71, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 72; or (e) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 39, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 73, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 74, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or (f) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 42, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 76, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 77, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 78; or (g) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 43,

a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 45, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 79, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 80, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 81; or (h) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 47, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 48, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 82, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 83, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 84; or (i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 50, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 51, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 85, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 86, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or (j) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 53, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 54, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 90; or (k) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 91, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 92, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 93; or (l) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 59, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 60, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 95, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 96; or (m) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 413, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 414, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 415, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 455, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 456, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 457; or (n) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 416, a VH CDR2 comprising the amino acid sequence of SEQ ID

NO: 417, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 418, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 458, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 459, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 460; or (o) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 419, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 420, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 421, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 461, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 462, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 463; or (p) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 422, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 423, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 424, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 464, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 465, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 466; or (q) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 425, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 426, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 427, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 467, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 468, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 469; or (r) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 428, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 429, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 430, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 470, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 471, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 472; or (s) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 431, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 432, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 433, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 473, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 474, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 475; or (t) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 434, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 435, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 436, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 476, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 477, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 478; or (u) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 437, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a VH CDR3 comprising the amino acid sequence of SEQ

ID NO: 439, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 479, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 480, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 481; or (v) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 440, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 441, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 442, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 482, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 483, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 484; or (w) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 443, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 444, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 445, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 485, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 486, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 487; or (x) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 446, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 447, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 448, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 488, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 489, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 490; or (y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 449, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 450, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 451, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 491, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 492, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 493; or (z) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 452, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 453, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 454, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 494, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 495, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 496; or (aa) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 857, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 858, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 859, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 892, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 893, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 894; or (bb) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 860, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 861, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 862, a VL CDR1 comprising the amino acid sequence of SEQ

ID NO: 895, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 896, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 897; or (cc) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 863, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 864, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 865, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 898, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 899, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 900; or (dd) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 866, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 867, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 868, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 901, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 902, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 903; or (ee) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 869, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 870, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 871, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 904, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 905, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 906; or (ff) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 872, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 873, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 874, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 907, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 908, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 909; or (gg) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 875, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 876, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 877, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 910, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 911, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 912; or (hh) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 1000, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 879, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 913, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 914, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 915; or (ii) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 880, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 881, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 882, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 916, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 917, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 918; or (jj) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 883, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 884, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 885, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 920, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 921; or (kk) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 886, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 887, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 888, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 922, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 923, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 924; or (ll) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 889, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 890, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 891, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 925, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 926, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 927.

[0009] Aspects of the invention are further drawn towards an isolated scFv antibody, that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising: (a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 61, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 62, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 63; or (b) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 29, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 30, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 65, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 66; or (c) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 32, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 33, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 67, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 68, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 69; or (d) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 34,

a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 35, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 36, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 70, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 71, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 72; or (e) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 39, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 73, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 74, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or (f) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 42, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 76, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 77, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 78; or (g) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 45, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 79, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 80, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 81; or (h) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 47, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 48, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 82, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 83, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 84; or (i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 50, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 51, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 85, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 86, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or (j) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 53, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 54, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 90; or (k) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence of SEQ ID

NO: 56, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 91, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 92, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 93; or (l) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 59, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 60, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 95, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 96; or (m) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 413, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 414, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 415, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 455, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 456, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 457; or (n) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 416, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 417, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 418, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 458, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 459, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 460; or (o) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 419, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 420, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 421, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 461, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 462, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 463; or (p) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 422, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 423, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 424, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 464, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 465, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 466; or (q) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 425, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 426, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 427, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 467, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 468, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 469; or (r) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 428, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 429, a VH CDR3 comprising the amino acid sequence of SEQ

ID NO: 430, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 470, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 471, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 472; or (s) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 431, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 432, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 433, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 473, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 474, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 475; or (t) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 434, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 435, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 436, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 476, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 477, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 478; or (u) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 437, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 439, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 479, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 480, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 481; or (v) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 440, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 441, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 442, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 482, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 483, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 484; or (w) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 443, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 444, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 445, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 485, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 486, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 487; or (x) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 446, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 447, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 448, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 488, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 489, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 490; or (y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 449, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 450, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 451, a VL CDR1 comprising the amino acid sequence of SEQ

ID NO: 491, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 492, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 493; or (z) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 452, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 453, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 454, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 494, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 495, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 496; or (aa) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 857, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 858, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 859, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 892, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 893, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 894; or (bb) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 860, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 861, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 862, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 895, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 896, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 897; or (cc) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 863, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 864, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 865, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 898, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 899, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 900; or (dd) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 866, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 867, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 868, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 901, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 902, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 903; or (ee) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 869, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 870, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 871, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 904, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 905, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 906; or (ff) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 872, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 873, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 874, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 907, a VL CDR2 comprising the amino acid sequence of SEQ

ID NO: 908, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 909; or (gg) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 875, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 876, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 877, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 910, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 911, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 912; or (hh) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 1000, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 879, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 913, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 914, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 915; or (ii) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 880, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 881, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 882, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 916, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 917, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 918; or (jj) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 883, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 884, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 885, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 920, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 921; or (kk) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 886, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 887, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 888, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 922, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 923, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 924; or (ll) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 889, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 890, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 891, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 925, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 926, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 927.

[0010] Still further, aspects of the invention are drawn to an isolated antibody or fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain variable region comprising an amino acid sequence selected from

the group consisting of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 1001, 1003, 1005, 1007, 1009, 1011, 1013, 1015, 1017, 1019, 1021, and 1023 and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 368, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 1002, 1004, 1006, 1008, 1010, 1012, 1014, 1016, 1018, 1020, 1022, and 1024.

[0011] Also, aspects of the invention are drawn to an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 1001, 1003, 1005, 1007, 1009, 1011, 1013, 1015, 1017, 1019, 1021, and 1023 and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 368, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 1002, 1004, 1006, 1008, 1010, 1012, 1014, 1016, 1018, 1020, 1022, and 1024.

[0012] For example, an embodiment is drawn to an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 2.

[0013] Another embodiment is drawn to an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 2.

[0014] A further embodiment is drawn to an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 3, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 4.

[0015] An embodiment is also drawn to an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 3, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 4.

[0016] An embodiment is drawn to an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 5, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 6.

[0017] Also, embodiments are drawn to an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 5, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 6.

[0018] Still further, embodiments are drawn to an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 7, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 8.

[0019] Also, embodiments are drawn to an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 7, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 8.

[0020] Further embodiments are drawn to an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 9, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 10.

[0021] Also, embodiments are drawn to an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 9, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 10.

[0022] Embodiments are drawn to an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 11, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 12.

[0023] Embodiments are also drawn to an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 11, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 12.

[0024] Further, embodiments are drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 13, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 14.

[0025] Still further, embodiments are drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 13, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 14.

[0026] Also, embodiments are drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 15, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 16.

[0027] Still further, embodiments are drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 15, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 16.

[0028] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 17, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 18.

[0029] Further, embodiments are drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 17, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 18.

[0030] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 19, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 20.

[0031] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 19, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 20.

[0032] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 21, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 22.

[0033] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 21, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 22.

[0034] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 23, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 24.

[0035] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 23, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 24.

[0036] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 385, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 386.

[0037] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 385, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 386.

[0038] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 387, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 388.

[0039] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 387, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 388.

[0040] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 389, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 390.

[0041] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 389, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 390.

[0042] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 391, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 392.

[0043] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 391, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 392.

[0044] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 393, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 394.

[0045] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 393, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 394.

[0046] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 395, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 396.

[0047] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 395, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 396.

[0048] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 397, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 398.

[0049] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 397, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 398.

[0050] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 399, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 400.

[0051] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 399, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 400.

[0052] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 401, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 402.

[0053] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 401, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 402.

[0054] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 403, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 404.

[0055] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 403, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 404.

[0056] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 405, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 406.

[0057] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 405, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 406.

[0058] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 407, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 408.

[0059] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 407, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 408.

[0060] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 409, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 410.

[0061] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 409, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 410.

[0062] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 411, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 412.

[0063] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 411, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 412.

[0064] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1001, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1002.

[0065] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1001, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1002.

[0066] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1003, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1004.

[0067] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1003, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1004.

[0068] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1005,

and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1006.

[0069] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1005, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1006.

[0070] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1007, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1008.

[0071] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1007, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1008.

[0072] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1009, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1010.

[0073] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1009, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1010.

[0074] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1011, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1012.

[0075] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1011, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1012.

[0076] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1013, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1014.

[0077] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1013, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1014.

[0078] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1015, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1016.

[0079] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid

sequence about 95% identical to SEQ ID NO: 1015, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1016.

[0080] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1017, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1018.

[0081] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1017, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1018.

[0082] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1019, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1020.

[0083] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1019, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1020.

[0084] Embodiments are also drawn towards n isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1021, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1022.

[0085] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1021, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1022.

[0086] Embodiments are also drawn towards an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1023, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1024.

[0087] Embodiments are also drawn towards an isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1023, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1024.

[0088] Aspects of the invention are also drawn towards an isolated monoclonal antibody or antigen-binding fragment of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, or 79, wherein the isolated monoclonal antibody or antigen-binding fragment comprises a wildtype Fc or a modified Fc.

[0089] Further, aspects of the invention are drawn to an isolated bispecific antibody comprising an antibody or fragment as described herein, and a second antigen-binding fragment having specificity to a molecule on an immune cell. For example, the molecule is selected from the group consisting of CCR4, B7H3, B7H4, CD27, CD28, CD40, CD40L, CD47, CD122, CTLA-4, GITR, GITRL, ICOS, ICOSL, LAG-3, LIGHT, OX-40, OX40L, PD-1, TIM3, 4-1BB, TIGIT, VISTA, HEVM, BTLA, CD47, PDL1, MICA, MICB, and KIR.

[0090] In embodiments, the fragment and the second fragment each is independently selected from a Fab fragment, a single-chain variable fragment (scFv), or a single-domain antibody.

[0091] Embodiments can further comprise a Fc fragment. For example, the Fc fragment comprises a wildtype Fc fragment or a modified Fc fragment.

[0092] Aspects of the invention are drawn towards a nucleic acid encoding an antibody as described herein.

[0093] Still further, aspects of the invention are drawn towards a nucleic acid encoding a bispecific antibody as described herein.

[0094] Also, aspects of the invention are drawn towards a pharmaceutical composition comprising the antibody or fragment thereof as described herein, and a pharmaceutically acceptable carrier or excipient.

[0095] Embodiments can further comprise at least one additional therapeutic agent. For example, the therapeutic agent can be a toxin, a radiolabel, a siRNA, a small molecule, or a cytokine.

[0096] Aspects of the invention are drawn to a pharmaceutical composition comprising the bispecific antibody as described herein, and a pharmaceutically acceptable carrier or excipient.

[0097] In embodiments, the pharmaceutical composition can further comprise at least one additional therapeutic agent. For example, the therapeutic agent can be a toxin, a radiolabel, a siRNA, a small molecule, or a cytokine.

[0098] Further, aspects of the invention are drawn to an isolated cell comprising one or more polynucleotide(s) encoding an antibody or fragment as described herein.

[0099] Also, aspects of the invention are drawn towards an isolated cell comprising one or more polynucleotide(s) encoding a bispecific antibody or fragment thereof as described herein.

[00100] Further, aspects of the invention are drawn towards a vector comprising a nucleic acid as described herein.

[00101] Also, aspects of the invention are drawn to a cell comprising a vector as described herein.

[00102] Aspects of the invention are drawn to methods of treating a cancer in a subject. For example, the method comprises administering to a subject a therapeutically effective amount of the CTLA-4 antibody or fragment thereof as described herein. For example, the method comprises administering to a subject a therapeutically effective amount of a CTLA-4 bispecific antibody as described herein.

[00103] Aspects of the invention are also drawn towards a chimeric antigen receptor (CAR). In embodiments, the CAR comprises an intracellular signaling domain, a transmembrane domain and an extracellular domain, wherein the extracellular domain is an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4), wherein the monoclonal antibody or fragment thereof comprises a heavy chain, light chain, or combination thereof, wherein the heavy chain comprises (a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 61, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 62, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 63; or (b) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 29, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 30, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 65, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 66; or (c) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 32, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 33, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 67, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 68, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 69; or (d) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 35, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 36, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 70, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 71, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 72; or (e) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 39, a VL CDR1 comprising the amino

acid sequence of SEQ ID NO: 73, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 74, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or (f) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 42, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 76, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 77, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 78; or (g) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 45, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 79, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 80, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 81; or (h) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 47, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 48, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 82, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 83, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 84; or (i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 50, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 51, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 85, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 86, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or (j) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 53, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 54, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 90; or (k) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 91, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 92, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 93; or (l) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 59, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 60, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a VL CDR2 comprising the amino

acid sequence of SEQ ID NO: 95, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 96; or (m) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 413, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 414, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 415, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 455, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 456, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 457; or (n) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 416, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 417, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 418, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 458, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 459, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 460; or (o) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 419, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 420, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 421, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 461, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 462, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 463; or (p) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 422, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 423, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 424, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 464, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 465, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 466; or (q) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 425, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 426, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 427, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 467, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 468, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 469; or (r) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 428, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 429, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 430, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 470, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 471, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 472; or (s) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 431, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 432, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 433, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 473, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 474, and a VL CDR3 comprising

the amino acid sequence of SEQ ID NO: 475; or (y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 434, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 435, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 436, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 476, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 477, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 478; or (u) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 437, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 439, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 479, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 480, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 481; or (v) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 440, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 441, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 442, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 482, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 483, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 484; or (w) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 443, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 444, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 445, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 485, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 486, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 487; or (x) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 446, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 447, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 448, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 488, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 489, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 490; or (y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 449, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 450, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 451, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 491, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 492, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 493; or (z) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 452, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 453, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 454, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 494, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 495, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 496; or (aa) a VH CDR1

comprising the amino acid sequence of SEQ ID NO: 857, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 858, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 859, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 892, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 893, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 894; or (bb) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 860, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 861, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 862, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 895, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 896, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 897; or (cc) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 863, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 864, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 865, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 898, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 899, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 900; or (dd) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 866, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 867, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 868, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 901, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 902, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 903; or (ee) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 869, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 870, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 871, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 904, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 905, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 906; or (ff) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 872, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 873, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 874, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 907, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 908, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 909; or (gg) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 875, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 876, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 877, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 910, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 911, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 912; or (hh) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a VH CDR2

comprising the amino acid sequence of SEQ ID NO: 1000, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 879, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 913, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 914, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 915; or (ii) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 880, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 881, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 882, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 916, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 917, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 918; or (jj) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 883, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 884, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 885, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 920, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 921; or (kk) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 886, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 887, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 888, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 922, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 923, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 924; or (ll) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 889, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 890, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 891, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 925, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 926, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 927. For example, the transmembrane domain comprises CD28.

[00104] In embodiments, the transmembrane domain further comprises a stalk region positioned between the extracellular domain and the transmembrane domain.

[00105] Embodiments can further comprise one or more additional costimulatory molecules positioned between the transmembrane domain and the intracellular signaling domain. For example, the costimulatory molecules is CD28, 4-1BB, ICOS, or OX40. For example, the intracellular signaling domain comprises a CD3 zeta chain.

[00106] In embodiments, the antibody is a Fab or a scFV.

[00107] Aspects of the invention are also drawn to a nucleic acid encoding a CAR as described herein. In embodiments, the nucleic acid can further comprise a nucleic acid encoding a polypeptide positioned after the intracellular signaling domain. For example, the polypeptide is an antibody or a cytokine, such as an scFV.

[00108] Aspescts of the invention are drawn towards a nucleic acid encoding a CAR, wherein the CAR comprises an intracellular signaling domain, a transmembrane domain and an extracellular domain, further comprising a nucleic acid encoding a polypeptide positioned after the intracellular signaling domain, wherein the polypeptide comprises an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4), wherein the monoclonal antibody or fragment thereof comprises a heavy chain, light chain, or combination thereof, wherein the heavy chain comprises (a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 61, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 62, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 63; or (b) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 29, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 30, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 65, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 66; or (c) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 32, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 33, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 67, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 68, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 69; or (d) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 35, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 36, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 70, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 71, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 72; or (e) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 39, a VL CDR1 comprising the amino acid sequence of SEQ ID

NO: 73, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 74, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or (f) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 42, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 76, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 77, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 78; or (g) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 45, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 79, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 80, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 81; or (h) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 47, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 48, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 82, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 83, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 84; or (i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 50, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 51, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 85, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 86, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or (j) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 53, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 54, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 90; or (k) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 91, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 92, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 93; or (l) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 59, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 60, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a VL CDR2 comprising the amino acid sequence of SEQ

ID NO: 95, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 96; or (m) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 413, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 414, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 415, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 455, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 456, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 457; or (n) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 416, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 417, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 418, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 458, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 459, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 460; or (o) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 419, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 420, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 421, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 461, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 462, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 463; or (p) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 422, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 423, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 424, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 464, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 465, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 466; or (q) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 425, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 426, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 427, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 467, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 468, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 469; or (r) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 428, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 429, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 430, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 470, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 471, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 472; or (s) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 431, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 432, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 433, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 473, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 474, and a VL CDR3 comprising the amino acid sequence of

SEQ ID NO: 475; or (t) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 434, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 435, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 436, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 476, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 477, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 478; or (u) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 437, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 439, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 479, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 480, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 481; or (v) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 440, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 441, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 442, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 482, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 483, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 484; or (w) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 443, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 444, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 445, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 485, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 486, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 487; or (x) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 446, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 447, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 448, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 488, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 489, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 490; or (y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 449, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 450, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 451, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 491, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 492, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 493; or (z) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 452, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 453, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 454, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 494, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 495, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 496; or (aa) a VH CDR1 comprising the amino acid

sequence of SEQ ID NO: 857, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 858, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 859, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 892, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 893, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 894; or (bb) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 860, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 861, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 862, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 895, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 896, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 897; or (cc) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 863, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 864, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 865, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 898, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 899, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 900; or (dd) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 866, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 867, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 868, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 901, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 902, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 903; or (ee) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 869, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 870, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 871, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 904, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 905, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 906; or (ff) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 872, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 873, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 874, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 907, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 908, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 909; or (gg) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 875, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 876, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 877, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 910, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 911, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 912; or (hh) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a VH CDR2 comprising the amino

acid sequence of SEQ ID NO: 1000, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 879, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 913, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 914, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 915; or (ii) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 880, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 881, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 882, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 916, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 917, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 918; or (jj) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 883, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 884, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 885, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 920, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 921; or (kk) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 886, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 887, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 888, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 922, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 923, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 924; or (ll) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 889, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 890, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 891, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 925, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 926, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 927..

[00109] Aspects of the invention are drawn towards a vector comprising the nucleic acid as describd herein.

[00110] Aspects of the invention are also drawn to a cell comprising a vector as described herein.

[00111] Aspects of the invention are drawn towards a genetically engineered cell which expresses and bears on the cell surface membrane a chimeric antigen receptor as described herein. For example, the cell is a T-cell or an NK cell. For example, the T cell is CD4+ or CD8+.

[00112] Embodiments can further comprise a mixed population of CD4+ and CD8 cells+.

[00113] Aspects of the invention are also drawn towards a genetically engineered cell which express and bear on the cell surface membrane a chimeric antigen receptor, and which is further engineered to express and secrete a polypeptide, wherein polypeptide is an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4), wherein the monoclonal antibody or fragment thereof comprises a heavy chain, light chain, or combination thereof, wherein the heavy chain comprises (a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 61, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 62, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 63; or (b) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 29, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 30, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 65, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 66; or (c) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 32, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 33, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 67, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 68, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 69; or (d) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 35, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 36, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 70, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 71, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 72; or (e) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 39, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 73, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 74, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or (f) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 41, a VH CDR3 comprising the amino acid sequence of SEQ

ID NO: 42, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 76, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 77, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 78; or (g) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 45, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 79, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 80, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 81; or (h) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 47, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 48, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 82, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 83, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 84; or (i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 50, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 51, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 85, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 86, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or (j) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 53, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 54, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 90; or (k) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 91, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 92, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 93; or (l) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 59, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 60, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 95, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 96; or (m) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 413, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 414, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 415, a VL CDR1 comprising the amino acid sequence of SEQ ID

NO: 455, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 456, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 457; or (n) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 416, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 417, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 418, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 458, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 459, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 460; or (o) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 419, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 420, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 421, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 461, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 462, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 463; or (p) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 422, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 423, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 424, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 464, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 465, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 466; or (q) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 425, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 426, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 427, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 467, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 468, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 469; or (r) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 428, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 429, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 430, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 470, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 471, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 472; or (s) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 431, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 432, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 433, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 473, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 474, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 475; or (t) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 434, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 435, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 436, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 476, a VL CDR2 comprising the amino acid sequence of SEQ

ID NO: 477, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 478; or (u) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 437, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 439, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 479, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 480, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 481; or (v) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 440, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 441, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 442, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 482, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 483, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 484; or (w) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 443, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 444, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 445, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 485, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 486, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 487; or (x) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 446, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 447, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 448, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 488, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 489, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 490; or (y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 449, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 450, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 451, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 491, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 492, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 493; or (z) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 452, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 453, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 454, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 494, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 495, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 496; or (aa) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 857, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 858, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 859, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 892, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 893, and a VL CDR3 comprising the amino acid sequence of

SEQ ID NO: 894; or (bb) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 860, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 861, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 862, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 895, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 896, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 897; or (cc) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 863, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 864, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 865, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 898, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 899, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 900; or (dd) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 866, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 867, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 868, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 901, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 902, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 903; or (ee) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 869, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 870, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 871, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 904, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 905, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 906; or (ff) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 872, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 873, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 874, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 907, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 908, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 909; or (gg) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 875, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 876, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 877, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 910, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 911, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 912; or (hh) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 1000, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 879, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 913, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 914, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 915; or (ii) a VH CDR1 comprising the

amino acid sequence of SEQ ID NO: 880, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 881, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 882, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 916, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 917, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 918; or (jj) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 883, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 884, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 885, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 920, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 921; or (kk) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 886, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 887, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 888, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 922, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 923, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 924; or (ll) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 889, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 890, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 891, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 925, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 926, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 927.

[00114] Other objects and advantages of this invention are readily apparent from the ensuing description.

BRIEF DESCRIPTION OF THE FIGURES

[00115] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[00116] **FIG. 1** shows binding ELISA with PEG purified phage at varying dilutions.

[00117] **FIG. 2** shows FACS confirms CTLA-4 phages can bind to CTLA-4-expressing 1G5 Jurkat cells.

[00118] **FIG. 3** provides anti-CTLA-4 antibody amino acid (AA) and nucleotide (Nuc) sequences. "HC" is heavy chain, and "LC" is light chain.

[00119] **FIG. 4 – FIG. 8** provides anti-CTLA-4 antibody amino acid (AA) and nucleotide (Nuc) sequences.

[00120] **FIG. 9 – FIG. 11** provides anti-CTLA-4 antibody amino acid (AA) and nucleotide (Nuc) sequences.

[00121] **FIG. 12** shows percent competition with CD80 hFc for binding to CTLA4 on 1G5 Jurkat. 1G5 Jurkat cells were transduced to overexpress CTLA4. Cells were incubated with soluble antibody at the indicated concentration, washed, then incubated with labeled CD80-Fc. Samples were read on a BD FACSCanto II. Decrease in fluorescence was used to indicate blockade of CD80 binding to the CTLA4 on the surface of the cells.

[00122] **FIG. 13** shows a ribbon diagram adapted from Metzler, William J., et al. "Solution Structure of Human CTLA-4 and Delineation of a CD80/CD86 Binding Site Conserved in CD28."

[00123] **FIG. 14** shows ribbon diagrams adapted from Stamper, Carin C., et al. "Crystal Structure of the B7-1/CTLA-4 Complex That Inhibits Human Immune Responses." *Nature.*

[00124] **FIG. 15** shows schematics of mechanisms to suppress immune response.

[00125] **FIG. 16** shows ribbon diagrams of existing therapies: Ipilimumab- IgG1 and Tremelimumab- IgG2. Panels A and B show ribbon diagrams adapted from Ramagopal, Udupi A., et al. "Structural Basis for Cancer Immunotherapy by the First-in-Class Checkpoint Inhibitor Ipilimumab." Panel C shows a ribbon diagram adapted from He, Mengnan, et al. "Remarkably Similar CTLA-4 Binding Properties of Therapeutic Ipilimumab and Tremelimumab Antibodies."

[00126] **FIG. 17** shows a chart of exemplary panning results for anti-CTLA4 antibodies. Rounds: 1, 1b, 2, 2b, 3, 3b. Mouse CTLA4 were introduced in rounds 3 and 3b. 10 unique antibodies were the result.

[00127] **FIG. 18** shows a chart of exemplary kinetic analysis of aCTLA4 antibodies.

[00128] **FIG. 19** shows a chart of exemplary competition analysis of aCTLA4 antibodies.

[00129] **FIG. 20** shows a graph of FACS of aCTLA4 antibodies binding to T cells. E1-D7 binds significantly more CTLA4 on T cells compared to T2-C10. An anti-CTLA4 ab from biolegend was used at a single point (recommended staining conc) for the control. Ipi IgG is an antibody cloned in the lab to represent ipilimumab, it is not a commercial prep or biosimilar.

[00130] **FIG. 21** shows exemplary FACS of aCTLA4 Abs binding to T Cells.

[00131] **FIG. 22** shows exemplary graphs of ELISA results of mouse/human CTLA4 cross reactivity. E1-D7 cross reacts with mouse CTLA4.

[00132] **FIG. 23** shows a schematic of exemplary mechanisms of T cells adapted from P. Ott et al. 2014.

[00133] **FIG. 24** shows a schematic of an MLR assay. Schematic courtesy of Explicyte. Protocol: Co-culture of CD4+ T cells with monocyte-derived DCs each from different donors. This indicated allorecognition of the dendritic cells leads to activation of T cells. DCs expressing PDL1 can suppress T cell activation. Addition of immune checkpoint inhibitors can recover T cell from suppression. We investigated whether anti-PD1 enhances T cell activation. Measured IFNy and IL2 cytokine production, indicators of T cell activation.

[00134] **FIG. 25** shows data from immunophenotyping of monocytes, imMo-DCs, and mMo-DCs adapted from Miltenyi. In this protocol Isolate CD14+ monocytes using Miltenyi CD14+ microbeads were cultured in Miltenyi Mo-DC media (pre-prepared media with GM-CSF + IL4) and cultured for 5 days. Then, TNF-α (1000 U/ml), IL-1β (5 ng/ml), IL-6 (10 ng/ml) and prostaglandin E2 (PGE2) (1 μM) was added and cultured for 2 days to mature DC. mMo-DCs express various DC markers that are involved in the formation of immunological synapses between DCs and naive T cells, including CD80, CD86, and MHC II (HLA-DR). Mature Mo-DCs also expressed DC activation markers CD83, CD40, and CCR7.

[00135] **FIG. 26** shows data and analysis of DC donor AD staining.

[00136] **FIG. 27** shows graphs of exemplary MLR1 data: measuring IFNγ production. We investigated if E1-D7 suppressed T cell activation. A decrease in IFNy is seen in wells treated

with E1-D7 compared to T cells + DC only, anti-PD1 treatment, and irrelevant Ab control. An absorbance value of 4 was used to represent saturation.

[00137] **FIG. 28** shows graphs of exemplary data of the combination of aCTLA4/aPD-1 MLR: IFNγ production.

[00138] **FIG. 29** shows an exemplary schematic of the second panning using CTLA4-PMPLs.

[00139] **FIG. 30** shows exemplary graphs of data from binding ELISA with PEG purified phage at varying dilutions.

[00140] **FIG. 31** shows exemplary FACS confirming our CTLA4 phages can bind to CTLA-4 expressing 1G5 Jurkat cells.

[00141] **FIG. 32** shows a chart of exemplary kinetic screening data of aCTLA4 scFv-Fc sup.

[00142] **FIG. 33** shows an exemplary binding curve for hCTLA4.

[00143] **FIG. 34** shows an exemplary binding curve for mCTLA4.

[00144] **FIG. 35** shows a BSA negative control binding curve.

[00145] **FIG. 36** shows a chart of data and observations. The data is arranged in decreasing order of Association response at 25nM concentration of antibodies. All candidate antibodies have higher dissociation rates than Ipilimumab and BiolegendaCTLA4 (commercial controls). Most candidates seem to have a higher association response than the commercial controls. 4 candidates (highlighted in the table) have lower dissociation constants than E1-D7 (Taylor's Antibody – Lab Control). E2-D10 and E1-A12 have identical heavy chains but have different families of light chains. The difference in their response rates is mediated by light chain binding. E2-H10 also belongs to the same Vh family as the two above.

[00146] **FIG. 37** shows a chart of exemplary data from a competition assay. **CD80 blockade**: All candidate antibodies block CD80 binding to some extent, but none more than Ipilimumab, so I selected for candidates that have higher blockade (lower values of second association) than E1-D7 (lab control, Taylor's candidate). **CD86 blockade**: All candidates have negative values of second association, signaling they all block CD86 completely

(normalized values = 0). I selected for candidates that have negative values closer to zero when compared to Ipilimumab because higher negative values could indicate antibody dissociation. E1-A8 and E2-A4 belong to the same germline family. **E1-D7 blockade:** Highlighted candidates block E1-D7 binding better than Ipilimumab. **Ipilimumab blockade:** Highlighted candidates block Ipilimumab binding better than E1-D7. All candidates that block CD80 and CD86 performed relatively poorly in Kinetics.

[00147] **FIG. 38** shows an exemplary graph of CTLA4 binding. Jurkat cells were transduced with hCTLA4 and used to generate a binding curve.

[00148] **FIG. 39** shows a schematic of a PROMEGA lucierfase reporter assay adapted from www.moleculardevices.com/en/assets/app-note/br/characterize-biologics-for-immune-checkpoint-blockade-with-reporter-bioassays-using-spectramax-microplate-readers#gref.

[00149] **FIG. 40** shows graphs of exemplary Promega CTLA4 bioassay data. Anti-CTLA4 scFv-Fcs were tested against an Ipi biosimilar IgG. Plates were read using a BMG polarstar omega with an interval of either 1 second (left column) or 10 seconds (right column). E1-B10, E1-A8, E2-A4, and E1-D7 show similar activity at about 40% of Ipi. On plate 2, E2-G9 shows comparable activity to ipi however E2-H10, E1-A4, and E2-H12 show minimal improvement.

[00150] **FIG. 41** shows an illustration of a bispecific design. BsAbs constructed with the IgG1 hinge show a mix of monomer and dimer when expressed so to increase dimerization frequency we switched to an IgG3 hinge. We initially built two constructs, one with a (G4S)5 linker preceding the IgG3 hinge and one without the leading linker. The second linker was maintained at 5 repeats to provide ample space for the 2nd scFv to reach binding sites without interference from the hinge.

[00151] **FIG. 42** shows sequences of IgG3 hinge linker sequences.

[00152] **FIG. 43** shows a picture of an exemplary labeled SDS Page Gel for Non-reduced and Reduced E1D7-IgG3 hinge-P4B3M3 and P4B3M3-IgG3 hinge-E1D7 bsAbs.

[00153] **FIG. 44** shows a chart of exemplary data. SA sensors were loaded with biotinylated CTLA4 or PD1 and the indicated abs were allowed to associate/disassociate. Due to sensor drift, the off rates of the PD1 loaded sensors are unreliable.

[00154] **FIG. 45** shows data from exemplary dual binding assays. CTLA4+, PD1+, or CTLA4+PD1+ Jurkat cells were first coated with the indicated amount of mono or bispecific protein. Soluble protein was next added and allowed to bind to free arms. As shown here, monospecific abs are not able to bind significant amounts of soluble antigen, however when bound to PD1 expressing cells, the bsAbs are able to capture soluble CTLA4 from solution.

[00155] **FIG. 46** shows non-limiting, exemplary data from a competition assay for Ab (including combination mAbs) vs CD80 hFc for CTLA4+/PD1+ 1G5 Jurkat. BsAb demonstrates remarkably improved competition of CD80 binding to PD1+CTLA4+ jurkat cells when compared to a monospecific antibody and a cocktail.

[00156] **FIG. 47** shows non-limiting, exemplary data from a % competition assay with CD80 hFc for binding to CTLA4 on 1G5 Jurkat. CD80 competition assay using CTLA4 transduced Jurkat cells: Four bispecific constructs were tested for CD80 competition. Two had the full 5,5 linker configuration and two had the abbreviated 0,5 linker. We also switched the order of the aPD1/aCTLA4 abs in the final construct. As shown here, E1-D7 and E1-D7+P4B3m3 combination therapy leads to moderate competition, however the creation of the bsAb shows a pronounced increase in CD80 competition, likely due to the additional binding potential generated by the anti-PD1 domain.

[00157] **FIG. 48** shows photos and illustrations of clear cell renal cell carcinoma panel (A) characteristics (adapted from Li et al, 2019), panel (B) model for cellular differentiation (adapted from Tun et.al, 2010), and panel (C) epidemiology (adapted from Hsieh et al, 2019).

[00158] **FIG. 49** shows a graph of OS of ccRCC patients adapted from Feng et al., 2019.

[00159] **FIG. 50** shows graphs of the representation of immune populations of ccRCC adapted from Chevrier et al., 2017.

[00160] **FIG. 51** shows illustrations and graphs of the CTLA4 signaling pathway. Panel A shows an illustration of the CTLA4 signalling pathway. Panel B shows a graph CTLA4 overexpression in ccRCC (adapted from Lie et al, 2020). Panel C shows an illustration of Ipilimumab and CTLA4 blockade.

[00161] **FIG. 52** shows pictures and illustrations of the PD1 signalling pathway adapted from Kim et al., 2021. Panel A shows the PD1-PDL1 signalling pathway. Panel B shows

histology images of PD1 overexpression in ccRCC. Panel C shows an illustration of PD1 blockage and non-limiting effects.

[00162] FIG. 53 shows illustrations of dual checkpoint blockade by bispecific antibodies. Panel A shows a schematic dual CTLA4/PDL checkpoint blockade. Panel B shows non-limiting, exemplary bispecific antibody formats.

[00163] FIG. 54 shows a table of exemplary anti-CTLA4/antiPD1 bispecifics used in the clinic.

[00164] FIG. 55 shows a schematic of a non-limiting, exemplary experimental design to evaluate the binding affinity of anti-CTLA4 candidates to human and mouse CTLA4 at various concentrations using ELISA.

[00165] FIG. 56 shows non-limiting data and results of ELISA binding curve. Panel A shows ELISA binding curve to indicate binding affinity of anti-CTLA4 candidates to hCTLA4. Panel B shows ELISA binding curve to indicate binding affinity of anti-CTLA4 candidates to mCTLA4. Panel C shows ELISA binding curve to indicate binding affinity of anti-CTLA4 candidates to BSA (negative control).

[00166] FIG. 57 shows a non-limiting, exemplary experimental design to characterize the kinetic properties of the antibody candidates using BLI-Octet.

[00167] FIG. 58 shows non-limiting, data indicating the kinetic properties of anti-CTLA4 candidates. All tested candidates have higher dissociation rates when compared to Ipilimumab, even when they have a higher association response. Among the candidates, C, B, and G appear to have the lowest dissociation rates. KD – Dissociation constant, Kon – Rate of association, Kon – Rate of association.

[00168] FIG. 59 shows a schematic of a non-limiting, exemplary experimental design to determine the ability of anti-CTLA4 antibodies to block CD80/CD86/Ipilimumab binding and determine the similarity in the localization of antibodies and ligands on the surface of CTLA4.

[00169] FIG. 60 shows a chart of the percentage blockade of CD80/CD86/Ipilimumab binding to CTLA4 by anti-CTLA4 candidates. **CD80:** Ipilimumab blocks CD80 to the highest extent. The candidates that show the highest CD80 blockade: I, E, J. **CD86:** All

candidates show 100% blockade of CD86 binding. This could be due to documented lower affinity of CD86 binding to CTLA4. **Ipilimumab:** All candidates block the binding of Ipilimumab to CTLA4 to some extent, even those that cross-react with mCTLA4.

[00170] **FIG. 61** shows ribbon diagrams Ipilimumab complexes adapted from He M, Chai Y, Qi J, Zhang CWH, Tong Z, Shi Y, Yan J, Tan S, Gao GF. Remarkably similar CTLA-4 binding properties of therapeutic ipilimumab and tremelimumab antibodies. Oncotarget. 2017 May 19;8(40):67129-67139. doi: 10.18632/oncotarget.18004. PMID: 28978021; PMCID: PMC5620161. Panel A shows Ipilimumab complexed with hCTLA4 – Contact residues highlighted. Panel B shows Ipilimumab complexed with mCTLA4 – Aligned epitope highlighted.

[00171] **FIG. 62** shows ribbon diagrams of CD80 complexes adapted from Stamper CC, Zhang Y, Tobin JF, Erbe DV, Ikemizu S, Davis SJ, Stahl ML, Seehra J, Somers WS, Mosyak L. Crystal structure of the B7-1/CTLA-4 complex that inhibits human immune responses. Nature. 2001 Mar 29;410(6828):608-11. doi: 10.1038/35069118. Erratum in: Nature 2001 May 31;411(6837):617. PMID: 11279502. Panel A shows CD80 complexed with hCTLA4 – Contact residues highlighted. Panel B shows CD80 complexed with mCTLA4 – Aligned epitope highlighted.

[00172] **FIG. 63** shows a non-limiting, exemplary schematic of an experimental design to determine the binding affinity of the candidate antibodies to Jurkat cells that express CTLA4.

[00173] **FIG. 64** shows a non-limiting, exemplary binding curve of the binding affinity of anti-CTLA4 candidates to CTLA4+ Jurkat cells.

[00174] **FIG. 65** shows a non-limiting, exemplary schematic of an experimental design to assess the biological significance of antibody binding in facilitating CD28 signalling.

[00175] **FIG. 66** shows non-limiting, exemplary graphs of fold induction of Luciferase vs. concentration of anti-CTLA4 candidates. Across both plates, Ipilimumab shows the highest induction of Luciferase expression. Five of the 8 tested candidates: E, H, J, F, and I, show a similar response.

[00176] **FIG. 67** shows anti-CTLA-4 antibody germline alignment.

[00177] **FIG. 68** shows anti-CTLA-4 antibody amino acid sequences.

[00178] **FIG. 69** shows anti-CTLA-4 antibody nucleic acid sequences.

DETAILED DESCRIPTION

[00179] **Abbreviations and Definitions**

[00180] Detailed descriptions of one or more embodiments are provided herein. It is to be understood, however, that the present invention may be embodied in various forms. Therefore, specific details disclosed herein are not to be interpreted as limiting, but rather as a basis for the claims and as a representative basis for teaching one skilled in the art to employ the present invention in any appropriate manner.

[00181] The singular forms "a", "an" and "the" include plural reference unless the context clearly dictates otherwise. The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one."

[00182] Wherever any of the phrases "for example," "such as," "including" and the like are used herein, the phrase "and without limitation" is understood to follow unless explicitly stated otherwise. Similarly, "an example," "exemplary" and the like are understood to be nonlimiting.

[00183] The term "substantially" allows for deviations from the descriptor that do not negatively impact the intended purpose. Descriptive terms are understood to be modified by the term "substantially" even if the word "substantially" is not explicitly recited.

[00184] The terms "comprising" and "including" and "having" and "involving" (and similarly "comprises", "includes," "has," and "involves") and the like are used interchangeably and have the same meaning. Specifically, each of the terms is defined consistent with the common United States patent law definition of "comprising" and is therefore interpreted to be an open term meaning "at least the following," and is also interpreted not to exclude additional features, limitations, aspects, etc. Thus, for example, "a process involving steps a, b, and c" means that the process includes at least steps a, b and c. Wherever the terms "a" or "an" are used, "one or more" is understood, unless such interpretation is nonsensical in context.

[00185] The term "about" is used herein to mean approximately, roughly, around, or in the region of. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In

general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20 percent up or down (higher or lower).

[00186] **CTLA-4**

[00187] Human antibody-phage screens were performed against human CTLA-4 (rounds 1-3) or muring CTLA-4 (Round 3). The first set of antibodies was discovered via panning against the soluble protein, and the second set was discovered by PMPL panning.

[00188] The binding activity have been characterized for a panel of human monoclonal antibodies against human CTLA-4. Anti-CTLA-4 immunotherapy is being evaluated as part of the burgeoning field of ImmunoOncology. The anti-CTLA-4 mAbs described herein can have therapeutic potential. CTLA-4 antibodies have been identified with varying affinity towards CTLA-4.

[00189] Aspects of the invention provide isolated antibodies specific against CTLA-4. The term "isolated" as used herein with respect to cells, nucleic acids, such as DNA or RNA, refers to molecules separated from other DNAs or RNAs, respectively, that are present in the natural source of the macromolecule. The term "isolated" can also refer to a nucleic acid or peptide that is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. For example, an "isolated nucleic acid" can include nucleic acid fragments which are not naturally occurring as fragments and would not be found in the natural state. "Isolated" can also refer to cells or polypeptides which are isolated from other cellular proteins or tissues. Isolated polypeptides can include both purified and recombinant polypeptides. The isolated antibodies were identified through the use of a 27 billion member human single-chain antibody (scFv) phage library panned against soluble or paramagnetic proteoliposomes displayed CTLA4 as the selection target. These antibodies represent a new class of monoclonal antibodies against CTLA-4. The monoclonal CTLA-4 antibodies discussed herein can also be used in the construction of multi-specific antibodies or as the payload for a genetically engineered cell, such as a CAR-T cell, a CAR-NK cell, or a genetically engineered B cell.

[00190] Unique recombinant monoclonal CTLA-4 antibodies are described herein. "Recombinant" as it pertains to polypeptides (such as antibodies) or polynucleotides refers to a form of the polypeptide or polynucleotide that does not exist naturally, a non-limiting

example of which can be created by combining polynucleotides or polypeptides that would not normally occur together.

[00191] The amino acid sequence of the monoclonal CTLA-4 antibodies are provided herein (see Tables 1-26); the amino acid sequences of the heavy and light chain complementary determining regions CDRs of the CTLA-4 antibodies are underlined (CDR1), **underlined and bolded** (**CDR2**), or ***underlined, italicized, and bolded*** (***CDR3***) below:

Table 1. CTLA-4-PMPL-Rd2-A4 (E1-A4) Ab Variable Region amino acid sequences
V_H chain of E1-A4
QVQLVQSGAEVKKPGSSVKVSCKASGGTFSTYPISWVRQAPGQGLEWMGG**IIPILGTP**KYAQKFQ.D RVTITADESTSTAYMELSSLRSDDTAAYYC***AQDNGAFDT***WGQGTMVTVSS **(SEQ ID NO: 1)**
V_L chain of E1-A4
QSALTQPRSVSGSPGQSVTISCTGTSSDVGGSDYVSWYQQHPGKAPKLIIY**EVS**KRPSGVSDRFSGS KSGNTASLRISGLQAQDEADYYC***CSYAGSSTFV***FGSGTEVTVL **(SEQ ID NO: 2)**

Table 2. CTLA-4-PMPL-Rd2-A8 (E1-A8) Ab Variable Region amino acid sequences
V_H chain of E1-A8
QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYVMSWVRQAPGKGLEWVSS**ISGSGGST**DYADSVKGR FPISRDNSKNTLYLEMNSLRAEDTAVYYC***ARGGSAWSLDI***WGQGTTVTVSS **(SEQ ID NO: 3)**
V_L chain of E1-A8
DIQMTQSPSSVSASIGDRVTITCRASQDISNSLAWYQQKPGKAPKLLIY**GAS**NLRSGVP.SRFSGGG SGTYFTLTISSLQPEDFATYYC***QQGNSFPIT***FGQGTRLEIK **(SEQ ID NO: 4)**

Table 3. CTLA-4-PMPL-Rd2-A9 (E1-A9) Ab Variable Region amino acid sequences
V_H chain of E1-A9
EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGI**INPSGGST**SYAQKFQGR VTMTRDTSTSTVYMELSSLRSEDTAVYYC***ARELKRGDYYYYYGMDV***WGQGTTVTVSS **(SEQ ID NO: 5)**
V_L chain of E1-A9
QPVLTQPHSVSESPGKTVTISCTRSGGSFADNYVQWYQQRPGSAPTLMIY**EHH**QRPFGVPDRFSGSI DSSSNSASLTISGLKTEDEADYYC***QSYDSSTPVV***FGGGTKLTVL **(SEQ ID NO: 6)**

Table 4. CTLA-4-PMPL-Rd2-A10 (E1-A10) Ab Variable Region amino acid sequences
V_H chain of E1-A10
QVQLVQSGGGLVQSGGSLRLSCAASGFTFSGYDMHWVRQAAGKGLEWVSN**IGIRGDT**YYSDSVKGRF IISRENAKSSLYLQMNSLRAGDTAVYYC***VRDPSGHGMDV***WGKGTTVTVSS **(SEQ ID NO: 7)**

V_L chain of E1-A10
QPVLTQPPSVSVAPGQTARITCGGNNIGSKSVHWYQQKPGQAPVLVVY**DDS**DRPSGIPERFSGSNSG NTATLTISRVEAGDEADYYC***QVWANSTVV***FGGGTKVTVL **(SEQ ID NO: 8)**

Table 5. CTLA-4-PMPL-Rd2-A12 (E1-A12) Ab Variable Region amino acid sequences

V_H chain of E1-A12
QVQLVQSGGEVKKPGASVKVSCKASGDTFSRYGITWVRQAPGQGLEWMGW**MSTVTGNT**NSAQKFQGR VFLTRDTSTSTAYLELRSLRPDDTAVYYC***ARGLCRDSSCLTPYYYYGMDV***WGKGTLVTVSS **(SEQ ID NO: 9)**
V_L chain of E1-A12
QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTTGHYPYWFQQKPGQAPTTLIY**DAT**HKHSWTPARFSGS VLGGKAALTLSGAQPEDEADYYC***LLSYSGARV***FGGGTKLTVL **(SEQ ID NO: 10)**

Table 6. CTLA-4-PMPL-Rd2-B6 (E1-B6) Ab Variable Region amino acid sequences

V_H chain of E1-B6
QVQLQQSGTEVKKPGASVKVSCKASGYIFTSYGFTWVRQAPGQGLEWMGW**ISSYNGNT**DYAQKFE.G RVTMTTDTSTTTAYMELRGLKSDDTAMYYC***ARGPQMDV***WGQGTTVTVSS **(SEQ ID NO: 11)**
V_L chain of E1-B6
QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIY**GNS**SRPSGVP.DRFSG SKSGTSASLAISGLQSEDEADYYC***LSWDESLNAYV***FGSGTKVTVL **(SEQ ID NO: 12)**

Table 7. CTLA-4-PMPL-Rd2-B10 (E1-B10) Ab Variable Region amino acid sequences

V_H chain of E1-B10
QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA**ISGSGGST**YYADSVK.G RFTISRDNSKNTLYLQMNSLRAEDTAVYYC***AREEGITGTGFDY***WGQGTLVTVSS **(SEQ ID NO: 13)**
V_L chain of E1-B10
QTVVTQEPSFSVSPGGTVTLTCGLSSGSVSTSYYPSWYQQTPGQAPRTLIY**TTN**TRSSGVPDRFSGS ILGNKAALTITGAQADDESDYYC***VLYMGSGIWV***FGGGTKLTVL **(SEQ ID NO: 14)**

Table 8. CTLA-4-PMPL-Rd2-B11 (E1-B11) Ab Variable Region amino acid sequences

V_H chain of E1-B11
EVQLVQSGGGLVQPGGSLRLSCAASGFTFSDHYMDWVRQAPGKGLEWVGR**SRNKANSYTT**EYAASVK GRFTISRDESENSLYLQMNSLRAEDTAVYYC***ARARGYMDV***WGKGTTVTVSS **(SEQ ID NO: 15)**
V_L chain of E1-B11
NFMLTHPHSVSESPGKTVTISCTRSSGSIASYFVQWYQQRPGSSPTTVIY**DDN**QRPSGVPDRFSGSI DSSSNSASLTISGLKTEDEADYYC***QSYHSSTFYV***FGTGTKVTVL **(SEQ ID NO: 16)**

Table 9. CTLA-4-PMPL-Rd2-B12 (E1-B12) Ab Variable Region amino acid sequences
V_H chain of E1-B12
QVQLVQSGGEVKKPGASVKVSCKASGDTFSRYGITWVRQAPGQGLEWMGW**MSTVTGNT**NSAQKFQGR VFLTRDTSTSTAYLELRSLRPDDTAVYYC***ARGLCRDSSCLTPYYYYGMDV***WGKGTLVTVSS **(SEQ ID NO: 17)**
V_L chain of E1-B12
QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTTGHYPYWFQQKPGQAPTTLIY**DAT**HKHSWTPARFSGS VLGGKAALTLSGAQPEDEADYYC***LLSYSGARV***FGGGTKLTVL **(SEQ ID NO: 18)**

Table 10. aCTLA-4_T2-C10 (T2-C10) Ab Variable Region amino acid sequences
V_H chain of T2-C10
EVQLVQSGGGVVQPGRSLRLSCAASGFTFSSYAMHWVRQAPGKGLEWVAV**ISYDGSNK**YYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYC***ARDFSSSFLLGGY***WGQGTLVTVSS **(SEQ ID NO: 19)**
V_L chain of T2-C10
LPVLTQSSSASASLGSSVKLTCTLSSGHSSYIIAWHQQQPGKAPRYLMK**LEGSGSY**NKGSGVPDRFS GSSSGADRYLTISNLQSEDEADYYC***ETWDSNLPSWV***FGGGTKLTVL **(SEQ ID NO: 20)**

Table 11. CTLA-4-PMPL-Rd2-C12 (E1-C12) Ab Variable Region amino acid sequences
V_H chain of E1-C12
QVQLVQSGAEVKKPGASVKVSCKASGYIFTSYGFTWVRQAPGQGLEWMGW**ISSYNGNT**DYAQKFEGR VTMTTDTSTTTAYMELRGLKSDDTAMYYC***ARGPQMDV***WGQGTTVTVSS **(SEQ ID NO: 21)**
V_L chain of E1-C12
QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIY**GNS**SRPSGVPDRFSGS KSGTSPSLAISGLQSEDEADYYC***LSWDESLNAYV***FGSGTKVTVL **(SEQ ID NO: 22)**

Table 12. aCTLA-4_E1-D7 (E1-D7) Ab Variable Region amino acid sequences
V_H chain of E1-D7
QVQLQESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQPPGEGLEWIGH**ISYSGNT**YYNPSLRSRF SISKDTSKNQFSLHLRSVTAADTAVYYC***ARLPYCSGGNCYDMDV***WGQGTLVTVSS **(SEQ ID NO: 23)**
V_L chain of E1-D7
NFMLTQPHSMSESPGKTVTISCTRSSGSIASNYVQWFQQRPGSAPTTVIY**EDN**QRPSGVPDRFSGSI DRSSNSASLIISGLKTEDEADYYC***QSYDSTNVV***FGGGTKLTVL **(SEQ ID NO: 24)**

Table 13. CTLA-4-PMPL-Rd2-E2-A4 (E2-A4) Ab Variable Region amino acid sequences
V_H chain of E2-A4

QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYVMSWVRQAPGKGLEWVSS**ISGSGGST**DYA DSVKGRFPISRDNSKNTLYLEMNSLRAEDTAVYYC***ARGGSAWSLDI***WGQGTTVTVSS **(SEQ ID NO: 385)**
V_L chain of E2-A4
DIQMTQSPSSVSASIGDRVTITCRASQDISNSLAWYQQKPGKAPKLLIY**GAS**NLRSGVPSR FSGGGSGTYFTLTISSLQPEDFATYYC***QQGNSFPIT***FGQGTRLEIK **(SEQ ID NO: 386)**

Table 14. CTLA-4-PMPL-Rd2-E2-A7 (E2-A7) Ab Variable Region amino acid sequences
V_H chain of E2-A7
QVQLVQSGGSVVRPGRSLRLACAASGFTFRSYAMHWVRQTPGKGLEWVAV**ISYDGDNT**FYADAVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYC***AKLGVTTYAFDI***WGQGTLVTVSS **(SEQ ID NO: 387)**
V_L chain of E2-A7
QSALTQPRSVSGSPGQSVTISCTGTSSDVGGYKYVSWYQHHPGKAPKLMIY**DVS**ERPSGVPDRFSGS KSGNTASLTISGLQAEDEADYYC***SSYAGSNSHFV***FGTGTKVTVL **(SEQ ID NO: 388)**

Table 15. CTLA-4-PMPL-Rd2-E2-A10 (E2-A10) Ab Variable Region amino acid sequences
V_H chain of E2-A10
QVQLQQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGR**IIPILGIA**NYAQKFQGR VTITADESTSTAYMELSSLRSEDTAVYYC***ARDWDY***WGQGTLVTVSS **(SEQ ID NO: 389)**
V_L chain of E2-A10
QTVVTQEPSFSVAPGGTVTLTCALSSGSVSSNYHPSWFQQTPGQAPRTLIY**NTD**IRSHGVPDRFSGS LLGNKAALTITGAQPNDESEYYC***ALYMGSGISI***FGGGTKVTVL **(SEQ ID NO: 390)**

Table 16. CTLA-4-PMPL-Rd2-E2-A12 (E2-A12) Ab Variable Region amino acid sequences
V_H chain of E2-A12
QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSA**ISGSGGST**YYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYC***AREEGITGTGFDY***WGQGTLVTVSS **(SEQ ID NO: 391)**
V_L chain of E2-A12
QTVVTQEPSFSVSPGGTVTLTCGLSSGSVSTSYYPSWYQQTPGQAPRTLIY**TTN**TRSSGVPDRFSGS ILGNKAALTITGAQADDESDYYC***VLYMGSGIWV***FGGGTKLTVL **(SEQ ID NO: 392)**

Table 17. CTLA-4-PMPL-Rd2-E2-C4 (E2-C4) Ab Variable Region amino acid sequences
V_H chain of E2-C4
EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGI**INPSGGST**SYAQKFQGR VTMTRDTSTSTVYMELSSLRSEDTAVYYC***ARELKRGDYYYYYGMDV***WGQGTTVTVSS **(SEQ ID NO: 393)**
V_L chain of E2-C4

QPVLTQPHSVSESPGKTVTISCTRSGGSFADNYVQWYQQRPGSAPTLMIY**EHH**QRPFGVPDRFSGSI DSSSNSASLTISGLKTEDEADYYC***QSYDSSTPVV***FGGGTKLTVL **(SEQ ID NO: 394)**

Table 18. CTLA-4-PMPL-Rd2-E2-D4 (E2-D4) Ab Variable Region amino acid sequences
V_H chain of E2-D4
QVQLVQSGAEVKKPGASVKLSCKGSGYTFITDYIHWVRQAPGQGLEWMGR**LIPSDGST**IYAQKFRGR VTMTRDTSTRTVYMELSSLRSEDTALYYC***ARDGSHYDFDN***WGQGTLVTVSS **(SEQ ID NO: 395)**
V_L chain of E2-D4
QPVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLIIY**EVN**KRPSGVPDRFSGS KSGNTASLTVSGLQAEDEADYYC***SSYSSSSTLV***FGGGTKLTVL **(SEQ ID NO: 396)**

Table 19. CTLA-4-PMPL-Rd2-E2-E5 (E2-E5) Ab Variable Region amino acid sequences
V_H chain of E2-E5
QVQLVQSGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSS**ITGNGGST**YYADSVKGR FTISRDNSKNTLYLQMNSLRAEDTAVYYC***AREEGITGTGFDY***WGQGTLVTVSS **(SEQ ID NO: 397)**
V_L chain of E2-E5
HTVVTQEPSFSVTPGGTVTLTCGLSSGSISTSYYPIWYQHTPGQAPRTLIY**TTN**TPSSGVPDRFSGS ILGNKAALTITGAQEDDESDYYC***VLYMGSGIWV***FGGRTKLTVL **(SEQ ID NO: 398)**

Table 20. CTLA-4-PMPL-Rd2-E2-F1 (E2-F1) Ab Variable Region amino acid sequences
V_H chain of E2-F1
QVQLVQSGAEVKKPGASVKVSCKASGYIFTSYGFTWVRQAPGQGLEWMGW**ISSYNGNT**DYAQKFEGR VTMTTDTSTTTAYMELRGLKSDDTAMYYC***ARGPQMDV***WGQGTTVTVSS **(SEQ ID NO: 399)**
V_L chain of E2-F1
QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIY**GNS**SRPSGVPDRFSGS KSGTSASLAISGLQSEDEADYYC***LSWDESLNAYV***FGSGTKVTVL **(SEQ ID NO: 400)**

Table 21. CTLA-4-PMPL-Rd2-E2-G5 (E2-G5) Ab Variable Region amino acid sequences
V_H chain of E2-G5
EVQLVESGAEVRKPGESLTISCKASGYTFTSYGISWVRQAPGQGLEWMGW**ISAYNGNT**NYAQKLQGR VTMTTDTSTSTAYMELRSLRSDDTAVYYC***ATDLWPIYCSGGSCYETSYYGMDV***WGQGTLVTVSS **(SEQ ID NO: 401)**
V_L chain of E2-G5
QPGLTQPPSASGTPGQRVTLSCSGSSSNIGSNYVFWYQQLPGTAPKLLIY**SNN**QRPSGVPDRFSASK SGTSASLAISGLRSEDEADYYC***AAWDDSLSGWV***FGGGTKLTVL **(SEQ ID NO: 402)**

Table 22. CTLA-4_PMPL-Rd2-E2-G9 (E2-G9) Ab Variable Region amino acid sequences
V_H chain of E2-G9
QVQLVQSGAEVKKPGASVKLSCKGSGYTFITDYIHWVRQAPGQGLEWMGR**LIPSDGST**IYAQKFRGR VTMTRDTSTRTVYMELSSLRSEDTALYYC***ARDGSHYDFDN***WGQGTLVTVSS **(SEQ ID NO: 403)**
V_L chain of E2-G9
QPVLTQPRSVSGSPGQSVTISCTGTSSDVGGYNYVSWYQQHPGKAPKLIIY**EVN**KRPSGVPDRFSGS KSGNTASLTVSGLQAEDEADYYC***SSYSSSSTLV***FGGGTKLTVL **(SEQ ID NO: 404)**

Table 23. CTLA-4-PMPL-Rd2-E2-H5 (E2-H5) Ab Variable Region amino acid sequences
V_H chain of E2-H5
EVQLVESGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGI**INPSGGST**SYAQKFQGR VTMTRDMSTSTVYMELSSLRSEDTAVYYC***AREEMAPFLSNYGMDV***WGQGTMVTVSS **(SEQ ID NO: 405)**
V_L chain of E1-H5
NFMLTHPHSVSESPGKTVTISCTGSSDSLASNYVQWYQQRPGSAPTTVIY**ENN**QRPSGVPDRFSGSI DGSSNSASLTISALETEDEADYYC***QSYDGTPV***FGTGTKLTVL **(SEQ ID NO: 406)**

Table 24. CTLA-4_PMPL-Rd2-E2-H8 (E2-H8) Ab Variable Region amino acid sequences
V_H chain of E2-H8
EVQLVQSGGGLIQPGGSLRLSCAASGFTVSSEYMTWVRQAPGKGLEWVSN**IYTSGPT**YYADSVKGRF TISRDNAKNSLYLQMNSLRAEDTAVYYC***ARVGNGGGYNL***WGQGTLVTVSS **(SEQ ID NO: 407)**
V_L chain of E2-H8
QSALTQPASVSGSPGQSITISCTGTSGDVGAHDYVSWYQQHPGKAPKLMIY**EGS**KRPSGVSNRFSGS KSGNTASLTVSGLQAEDEADYYC***SSFAGTNNYV***FGTGTKVAVL **(SEQ ID NO: 408)**

Table 25. CTLA-4_PMPL-Rd2-E2-H9 (E2-H9) Ab Variable Region amino acid sequences
V_H chain of E2-H9
EVQLVESGGGLVQPGGSLRLPCAASGFTFSSYAMSWVRQAPGKGLEWVSV**ISGSGTNT**HYADSVKGR FTISRDNFKNTVYLQVNSPRAEDTAVYYC***VREFGGPSNY***WGQGTLVTVSS **(SEQ ID NO: 409)**
V_L chain of E2-DH9
QSVLTHPPSVSGAPGQRVTISCTGNSSNIGAPYDVHWYQQLPGTAPKLLIY**ANK**YRPSGVPDRFSGS KSGTSASLAISGLRSKDEADYYC***AAWDDSLGGLYV***FGTGTKVTVL **(SEQ ID NO: 410)**

Table 26. CTLA-4_PMPL-Rd2-E2-H10 (E2-H10) Ab Variable Region amino acid sequences
V_H chain of E2-H10
QVQLVQSGGEVKKPGASVKVSCKASGDTFSRYGITWVRQAPGQGLEWMGW**MSTVTGNT**NSAQKFQGR VFLTRDTSTSTAYLELRSLRPDDTAVYYC***ARGLCRDSSCLTPYYYYGMDV***WGKGTLVTVSS **(SEQ ID NO: 411)**

V_L chain of E2-H10
QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTTGHYPYWFQQKPGQAPTTLIY**DAT**HKHSWTPARFSGS VLGGKAALTLSGAQPEDEADYYC***LLSYSGARV***FGGGTKLTVL **(SEQ ID NO: 412)**

Table 57. hCTLA4-Rd3b-T1-E6 (T1-E6) Ab Variable Region amino acid sequences
V_H chain of T1-E6
QVQLQESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQPPGEGLEWIGH**ISYSGNT**YYNPSLRSRF SISKDTSKNQFSLHLRSVTAADTAVYYC***ARLPYCSGGNCYDMDV***WGQGTLVTVSS **(SEQ ID NO: 1001)**
V_L chain of T1-E6
NFMLTQPHS.MSESPGKTVTISCTRSSGSIASNYVQWFQQRPGSAPTTVIY**EDN**QRPSGVPDRFSGSID RSSNSASLIISGLKTEDEADYYC***HSYDSTNVV***FGGGTKLTVL **(SEQ ID NO: 1002)**

Table 58. hCTLA4-Rd3b-E4-F2 (E4-F2) Ab Variable Region amino acid sequences
V_H chain of E4-F2
QVQLVQSGGGLVQPGRSLRLSCRGSGFTFGDYAMSWVRQAPGKGLEWIAF**ITAKAHGGVT**EYAASV K.GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC***SNQRWLSSPL***WGQGTTVTVSS **(SEQ ID NO: 1003)**
V_L chain of E4-F2
LPVLTQAPS.ASGTPGQRVTISCSGSSSNIGSNTVNWYQHLPGTAPKLLIY**SNN**QRPSGVPDRFSGSKSG TSASLAISGLRSEDEADYYC***AAWDDSLSGQV***FGGGTKLTVL **(SEQ ID NO: 1004)**

Table 59. hCTLA4-Rd3b-T1-A3 (T1-A3) Ab Variable Region amino acid sequences
V_H chain of T1-A3
QVQLVQSGGGLVQPGRSLRLSCRGSGFTFGDYAMSWVRQAPGKGLEWIAF**IRAKAHGGVT**EYAASV K.GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC***SNQRWLSSPL***WGQGTTVTVSS **(SEQ ID NO: 1005)**
V_L chain of T1-A3
LPVLTQAPS.ASGTPGQRVTISCSGSSSNIGSNTVNWYQHLPGTAPKLLIY**SNN**QRPSGVPDRFSGSKSG TSASLAISGLRSEDEADYYC***AAWDDSLSGQV***FGGGTKLTVL **(SEQ ID NO: 1006)**

Table 60. hCTLA4-T1-A6 (T1-A6) Ab Variable Region amino acid sequences
V_H chain of T1-A6
QVQLVQSGG.GLVQPGGSLRLSCAASGFTFSSYSMNWVRQAPGKGLEWVSS**ISSSSSYI**YYADSVKGR FTISRDNAKNSLYLQMNSLRDEDTAVYYC***ARGVGGTMKMDV***WGQGTLVTVSS **(SEQ ID NO: 1007)**

V_L chain of T1-A6
QSVLTQPPS.ASGTPGQTVTITCSGSDSNIGSNYVYWYQQLPGTAPKLLIY**RNN**QRPSGVPDRFSGSKS GTSASLAISGLRSEDEADYYC***AAWDDSLSGPV***FGGGTKLTVL **(SEQ ID NO: 1008)**

Table 61. hCTLA4-Rd3b-T1-A10 (T1-A10) Ab Variable Region amino acid sequences
V_H chain of T1-A10
QVQLVQSGGGLVQPGGSLRLSCAASGFGFKNYWMTWVRQAPGKGLEWVAN**IKKDGSEK**YYVDSVK GRFTSSRDNAKNSLYLQMNSLRAEDTAVYYC***ARGHFGMDV***WGPGTTVTVSS **(SEQ ID NO: 1009)**
V_L chain of T1-A10
SSELTQDPAVSVALGQTVRITCQGDSLRRYYASWYQQKPGQAPLVVIF**GKD**KRPSGIPDRFSGSRSGNT ASLTITATQAEDEADYYC***GSRDSSGTRVV***FGGGTKVTRP **(SEQ ID NO: 1010)**

Table 62. hCTLA4-Rd3b-E2-D5 (E2-D5) Ab Variable Region amino acid sequences
V_H chain of E2-D5
QVQLVQSGGGLVQPGGSLRLSCAASGFTFVSYAMSWVRQAPGKGLEWVSS**ISGSGGDT**YYADSVKG RFTISRDNSESRLYLQMNSLGPEDTALYYC***VKSKGGIRKYMEV***WGQGTMVTVSS **(SEQ ID NO: 1011)**
V_L chain of E2-D5
QPGLTQPPSVSKGLRQTATLTCTGNSNNVGNQGAAWLQQHQGHPPKLLFF**RNG**KRPSGISERFSASR SGSTASLTITELQPDDEADYYC***SAWDRSLVAWV***FGGGTRVTVL **(SEQ ID NO: 1012)**

Table 63. hCTLA4-Rd3b-E2-G6 (E2-G6) Ab Variable Region amino acid sequences
V_H chain of E2-G6
QVPWCVWGRLGPAWGVPDTLLCASGFTFVNYAMTWIRQAPGKGLEWVSC**IIGSGGDT**YYAHSVKG RITISKDNSQSRLYLLMNMLGPEDSVLYYC***VKSKGGIRKYMEV***WGQGTMVTVSS **(SEQ ID NO: 1013)**
V_L chain of E2-G6
HPGLTHPPSESKGLIHTATLTCTGNSNNVGNQGAPWLHHHHGHPPKLLFF**ING**KRPSWISKRFSASKS RSTASLTITELQPDDDADYYC***TAWDRSLVAWV***FGGGTRVTVL **(SEQ ID NO: 1014)**

Table 64. hCTLA4-Rd3b-E2-H3 (E2-H3) Ab Variable Region amino acid sequences
V_H chain of E2-H3

EVQLVQSGPEVKKPGDSVKVPCKASGYTFSTYGISWVRQAPGQGLEWMGW**VSAYRRNA**NYAQKFQ DRVTMTTDTSTNTAYMELKSLRSDDTAIYFC***ARKRYGAFDV***WGQGTMVTVSS **(SEQ ID NO: 1015)**
V_L chain of E2-H3
SYELTQPPSVSEGLRQTATLTCTGNSNNVGNQGAAWLQQHQGHPPKLLSY**RNN**NRPSGISERLSASRS GNTASLTITGLQPEDEADYYC***SAWDSSLSAVI***FGGGTKLTVL **(SEQ ID NO: 1016)**

Table 65. CTLA4pmpl-Rd2-E2-H12 (E2-H12) Ab Variable Region amino acid sequences
V_H chain of E2-H12
EVQLVQSGG.GLIQPGGSLRLSCAASGFTVSSEYMTWVRQAPGKGLEWVSN**IYTSGPT**YYADSVKGRF TISRDNAKNSLYLQMNSLRAEDTAVYYC***ARVGNGGGYNL***WGQGTLVTVSS **(SEQ ID NO: 1017)**
V_L chain of E2-H12
QSALTQPASVSGSPGQSITISCTGTSGDVGAHDYVSWYQQHPGKAPKLMIY**EGS**KRPSGVSNRFSGSK SGNTASLTVSGLQAEDEADYYC***SSFAGTNNYV***FGTGTKVAVL **(SEQ ID NO: 1018)**

Table 66. CTLA4pmpl-Rd2-E2-H2 (E2-H2) Ab Variable Region amino acid sequences
V_H chain of E2-H2
QVQLQQSGTEVKKPGASVKVSCKASGYIFTSYGFTWVRQAPGQGLEWMGW**ISSYNGNT**DYAQKFE GRVTMTTDTSTTTAYMELRGLKSDDTAMYYC***ARGPQMDV***WGQGTTVTVSS **(SEQ ID NO: 1019)**
V_L chain of E2-H2
QSVLTQPPSVSGAPGQRVTISCTGSSSNIGAGYDVHWYQQLPGTAPKLLIY**GNS**SRPSGVPDRFSGSKS GTSPSLAISGLQSEDEADYYC***LSWDESLNAYV***FGSGTKVTVL **(SEQ ID NO: 1020)**

Table 67. CTLA4pmpl-Rd2-E2-D10 (E2-D10) Ab Variable Region amino acid sequences
V_H chain of E2-D10
QVQLVQSGGEVKKPGASVKVSCKASGDTFSRYGITWVRQAPGQGLEWMGW**MSTVTGNT**NSAQKF QGRVFLTRDTSTSTAYLELRSLRPDDTAVYYC***ARGLCRDSSCLTPYYYYGMDV***WGKGTLVTVSS **(SEQ ID NO: 1021)**
V_L chain of E2-D10
QTVVTQEPSLTVSPGGTVTLTCGSSTGAVTSGHYPYWFQQKPGQAPRTLIY**DTT**NRHSWTPARFSGSL LGAKAALTLSGVQPEDEADYYC***LLSYSGDRV***FGGETKLTVL **(SEQ ID NO: 1022)**

Table 68. CTLA4pmpl-Rd2-E2-D11 (E2-D11) Ab Variable Region amino acid sequences
V_H chain of E2-D11
EVQLVQSGAEVKKPGASVKVSCKASGYTFTSYYMHWVRQAPGQGLEWMGI**INPSGGST**SYAQKFQG RVTMTRDTSTSTVYMELSSLRSEDTAVYYC***ARELKRGDYYYYYGMDV***WGQGTTVTVSS **(SEQ ID NO: 1023)**
V_L chain of E2-D11
QPVLTQPHSVSESPGKTVTISCTRSGGSFADNYVQWYQQRPGSAPTLMIY**EHH**QRPFGVPDRFSGSID SSSNSASLTISGLKTEDEADYYC***QSYDSSTPVV***FGGGTKLTVL **(SEQ ID NO: 1024)**

[00192] The nucleic acid sequence of the monoclonal CTLA-4 antibodies are provided herein (see Tables 27-52):

Table 27. CTLA-4-PMPL-Rd2-A4 (E1-A4) Ab Variable Region nucleic acid sequences
V_H chain of E1-A4
caggtgcagctggtgcagtctggagctgaggtgaagaagcctgggtcctcggtgaaagtctcctgca aggcttctggaggcacttttagcacctatcctatcagctgggtgcgacaggcccctggacaagggct tgagtggatgggaggg**attatccctattcttggaacacca**aagtacgcacagaagttccaggacaga gtcacgattaccgcggacgaatccacgagcacggcctacatggagctgagcagcctgagatcagacg acacggccgcctattattgt***gctcaagacaatggtgcttttgatacc***tggggccaagggacaatggt caccgtctcttcag **(SEQ ID NO: 193)**
V_L chain of E1-A4
cagtctgccctgactcagcctcgctcagtgtccgggtctcctggacagtcagtcaccatctcctgca ctggaaccagcagtgatgttggtggttctgactatgtctcctggtaccaacagcacccaggcaaagc ccccaaactcataatttat**gaggtcagt**aagcggccctcaggggtttctgatcgcttctctggctcc aagtctggcaacacggcctccctgagaatctcggggctccaggctcaggacgaggctgattattact gc***tgttcatatgctggaagtagtacttttgtc***ttcggtagtgggaccgaggtcaccgtcctgg **(SEQ ID NO: 194)**

Table 28. CTLA-4-PMPL-Rd2-A8 (E1-A8) Ab Variable Region nucleic acid sequences
V_H chain of E1-A8
caggtgcagctggtgcagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtg cagcctctggattcacgtttagcagctatgtcatgagttgggtccgccaggctccagggaaggggct ggagtgggtctcaagt**attagtggtagtggtggtagcaca**gactacgcagactccgtgaagggccgg ttccccatctccagagacaattccaagaacacattgtatctggaaatgaacagcctgagagctgagg acacggctgtatattactgt***gcgagaggaggcagtgcctggtcgcttgatatc***tggggccaagggac cacggtcaccgtctcctcag **(SEQ ID NO: 195)**
V_L chain of E1-A8
gacatccagatgacccagtctccatcttctgtgtctgcatctataggagacagagtcaccatcactt gtcgggcgagtcaggatattagcaactcgttagcctggtatcagcagaaaccagggaaagcccctaa actcctgatctat**ggtgcatcc**aatttgcgaagtggggtcccttcaaggttcagcggcggtggatct gggacgtatttcactctcactatcagtagcctacagcctgaagattttgcgacttactattgt***caac agggtaacagtttcccgatcacc***ttcggccaagggacgcgactggagattaaac **(SEQ ID NO: 196)**

Table 29. CTLA-4-PMPL-Rd2-A9 (E1-A9) Ab Variable Region nucleic acid sequences
V_H chain of E1-A9
gaggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgca aggcatctggatacaccttcaccagctactatatgcactgggtgcgacaggcccctggacaagggct tgagtggatgggaataatcaaccctagtggtggtagcacaagctacgcacagaagttccagggcaga gtcaccatgaccagggacacgtccacgagcacagtctacatggagctgagcagcctgagatctgagg acacggccgtgtattactgtgcgagagaactaaaacgcggggattactactactacggtatgga cgtctggggccaagggaccacggtcaccgtctcctca **(SEQ ID NO: 197)**
V_L chain of E1-A9
cagcctgtgctgactcagccgcactctgtgtcggagtctccggggaagacggtcaccatctcctgca cccgcagcggtggcagctttgccgacaactatgtgcagtggtaccaacagcgcccgggcagtgcccc caccctatgatctatgaacatcaccaaagacccttggggtccctgatcgattctctggctccatc gacagctcctccaactctgcctccctcaccatctctggactgaagactgaggacgaggctgactact actgtcagtcttatgatagcagcactcccgtggtattcggcggagggaccaagctgaccgtcctag **(SEQ ID NO: 198)**

Table 30. CTLA-4-PMPL-Rd2-A10 (E1-A10) Ab Variable Region nucleic acid sequences
V_H chain of E1-A10
caggtgcagctggtgcagtctgggggaggcttggtacagtctgggggtccctgagactctcctgtg cagcctctggattcaccttcagtggctacgacatgcactgggtccgccaagcagcaggaaaaggtct agagtgggtctcaaatattggtatacgtggtgacacatactattcagactccgtgaagggccgattc atcatctccagagaaaatgccaagagctccttgtatcttcaaatgaacagcctgagagccggggaca cggctgtgtattattgtgtaagagatccgtccggccacggtatggacgtctggggcaaagggaccac ggtcaccgtctcctcag **(SEQ ID NO: 199)**
V_L chain of E1-A10
cagcctgtgctgactcagccaccctcagtgtcagtggccccaggacagacggccaggattacctgtg gggaaacaacattggaagtaaaagtgtgcactggtaccagcagaagccaggccaggccctgtgtt ggtcgtctatgatgacagcgaccggccctcagggatccctgagcgattctctggctccaactctggg aacacggccaccctgaccatcagcagggtcgaagccggggatgaggccgactattactgtcaggtgt gggccaacagcactgtggtcttcggcggagggaccaaggtgaccgtcctgg **(SEQ ID NO: 200)**

Table 31. CTLA-4-PMPL-Rd2-A12 (E1-A12) Ab Variable Region nucleic acid sequences
V_H chain of E1-A12
caggtgcagctggtgcagtctggaggtgaggtgaagaagcctggggcctcagtgaaggtctcctgca aggcttctggtgacacctttagcaggtatgggatcacctgggtgcgtcaggcccctggacaagggct tgagtggatgggatggatgagcaccgtcactggaaacacaaactccgcgcagaagttccagggcaga gtcttcttgacccgagacacatccacgagcacagcctacttggagctgaggagcctgagacctgacg acacggccgtctattactgtgcgagaggactatgtcgtgatagcagctgcctaacccccctactacta ttacggtatggacgtctggggcaaaggcaccctggtcaccgtctcctcag **(SEQ ID NO: 201)**
V_L chain of E1-A12
cagactgtggtgactcaggagccctcactgactgtgtccccaggagggacagtcactctcacctgtg gctccagcactggagctgtcaccactggtcattatccctactggttccagcagaagcctggccaggc ccccacgacactgatttatgatgcaactcacaaacactcctggacccctgcccggttctcaggctcc

gtccttgggggcaaagctgccctgacccttтcgggtgcgcagcctgaagatgaggctgactattact gc***ctgctctcctatagtggtgctcgggtg***ttcggcggagggaccaagctgaccgtcctca **(SEQ ID NO: 202)**

Table 32. CTLA-4-PMPL-Rd2-B6 (E1-B6) Ab Variable Region nucleic acid sequences
V_H chain of E1-B6
caggtacagctgcagcagtcaggaactgaggtgaagaagcctggggcctcagtgaaagtctcctgca aggcttctggttacatctttacgagttatggttcacttgggtgcggcaggcccccggacaaggcct tgagtggatgggatgg***atcagttcttacaatggtaacaca***gactatgcacaaaagttcgagggcaga gtcaccatgaccacagacacatccacgaccacagcctatatggagttgaggggtctgaaatctgacg acacggccatgtattattgt***gcgagaggtccgcaaatggacgtc***tggggccaagggaccacggtcac cgtctcctca **(SEQ ID NO: 203)**
V_L chain of E1-B6
cagtctgtgctgactcagccaccctcagtgtctggggccccagggcagagggtcaccatctcctgca ctgggagcagctccaacatcggggcaggttatgatgtacactggtaccagcagcttccaggaacagc ccccaaactcctcatctat***ggtaacagc***agtcggccctcaggggtccctgaccgattctctggctcc aagtctggcacctcagcctccctggccatcagtgggctccagtctgaagatgaggctgattattatt gt***ctatcatgggatgaaagcctgaatgcttatgtc***tttggatctgggaccaaggtcaccgtcctgg **(SEQ ID NO: 204)**

Table 33. CTLA-4-PMPL-Rd2-B10 (E1-B10) Ab Variable Region nucleic acid sequences
V_H chain of E1-B10
caggtgcagctggtgcagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtg cagcctctggattcacctttagcagctatgccatgagctgggtccgccaggctccagggaaggggct ggagtgggtctcagct***attagtggtagtggtggtagcaca***tactacgcagactccgtgaagggccgg ttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagctgagg acacggctgtgtattactgt***gcgagagaagagggtataactggaactggctttgactac***tggggcca gggcaccctggtcaccgtctcctcag **(SEQ ID NO: 205)**
V_L chain of E1-B10
cagactgtggtgactcaggagccatcgttctcagtgtcccctggagggacagtcacactcacttgtg gcttgagctctggctcagtctctactagttactaccccagctggtaccagcagaccccaggccaggc tccacgcacactcatctac***accacaaac***actcgctcttctggggtccctgatcgcttctctggctcc atccttgggaacaaagctgccctcaccatcacgggggcccaggcagatgatgaatctgattattact gt***gtcctatatatgggtagtggcatttgggtg***ttcggcggagggaccaagctgaccgtcctag **(SEQ ID NO: 206)**

Table 34. CTLA-4-PMPL-Rd2-B11 (E1-B11) Ab Variable Region nucleic acid sequences
V_H chain of E1-B11
gaggtgcagctggtgcagtctgggggaggcttggtccagcctggagggtccctgagactctcctgtg cagcctctggattcacctttagtgaccactacatggactgggtccgccaggctccagggaaggggct ggagtgggttggccgt***agtagaaacaaagctaacagttacaccaca***gaatacgccgcgtctgtgaaa ggcagattcaccatctcaagagatgaatcagagaactcactgtatctgcaaatgaacagcctgagag ccgaggacacggctgtgtattactgt***gcgagagcgaggggctacatggacgtc***tggggcaaagggac cacggtcaccgtctcctca **(SEQ ID NO: 207)**
V_L chain of E1-B11

aattttatgctgactcacccccactctgtgtcggagtctccggggaagacggtaaccatctcctgca
cccgcagcagtggcagcattgccagctactttgtgcagtggtaccagcagcgcccgggcagttcccc
caccactgtgatctat**gacgataac**caaagaccctctggggtccctgatcggttctctggctccatc
gacagctcctccaactctgcctccctcaccatctctggactgaagactgaggacgaggctgactatt
actgt***cagtcttatcatagcagcacctttatgtc***ttcggaactgggaccaaggtcaccgtcctag
(SEQ ID NO: 208)

Table 35. CTLA-4-PMPL-Rd2-B12 (E1-B12) Ab Variable Region nucleic acid sequences
V_H chain of E1-B12
caggtgcagctggtgcagtctggaggtgaggtgaagaagcctggggcctcagtgaaggtctcctgca aggcttctggtgacacctttagcaggtatgggatcacctgggtgcgtcaggccctggacaagggct tgagtggatgggatgg**atgagcaccgtcactggaaacaca**aactccgcgcagaagttccagggcaga gtcttcttgacccgagacacatccacgagcacagcctacttggagctgaggagcctgagacctgacg acacggccgtctattactgt***gcgagaggactatgtcgtgatagcagctgcctaacccctactacta ttacggtatggacgtc***tggggcaaaggcaccctggtcaccgtctcctcag **(SEQ ID NO: 209)**
V_L chain of E1-B12
cagactgtggtgactcaggagccctcactgactgtgtccccaggagggacagtcactctcacctgtg gctccagcactggagctgtcaccactggtcattatccctactggttccagcagaagcctggccaggc ccccacgacactgatttat**gatgcaact**cacaaacactcctggacccctgcccggttctcaggctcc gtccttgggggcaaagctgccctgacccctttcgggtgcgcagcctgaagatgaggctgactattact gc***ctgctctcctatagtggtgctcgggtg***ttcggcggagggaccaagctgaccgtcctca **(SEQ ID NO: 210)**

Table 36. aCTLA-4_T2-C10 (T2-C10) Ab Variable Region nucleic acid sequences
V_H chain of T2-C10
gaggtgcagctggtgcagtctgggggaggcgtggtccagcctgggaggtccctgagactctcctgtg cagcctctggattcaccttcagtagctatgctatgcactgggtccgccaggctccaggcaaggggct ggagtgggtggcagtt**atatcatatgatggaagcaataaa**tactacgcagactccgtgaagggccga ttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagctgagg acacggctgtgtattactgt***gcgagagatttcagcagctcgttcctccttggtggctac***tggggcca gggaaccctggtcaccgtctcctcag **(SEQ ID NO: 211)**
V_L chain of T2-C10
ctgcctgtgctgactcaatcatcctctgcctctgcttccctgggatcctcggtcaagctcacctgca ctctgagcagtgggcacagtagctacatcatcgcatggcatcagcagcagccagggaaggcccctcg gtacttgatgaag**cttgaaggtagtggaagctac**aacaaggggagcggagttcctgatcgcttctca ggctccagctctggggctgaccgctacctcaccatctccaacctccagtctgaggatgaggctgatt attactgt***gagacctgggacagtaacctcccttcttgggtg***ttcggcggagggaccaagctgaccgt ccta **(SEQ ID NO: 212)**

Table 37. CTLA-4-PMPL-Rd2-C12 (E1-C12) Ab Variable Region nucleic acid sequences
V_H chain of E1-C12
caggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtctcctgca aggcttctggttacatctttacgagttatggtttcacttgggtgcggcaggcccccggacaaggcct tgagtggatgggatgg**atcagttcttacaatggtaacaca**gactatgcacaaaagttcgagggcaga gtcaccatgaccacagacacatccacgaccacagcctatatggagttgaggggtctgaaatctgacg

acacggccatgtattattgt***gcgagaggtccgcaaatggacgtc***tggggccaagggaccacggtcac cgtctcctca **(SEQ ID NO: 213)**
V_L chain of E1-C12
cagtctgtgctgactcagccaccctcagtgtctggggccccagggcagagggtcaccatctcctgca ctgggagcagctccaacatcggggcaggttatgatgtacactggtaccagcagcttccaggaacagc ccccaaactcctcatctat***ggtaacagc***agtcggccctcaggggtccctgaccgattctctggctcc aagtctggcacctcaccctccctggccatcagtgggctccagtctgaagatgaggctgattattatt gt***ctatcatgggatgaaagcctgaatgcttatgtc***tttggatctgggaccaaggtcaccgtcctgg **(SEQ ID NO: 214)**

Table 38. aCTLA-4_E1-D7 (E1-D7) Ab Variable Region nucleic acid sequences
V_H chain of E1-D7
caggtgcagctgcaggagtcgggggaggcgtggtccagcctgggaggtctctgagactctcctgtg cagcctctggattcaccttcagcagctatggcatgcactgggtccgccagcccccaggggagggcct ggagtggattgggcac***atctcttacagtggcaacact***tactacaacccgtcgctcagaagtcgattt agtatttcaaaagacacgtccaagaatcagttctccctgcacctgaggtctgtgactgccgcagaca cggccgtttattactgt***gccagactgccatattgtagtggtggtaactgctacgatatggacgtc***tg gggccaaggcaccctggtcaccgtctcctca **(SEQ ID NO: 215)**
V_L chain of E1-D7
aattttatgctgactcagccccactctatgtcggagtctccggggaagacggtgaccatctcctgca cccgcagcagtggcagcattgccagcaactatgtgcagtggttccagcagcgcccgggcagtgcccc caccactgtgatctat***gaggataac***caacgaccctctggggtccctgatcggttctctggctccatc gacaggtcctccaactctgcctccctcatcatctctggactgaagactgaggacgaggctgactact actgt***cagtcttatgatagcaccaatgtggta***ttcggcggagggaccaagctgaccgtcctg **(SEQ ID NO: 216)**

Table 39. CTLA-4-PMPL-Rd2-E2-A4 (E2-A4) Ab Variable Region nucleic acid sequences
V_H chain of E2-A4
caggtgcagctggtgcagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtg cagcctctggattcacgtttagcagctatgtcatgagttgggtccgccaggctccagggaaggggct ggagtgggtctcaagt***attagtggtagtggtggtagcaca***gactacgcagactccgtgaagggccgg ttccccatctccagagacaattccaagaacacattgtatctggaaatgaacagcctgagagctgagg acacggctgtatattactgt***gcgagaggaggcagtgcctggtcgcttgatatc***tggggccaagggac cacggtcaccgtctcctcag **(SEQ ID NO: 609)**
V_L chain of E2-A4
gacatccagatgacccagtctccatcttctgtgtctgcatctataggagacagagtcaccatcactt gtcgggcgagtcaggatattagcaactcgttagcctggtatcagcagaaaccagggaaagcccctaa actcctgatctat***ggtgcatcc***aatttgcgaagtggggtcccttcaaggttcagcggcggtggatct gggacgtatttcactctcactatcagtagcctacagcctgaagattttgcgacttactattgt***caac agggtaacagtttcccgatcacc***ttcggccaagggacgcgactggagattaaac **(SEQ ID NO: 610)**

Table 40. CTLA-4-PMPL-Rd2-E2-A7 (E2-A7) Ab Variable Region nucleic acid sequences
V_H chain of E2-A7

caggtgcagctggtgcagtctgggggaagtgtggtccggcctgggaggtccctgcgactcgcctgtg
cagcctctggattcactttcaggagttacgctatgcactgggtccgccagactccaggcaaggggct
ggagtgggtggcagtt**atatcatatgatggagacaacact**ttttatgcagacgccgtgaagggccgg
ttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagctgagg
acacggctgtgtattactgt***gcgaaactcggggtgactacgtatgcttttgatatc***tggggccaagg
aaccctggtcaccgtctcctcag
(SEQ ID NO: 611)

V_L chain of E2-A7

cagtctgccctgactcagcctcgctcagtgtccgggtctcctggacagtcagtcaccatctcctgca
ctggaaccagcagtgatgttggtggttataagtatgtctcctggtaccaacaccacccaggcaaagc
ccccaaactcatgatttat**gatgtcagt**gagcggccctcaggggtccctgatcgcttctctggctcc
aagtctggcaacacggcctccctgaccatctctgggctccaggcggaggatgaggctgattattact
gc***agctcatatgcaggcagcaacagtcattttgtc***ttcggcactgggaccaaagtcaccgtcctag
(SEQ ID NO: 612)

Table 41. CTLA-4-PMPL-Rd2-E2-A10 (E2-A10) Ab Variable Region nucleic acid sequences

V_H chain of E2-A10

caggtacagctgcagcagtcaggggctgaggtgaagaagcctgggtcctcggtgaaggtctcctgca
aggcttctggaggcaccttcagcagctatgctatcagctgggtgcgacaggcccctggacaagggct
tgagtggatgggaagg**atcatccctatccttggtatagca**aactacgcacagaagttccagggcaga
gtcacgattaccgcggacgaatccacgagcacagcctacatggagctgagcagcctgagatctgagg
acacggccgtgtattactgt***gcgagagattgggactac***tggggccagggcaccctggtcaccgtctc
ctcag
(SEQ ID NO: 613)

V_L chain of E2-A10

cagactgtggtgactcaggagccatcgttctcagtggcccctgggggacagtcacactcacttgtg
ccttgagctctggctcggtctctagtaactatcaccccagctggttccagcagaccccaggccaggc
gccacgcacactcatct**acaatacagac**atacgttctcatggggtccctgatcggttctctggctct
ctccttggaaacaaagcagccctcaccatcacgggggcccagccaaatgatgaatctgaatactact
gt***gctctctatatgggtagcggcatttcgata***ttcggcggagggaccaaggtgaccgtcctag
(SEQ ID NO: 614)

Table 42. CTLA-4-PMPL-Rd2-E2-A12 (E2-A12) Ab Variable Region nucleic acid sequences

V_H chain of E2-A12

caggtgcagctggtgcagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtg
cagcctctggattcacctttagcagctatgccatgagctgggtccgccaggctccagggaaggggct
ggagtgggtctcagct**attagtggtagtggtggtagcaca**tactacgcagactccgtgaagggccgg
ttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagctgagg
acacggctgtgtattactgt***gcgagagaagagggtataactggaactggctttgactac***tggggcca
gggcaccctggtcaccgtctcctcag
(SEQ ID NO: 615)

V_L chain of E2-A12

cagactgtggtgactcaggagccatcgttctcagtgtcccctggagggacagtcacactcacttgtg
gcttgagctctggctcagtctctactagttactaccccagctggtaccagcagaccccaggccaggc
tccacgcacactcatctac**accacaaac**actcgctcttctggggtccctgatcgcttctctggctcc
atccttgggaacaaagctgccctcaccatcacgggggcccaggcagatgatgaatctgattattact
gt***gtcctatatatgggtagtggcatttgggtg***ttcggcggagggaccaagctgaccgtcctag
(SEQ ID NO: 616)

Table 43. CTLA-4-PMPL-Rd2-E2-C4 (E2-C4) Ab Variable Region nucleic acid sequences
V_H chain of E2-C4
gaggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgca aggcatctggatacaccttcaccagctactatatgcactgggtgcgacaggcccctggacaagggct tgagtggatgggaata**atcaaccctagtggtggtagcaca**agctacgcacagaagttccagggcaga gtcaccatgaccagggacacgtccacgagcacagtctacatggagctgagcagcctgagatctgagg acacggccgtgtattactgt***gcgagagaactaaaacgcggggattactactactactacggtatgga cgtc***tggggccaagggaccacggtcaccgtctcctca
(SEQ ID NO: 617)
V_L chain of E2-C4
cagcctgtgctgactcagccgcactctgtgtcggagtctccggggaagacggtcaccatctcctgca cccgcagcggtggcagctttgccgacaactatgtgcagtggtaccaacagcgcccgggcagtgcccc caccttatgatctat**gaacatcac**caaagacccttttggggtccctgatcgattctctggctccatc gacagctcctccaactctgcctccctcaccatctctggactgaagactgaggacgaggctgactact actgt***cagtcttatgatagcagcactcccgtggta***ttcggcggagggaccaagctgaccgtcctag
(SEQ ID NO: 618)

Table 44. CTLA-4-PMPL-Rd2-E2-D4 (E2-D4) Ab Variable Region nucleic acid sequences
V_H chain of E2-D4
caggtgcagctggtgcagtctggagctgaggtgaagaagcctggggcctcagtgaagctttcctgca agggatctggatacaccttcatcaccgactatatacactgggtgcggcaggcccctggacaagggct tgagtggatgggaaga**ctcatccccagtgatggaagtaca**atttacgcacagaagttccggggcaga gtcaccatgaccagggacacgtccacgagaacggtctacatggagctgagcagcctgcgatcagagg acacggccctatattattgt***gcgagagatggtagtcattacgactttgacaac***tggggccagggcac cctggtcaccgtctcctcag
(SEQ ID NO: 619)
V_L chain of E2-D4
cagcctgtgctgactcagcctcgctcagtgtccgggtctcctggacagtcagtcaccatctcctgca ctggaaccagcagtgatgttggtggttataactatgtctcctggtaccaacaacacccaggcaaggc ccccaaactcatcatttat**gaggtcaat**aagcggccctcaggggtccctgatcgcttctctggctcc aagtctggcaacacggcctccctgaccgtctctgggctccaggctgaggatgaggctgattattact gc***agctcatattcgagcagcagcactttggtc***ttcggcgggggaccaagttgaccgtcctag
(SEQ ID NO: 620)

Table 45. CTLA-4-PMPL-Rd2-E2-E5 (E2-E5) Ab Variable Region nucleic acid sequences
V_H chain of E2-E5
caggtgcagctggtgcagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtg cagcctctggattcacctttagcagctatgccatgagctgggtccgccaggctccagggaaggggct ggagtgggtctcatct**attactggtaatggtggtagcaca**tactacgcagactccgtgaagggccgg ttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagctgagg acacggctgtgtattactgt***gcgagagaagagggtataactggaactggctttgactac***tggggcca gggcaccctggtcaccgtctcctcag
(SEQ ID NO: 621)
V_L chain of E2-E5
catactgtggtgactcaggagccatccttctcagtgacccctggagggacagtcacactcacttgtg gcttgagctctggctcaatctctactagttactaccccatctggtaccagcacaccccaggccaggc tccacgcacactcatctac**accacaaac**actccctcttctggggtccctgatcgcttctctggctcc

atccttgggaacaaagctgccctcaccatcacgggggcccaggaagatgatgaatctgattattact gt***gtcctatatatgggtagtggcatttgggtg***ttcggcggaaggaccaaactgaccgtcctag **(SEQ ID NO: 622)**

Table 46. CTLA-4-PMPL-Rd2-E2-F1 (E2-F1) Ab Variable Region nucleic acid sequences
V_H chain of E2-F1
caggtacagctgcagcagtcaggaactgaggtgaagaagcctggggcctcagtgaaagtctcctgca aggcttctggttacatctttacgagttatggttcacttgggtgcggcaggcccccggacaaggcct tgagtggatgggatgg***atcagttcttacaatggtaacaca***gactatgcacaaaagttcgagggcaga gtcaccatgaccacagacacatccacgaccacagcctatatggagttgaggggtctgaaatctgacg acacggccatgtattattgt***gcgagaggtccgcaaatggacgtc***tggggccaagggaccacggtcac cgtctcctca **(SEQ ID NO: 623)**
V_L chain of E2-F1
cagtctgtgctgactcagccaccctcagtgtctggggccccagggcagagggtcaccatctcctgca ctgggagcagctccaacatcggggcaggttatgatgtacactggtaccagcagcttccaggaacagc ccccaaactcctcatctat***ggtaacagc***agtcggccctcaggggtccctgaccgattctctggctcc aagtctggcacctcagcctccctggccatcagtgggctccagtctgaagatgaggctgattattatt gt***ctatcatgggatgaaagcctgaatgcttatgtc***tttggatctgggaccaaggtcaccgtcctgg **(SEQ ID NO: 624)**

Table 47. CTLA-4-PMPL-Rd2-E2-G5 (E2-G5) Ab Variable Region nucleic acid sequences
V_H chain of E2-G5
gaggtgcagctggtggagtctggagccgaggtgagaaagcccggagagtctctgacgatctcctgca aggcttctggttacacctttaccagctatggtatcagctgggtgcgacaggcccctggacaagggct tgagtggatgggatgg***atcagcgcttacaatggtaacaca***aactatgcacagaagctccagggcaga gtcaccatgaccacagacacatccacgagcacagcctacatggagctgaggagcctgagatctgacg acacggccgtgtattactgt***gcaacagatctatggcccatatattgtagtggtggtagctgctacga aacgagctactacggtatggacgtc***tggggccaaggcaccctggtcaccgtctcttca **(SEQ ID NO: 625)**
V_L chain of E2-G5
cagcctgggctgactcagccaccctcagcgtctgggacccccgggcagagggtcaccctctcttgtt ctggaagcagctccaacatcggaagtaattatgtattctggtaccagcagctcccaggaacggcccc caaactcctcatctat***agtaataat***cagaggccctcaggggtccctgaccgattctctgcctccaag tctggcacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgt***g cagcatgggatgacagcctgagtggttgggtg***ttcggcggagggaccaagctgaccgtcctag **(SEQ ID NO: 626)**

Table 48. CTLA-4-PMPL-Rd2-E2-G9 (E2-G9) Ab Variable Region nucleic acid sequences
V_H chain of E2-G9
caggtgcagctggtgcagtctggagctgaggtgaagaagcctggggcctcagtgaagctttcctgca agggatctggatacaccttcatcaccgactatatacactgggtgcggcaggcccctggacaagggct tgagtggatgggaaga***ctcatccccagtgatggaagtaca***atttacgcacagaagttccggggcaga gtcaccatgaccagggacacgtccacgagaacggtctacatggagctgagcagcctgcgatcagagg acacggccctatattattgt***gcgagagatggtagtcattacgactttgacaac***tggggccagggcac cctggtcaccgtctcctcag **(SEQ ID NO: 627)**
V_L chain of E2-G9

cagcctgtgctgactcagcctcgctcagtgtccgggtctcctggacagtcagtcaccatctcctgca ctggaaccagcagtgatgttggtggttataactatgtctcctggtaccaacaacacccaggcaaggc ccccaaactcatcatttat**gaggtcaat**aagcggccctcaggggtccctgatcgcttctctggctcc aagtctggcaacacggcctccctgaccgtctctgggctccaggctgaggatgaggctgattattact gc***agctcatattcgagcagcagcactttggtc***ttcggcgggggaccaagttgaccgtcctag **(SEQ ID NO: 628)**

Table 49. CTLA-4-PMPL-Rd2-E2-H5 (E2-H5) Ab Variable Region nucleic acid sequences
V_H chain of E2-H5
gaggtgcagctggtggagtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgca aggcatctggatacaccttcaccagctactatatgcactgggtgcgacaggcccctggacaagggct tgagtggatgggaata**atcaaccctagtggtggtagcaca**agctacgcacagaagttccagggcaga gtcaccatgaccagggacatgtccacgagcacagtctacatggagctgagcagcctgagatctgagg acacggctgtgtattactgt***gcgagagaggagatggccccgttcctttcgaactacggtatggacgt c***tggggccaagggacaatggtcaccgtctcttca **(SEQ ID NO: 629)**
V_L chain of E2-H5
aattttatgctgactcacccccactctgtgtcggagtctccggggaagacggtaaccatctcctgca ccggcagcagtgacagccttgccagcaactatgtgcagtggtaccagcagcgcccgggcagtgcccc caccactgtgatctat**gaaaataac**caaagaccctctggggtccctgatcgattctctggctccatc gacggctcctccaactctgcctccctcaccatctctgcactggagactgaggacgaggctgactact actgt***cagtcctatgatggcaccccggtg***ttcggcacagggaccaaactgaccgtcctcc **(SEQ ID NO: 630)**

Table 50. CTLA-4-PMPL-Rd2-E2-H8 (E2-H8) Ab Variable Region nucleic acid sequences
V_H chain of E2-H8
gaggtgcagctggtgcagtctggaggaggcttgatccagccgggggggtccctgagactctcctgcg cagcctctgggttcaccgtcagcagcgagtacatgacctgggtccgccaggctccagggaaggggct ggagtgggtctcaaat**atttatacaagtggtcccacc**tactacgcagactctgtgaagggccgattc accatctccagggacaacgccaagaactcactgtatctgcaaatgaacagcctgagagccgaggaca cggccgtgtattactgt***gcgagagtagggaatggaggtggctacaatttg***tggggccagggcaccct ggtcaccgtctcctcag **(SEQ ID NO: 631)**
V_L chain of E2-H8
cagtctgccctgactcagcctgcctccgtgtcagggtctcctggacagtcgatcaccatctcctgca ctggaaccagcggtgacgttggtgcgcatgactatgtctcgtggtaccaacaacacccgggcaaagc ccccaaactcatgatttat**gagggcagt**aagcggccctcaggggtttctaatcgcttctctggctcc aagtctggcaacacggcctccctgaccgtctctgggctccaggctgaggatgaggctgattactact gc***agctcatttgcaggaaccaacaattacgtc***ttcggaactgggaccaaggtcgccgtcctag **(SEQ ID NO: 632)**

Table 51. CTLA-4-PMPL-Rd2-E2-H9 (E2-H9) Ab Variable Region nucleic acid sequences
V_H chain of E2-H9
gaggtgcagctggtggagtctgggggaggcttggttcagccgggggggtccctaagactgccctgtg cagcctctggattcacgtttagcagctatgccatgagctgggtccgccaggctccagggaaggggct ggagtgggtctctgtt**ataagtggtagtggcactaataca**cactacgcagactccgtgaagggccgg ttcaccatctccagagacaatttcaagaacacggtatatctgcaagtgaacagcccgagagccgagg acacggccgtctattattgt***gttagagagttcggtggtccctcaaactac***tggggccagggcaccct ggtcaccgtctcctcag

(SEQ ID NO: 633)
V_L chain of E2-H9
cagtctgtgctgactcacccaccctcagtgtctggggccccagggcagagggtcaccatctcctgca ctgggaacagctccaacatcggggcaccttatgatgtacactggtaccagcagcttccaggaacagc ccccaaactcctcatttat**gctaacaag**tatcggccctcaggggtccctgaccgattctctggctcc aagtctggcacctcagcctccctggccatcagtgggctccggtccaaagatgaggctgattattact gt***gcagcctgggatgacagcctgggtggtctttatgtc***ttcggaactgggaccaaggtcaccgtcct ac
(SEQ ID NO: 634)

Table 52. CTLA-4-PMPL-Rd2-E2-H10 (E2-H10) Ab Variable Region nucleic acid sequences
V_H chain of E2-H10
caggtgcagctggtgcagtctggaggtgaggtgaagaagcctggggcctcagtgaaggtctcctgca aggcttctggtgacacctttagcaggtatgggatcacctgggtgcgtcaggcccctggacaagggct tgagtggatgggatgg**atgagcaccgtcactggaaacaca**aactccgcgcagaagttccagggcaga gtcttcttgacccgagacacatccacgagcacagcctacttggagctgaggagcctgagacctgacg acacggccgtctattactgt***gcgagaggactatgtcgtgatagcagctgcctaacccccctactacta ttacggtatggacgtc***tggggcaaaggcaccctggtcaccgtctcctcag
(SEQ ID NO: 635)
V_L chain of E2-H10
cagactgtggtgactcaggagccctcactgactgtgtccccaggagggacagtcactctcacctgtg gctccagcactggagctgtcaccactggtcattatccctactggttccagcaaaagcctggccaggc ccccacgacactgatttat**gatgcaact**cacaaacactcctggacccctgcccggttctcaggctcc gtccttgggggcaaagctgccctgacccttcgggtgcgcagcctgaagatgaggctgactattact gc***ctgctctcctatagtggtgctcgggtg***ttcggcggagggaccaagctgaccgtcctca
(SEQ ID NO: 636)

Table 69. hCTLA4-Rd3b-T1-E6_PelB-F_2021-02-10_E05 (T1-E6) Ab Variable Region nucleic acid sequences
V_H chain of T1-E6
caggtgcagctgcaggagtcgggggggaggcgtggtccagcctgggaggtctctgagactctcctgtg cagcctctggattcaccttcagcagctatggcatgcactgggtccgccagcccccaggggagggcct ggagtggattgggcac**atctcttacagtggcaacact**tactacaacccgtcgctcagaagtcgattt agtatttcaaaagacacgtccaagaatcagttctccctgcacctgaggtctgtgactgccgcagaca cggccgtttattactgt***gccagactgccatattgtagtggtggtaactgctacgatatggacgtc***tg gggccaaggcaccctggtcaccgtctcctca
(SEQ ID NO: 833)
V_L chain of T1-E6
aattttatgctgactcagccccactctatgtcggagtctccggggaagacggtgaccatctcctgca cccgcagcagtggcagcattgccagcaactatgtgcagtggttccagcagcgcccgggcagtgcccc caccactgtgatctat**gaggataac**caacgaccctctggggtccctgatcggttctctggctccatc gacaggtcctccaactctgcctccctcatcatctctggactgaagactgaggacgaggctgactact actgt***cattcttatgatagcaccaatgtggta***ttcggcggagggaccaagctgaccgtcctgg
(SEQ ID NO: 834)

Table 70. hCTLA4-Rd3b-E4-F2_PelB-F_2021-02-10_F06 (E4-F2) Ab Variable Region nucleic acid sequences
V_H chain of E4-F2
caggtgcagctggtgcagtctgggggaggcttggtacagccagggcggtccctgagactctcctgta gaggttctggattcacctttggtgattatgctatgagctgggtccgccaggctccagggaaggggct ggaatggatagctttc**attacagccaaggctcacggtggggtaaca**gaatatgccgcgtctgtgaaa ggcagattcaccatctcaagagatgattcaaagaacacggcgtatctgcaaatgaacagcctgaaaa ccgaggacacggccgtgtattactgc***agtaatcaacgatggttgtcgtcgcctctc***tggggccaagg gaccacggtcaccgtctcctcag **(SEQ ID NO: 835)**
V_L chain of E4-F2
ctgcctgtgctgactcaggcaccctcagcgtctgggacccccgggcagagggtcaccatctcttgtt ctggaagcagctccaacatcggaagtaatactgtaaactggtaccaacacctcccaggaacggcccc caaactcctcatctat**agtaataat**caacggccctcaggggtccctgaccgattctctggctccaag tctggcacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgt***g cagcatgggatgacagcctgagtggtcaagtg***ttcggcggagggaccaagctgaccgtcctag **(SEQ ID NO: 836)**

Table 71. hCTLA4-Rd3b-T1-A3_PelB-F_2021-02-10_B01(T1-A3) Ab Variable Region nucleic acid sequences
V_H chain of T1-A3
caggtgcagctggtgcagtctgggggaggcttggtacagccagggcggtccctgagactctcctgta gaggttctggattcacctttggtgattatgctatgagctgggtccgccaggctccagggaaggggct ggaatggatagctttc**attagagccaaggctcacggtggggtaaca**gaatatgccgcgtctgtgaaa ggcagattcaccatctcaagagatgattcaaagaacacggcgtatctgcaaatgaacagcctgaaaa ccgaggacacggccgtgtattactgc***agtaatcaacgatggttgtcgtcgcctctc***tggggccaagg gaccacggtcaccgtctcctcag **(SEQ ID NO: 837)**
V_L chain of T1-A3
ctgcctgtgctgactcaggcaccctcagcgtctgggacccccgggcagagggtcaccatctcttgtt ctggaagcagctccaacatcggaagtaatactgtaaactggtaccaacacctcccaggaacggcccc caaactcctcatctat**agtaataat**cagcggccctcaggggtccctgaccgattctctggctccaag tctggcacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgt***g cagcatgggatgacagcctgagtggtcaagtg***ttcggcggagggaccaagctgaccgtcctag **(SEQ ID NO: 838)**

Table 72. hCTLA4-T1-A6_PelB-F_2021-02-05_B04 (T1-A6) Ab Variable Region nucleic acid sequences
V_H chain of T1-A6
caggtgcagctggtgcagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtg cagcctctggattcacctttagtagctatagcatgaactgggtccgccaggctccagggaaggggct ggagtgggtctcatcc**attagtagtagtagtagttacata**tactacgcagactcagtgaagggccga ttcaccatctccagagacaacgccaagaactcactgtatctgcaaatgaacagcctgagagacgagg acacggctgtgtattactgt***gcgagaggtgtcgggggtactatgaagatggacgtc***tggggccaagg caccctggtcaccgtctcctcag **(SEQ ID NO: 839)**
V_L chain of T1-A6
cagtctgtgctgactcagccaccctcagcgtctgggacccccgggcagacggtcaccatcacttgtt ctggaagcgactccaacatcggaagtaattatgtatactggtaccagcagctcccaggaacggcccc caaactcctcatctat**aggaataat**cagcggccctcaggggtccctgaccgattctctggctccaag

tctggcacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgt***gcagcatgggatgacagcctgagtggtccggtg***ttcggcggagggaccaagctgaccgtcctag **(SEQ ID NO: 840)**

Table 73. hCTLA4-Rd3b-T1-A10_PelB-F_2021-02-10_F01 (T1-A10) Ab Variable Region nucleic acid sequences
V_H chain of T1-A10
caggtgcagctggtgcagtctgggggaggcttggtccagccgggggggtccctgcgactctcctgtg cagcctctggattcgggtttaagaactactggatgacctgggtccgccaggccccagggaaggggct ggagtgggtggccaat***ataaagaaagatggaagtgagaaa***tactatgtggactctgtgaagggccga ttcaccagctccagagacaacgccaagaactcactgtatctccaaatgaacagcctgagagccgagg acacggccgtatattactgt***gcgaggggtcatttcggtatggacgtc***tggggcccagggaccacggt caccgtctcctca **(SEQ ID NO: 841)**
V_L chain of T1-A10
tcttctgagctgactcaggaccctgctgtgtctgtggccttgggacagacagtcaggatcacatgcc aaggagacagcctcagaaggtattatgcaagctggtaccagcagaagccaggacaggcccctttggt tgtcatctttggcaaagacaagcggccctcggggatccccgaccgcttctctggctccaggtcagga aacacagcttccttgaccataactgcgacccaggcggaggatgaggctgattattattgt***ggctcac gggacagcagtggcacccgtgtggtc***ttcggcggagggaccaaggtgacccgtccta **(SEQ ID NO: 842)**

Table 74. hCTLA4-Rd3b-E2-D5_PelB-F_2021-02-10_B05 (E2-D5) Ab Variable Region nucleic acid sequences
V_H chain of E2-D5
caggtgcagctggtgcagtctgggggaggcttggtccagcctgggggtccctgagactctcctgtg cagcctctggattcacctttgtcagctatgccatgagctgggtccgccaggctccagggaaggggct ggagtgggtctcaagt***attagtggtagtggtggtgacaca***tactacgcagactccgtgaagggccgg ttcaccatctccagagacaattccgagagcaggctgtatttgcaaatgaacagcctgggacctgagg acacggccctttattactgt***gtgaagtcaaaaggggggaatacgaaagtatatggaggtc***tggggcca agggacaatggtcaccgtctcttcag **(SEQ ID NO: 843)**
V_L chain of E2-D5
cagcctgggctgactcagccaccctcggtgtccaagggcttgagacagaccgccacactcacctgca ctgggaacagcaacaatgttggcaaccaaggagcagcttggctgcagcagcaccagggccaccctcc caaactcctcttctttt***agaaatggc***aagcggccctcagggatctcagagagattctctgcatccagg tcaggaagtacagcctccctgaccattactgaactccagcctgatgacgaggctgactattactgc***tcagcatgggacaggagcctcgtagcttgggtg***ttcggcggagggaccagggtgaccgtcctag **(SEQ ID NO: 844)**

Table 75. hCTLA4-Rd3b-E2-G6_PelB-F_2021-02-10_C08 (E2-G6) Ab Variable Region nucleic acid sequences
V_H chain of E2-G6
caggtgccctggtgcgtctgggggaggcttggtccagcctgggggtccctgatactctcctgtgcg cctctggattcacctttgtcaactatgccatgacctggatccgccaggctccagggaaggggctgga gtgggtctcatgt***attattggtagtggtggtgacaca***tactacgcacactccgtgaaggggcggatc accatctccaaagacaattcccagagcaggctgtatttgctaatgaacatgctgggacctgaggact cggtcctttattactgt***gtgaagtcaaaaggggggaatacgaaagtatatggaggtc***tggggccaagg gacaatggtcaccgtctcttcag **(SEQ ID NO: 845)**

V_L chain of E2-G6
catcctgggctgactcatccaccctcggagtccaagggtttgatacataccgccacactcacctgca ctgggaacagcaacaatgttggcaaccaaggagcaccttggctgcatcaccaccatggccaccctcc caaactcctcttcttt**ataaatggc**aagcggccctcatggatctcaaagagattctctgcatccaag tcacgaagtacagcctccctgaccattactgaactccaacctgatgacgacgctgactattactgt***a cagcatgggacaggagcctcgtagcttgggtg***ttcggcggagggaccagggtgaccgtcctag **(SEQ ID NO: 846)**

Table 76. hCTLA4-Rd3b-E2-H3_PelB-F_2021-02-10_H08 (E2-H3) Ab Variable Region nucleic acid sequences
V_H chain of E2-H3
gaggtgcagctggtgcagtctgggcctgaggtgaagaagcctggggactcagtgaaggtcccctgca aggcttctggttacaccttctccacttatggtatcagttgggtgcgacaggcccctggacaagggct tgagtggatgggatgg**gtcagcgcttacagacgtaacgca**aactatgcacagaaattccaggacaga gtcaccatgaccacagacacatccacgaacacagcctacatggagctgaagagcctgagatctgacg acacggccatatatttctgt***gcgagaaagcgctacggtgcttttgatgtc***tggggccaagggacaat ggtcaccgtctcttcag **(SEQ ID NO: 847)**
V_L chain of E2-H3
tcctatgagctgactcagccaccctcggtgtccgagggcttgagacagaccgccacactcacctgca ctgggaacagcaacaatgttggcaaccaaggagcagcttggctgcagcagcaccagggccaccctcc caaactcctatcctac**aggaataac**aaccggccctcagggatctcagagagattatctgcatccagg tcaggaaacacagcctccctgaccattactggactccagcctgaggacgaggctgactattactgc***t cagcatgggacagcagcctcagtgctgtgata***ttcggcggagggaccaagctgaccgtcctag **(SEQ ID NO: 848)**

Table 77. CTLA4pmpl-Rd2-E2-H12_PelB-F_2021-08-06_H06 (E2-H12) Ab Variable Region nucleic acid sequences
V_H chain of E2-H12
gaggtgcagctggtgcagtctggaggaggcttgatccagccgggggggtccctgagactctcctgcg cagcctctgggttcaccgtcagcagcgagtacatgacctgggtccgccaggctccagggaaggggct ggagtgggtctcaaat**atttatacaagtggtcccacc**tactacgcagactctgtgaagggccgattc accatctccagggacaacgccaagaactcactgtatctgcaaatgaacagcctgagagccgaggaca cggccgtgtattactgt***gcgagagtagggaatggaggtggctacaatttg***tggggccagggcaccct ggtcaccgtctcctca **(SEQ ID NO: 849)**
V_L chain of E2-H12
cagtctgccctgactcagcctgcctccgtgtcagggtctcctggacagtcgatcaccatctcctgca ctggaaccagcggtgacgttggtgcgcatgactatgtctcgtggtaccaacaacacccgggcaaagc ccccaaactcatgatttat**gagggcagt**aagcggccctcaggggtttctaatcgcttctctggctcc aagtctggcaacacggcctccctgaccgtctctgggctccaggctgaggatgaggctgattactact gc***agctcatttgcaggaaccaacaattacgtc***ttcggaactgggaccaaggtcgccgtcctag **(SEQ ID NO: 850)**

Table 78. CTLA4pmpl-Rd2-E2-H2_PelB-F_2021-08-06_H05 (E2-H2) Ab Variable Region nucleic acid sequences
V_H chain of E2-H2

caggtacagctgcagcagtcaggaactgaggtgaagaagcctggggcctcagtgaaagtctcctgca
aggcttctggttacatctttacgagttatggtttcacttgggtgcggcaggcccccggacaaggcct
tgagtggatgggatgg**atcagttcttacaatggtaacaca**gactatgcacaaaagttcgagggcaga
gtcaccatgaccacagacacatccacgaccacagcctatatggagttgaggggtctgaaatctgacg
acacggccatgtattattgt***gcgagaggtccgcaaatggacgtc***tggggccaagggaccacggtcac
cgtctcctca
(SEQ ID NO: 851)

V_L chain of E2-H2

gacatccagatgacccagtctccatcttctgtgtctgcatctataggagacagagtcaccatcactt
gtcgggcgagtcaggatattagcaactcgttagcctggtatcagcagaaaccagggaaagcccctaa
actcctgatctat**ggtgcatcc**aatttgcgaagtggggtcccttcaaggttcagcggcggtggatct
gggacgtatttcactctcactatcagtagcctacagcctgaagattttgcgacttactattgt***caac
agggtaacagtttcccgatcacc***ttcggccaagggacgcgactggagattaaac
(SEQ ID NO: 852)

Table 79. CTLA4pmpl-Rd2-E2-D10_PelB-F_2021-08-06_H02 (E2-D10) Ab Variable Region nucleic acid sequences

V_H chain of E2-D10

caggtgcagctggtgcagtctggaggtgaggtgaagaagcctggggcctcagtgaaggtctcctgca
aggcttctggtgacacctttagcaggtatgggatcacctgggtgcgtcaggcccctggacaagggct
tgagtggatgggatgg**atgagcaccgtcactggaaacaca**aactccgcgcagaagttccagggcaga
gtcttcttgaccagagacacatccacgagcacagcctacttggagctgaggagcctgagacctgacg
acacggccgtctattactgt***gcgagaggactatgtcgtgatagcagctgcctaacccccctactacta
ttacggtatggacgtc***tggggcaaaggcaccctggtcaccgtctcctca
(SEQ ID NO: 853)

V_L chain of E2-D10

cagacggtggtgactcaggagccctcactgactgtgtccccaggagggacagtcactctcacctgtg
gctccagcactggagctgtcaccagtggtcattatccctactggttccagcagaagcctggccaagc
ccccaggacactgatttat**gatacaacc**aacagacactcctggactcctgcccggttctcaggctcc
ctccttggggccaaagctgccctgacactgtcaggtgtgcagcctgaggatgaggctgactattact
gc***ttgctctcctatagtggtgatcgagta***ttcggcggagagaccaaactgaccgtcctag
(SEQ ID NO: 854)

Table 80. CTLA4pmpl-Rd2-E2-D11_PelB-F_2021-08-06_A03 (E2-D11) Ab Variable Region nucleic acid sequences

V_H chain of E2-D11

gaggtgcagctggtgcagtctggggctgaggtgaagaagcctggggcctcagtgaaggtttcctgca
aggcatctggatacaccttcaccagctactatatgcactgggtgcgacaggcccctggacaagggct
tgagtggatgggaata**atcaaccctagtggtggtagcaca**agctacgcacagaagttccagggcaga
gtcaccatgaccagggacacgtccacgagcacagtctacatggagctgagcagcctgagatctgagg
acacggccgtgtattactgt***gcgagagaactaaaacgcggggattactactactactacggtatgga
cgtc***tggggccaagggaccacggtcaccgtctcctca
(SEQ ID NO: 855)

V_L chain of E2-D11

cagcctgtgctgactcagccgcactctgtgtcggagtctccggggaagacggtcaccatctcctgca
cccgcagcggtggcagctttgccgacaactatgtgcagtggtaccaacagcgcccgggcagtgcccc
caccttatgatctat**gaacatcac**caaagacccttttggggtccctgatcgattctctggctccatc
gacagctcctccaactctgcctccctcaccatctctggactgaagactgaggacgaggctgactact
actgt***cagtcttatgatagcagcactcccgtggta***ttcggcggagggaccaagctgaccgtcctag
(SEQ ID NO: 856)

[00193] The amino acid sequences of the heavy and light chain complementary determining regions of the CTLA-4 antibodies are shown in Table 53A-B below:

Table 53A. Heavy chain (V_H) complementary determining regions (CDRs) of the CTLA-4 antibodies

Sequence ID	V_H CDR1	V_H CDR2	V_H CDR3
E1-A4	GGTFSTYP **(SEQ ID NO: 25)**	IIPILGTP **(SEQ ID NO: 26)**	AQDNGAFDT **(SEQ ID NO: 27)**
E1-A8	GFTFSSYV **(SEQ ID NO: 28)**	ISGSGGST **(SEQ ID NO: 29)**	ARGGSAWSLDI **(SEQ ID NO: 30)**
E1-A9	GYTFTSYY **(SEQ ID NO: 31)**	INPSGGST **(SEQ ID NO: 32)**	ARELKRGDYYYYYGMDV **(SEQ ID NO: 33)**
E1-A10	GFTFSGYD **(SEQ ID NO: 34)**	IGIRGDT **(SEQ ID NO: 35)**	VRDPSGHGMDV **(SEQ ID NO: 36)**
E1-A12	GDTFSRYG **(SEQ ID NO: 37)**	MSTVTGNT **(SEQ ID NO: 38)**	ARGLCRDSSCLTPYYYYGMDV **(SEQ ID NO: 39)**
E1-B6	GYIFTSYG **(SEQ ID NO: 40)**	ISSYNGNT **(SEQ ID NO: 41)**	ARGPQMDV **(SEQ ID NO:42)**
E1-B10	GFTFSSYA **(SEQ ID NO: 43)**	ISGSGGST **(SEQ ID NO: 44)**	AREEGITGTGFDY **(SEQ ID NO: 45)**
E1-B11	GFTFSDHY **(SEQ ID NO: 46)**	SRNKANSYTT **(SEQ ID NO: 47)**	ARARGYMDV **(SEQ ID NO: 48)**
E1-B12	GDTFSRYG **(SEQ ID NO: 49)**	MSTVTGNT **(SEQ ID NO: 50)**	ARGLCRDSSCLTPYYYYGMDV **(SEQ ID NO: 51)**
T2-C10	GFTFSSYA **(SEQ ID NO: 52)**	ISYDGSNK **(SEQ ID NO: 53)**	ARDFSSSFLLGGY **(SEQ ID NO: 54)**
E1-C12	GYIFTSYG **(SEQ ID NO: 55)**	ISSYNGNT **(SEQ ID NO: 56)**	ARGPQMDV **(SEQ ID NO: 57)**
E2-A4	GFTFSSYV **(SEQ ID NO: 413)**	ISGSGGST **(SEQ ID NO: 414)**	ARGGSAWSLDI **(SEQ ID NO: 415)**
E2-A7	GFTFRSYA **(SEQ ID NO: 416)**	ISYDGDNT **(SEQ ID NO: 417)**	AKLGVTTYAFDI **(SEQ ID NO: 418)**
E2-A10	GGTFSSYA **(SEQ ID NO: 419)**	IIPILGIA **(SEQ ID NO: 420)**	ARDWDY **(SEQ ID NO: 421)**
E2-A12	GFTFSSYA **(SEQ ID NO: 422)**	ISGSGGST **(SEQ ID NO: 423)**	AREEGITGTGFDY **(SEQ ID NO: 424)**
E2-C4	GYTFTSYY **(SEQ ID NO: 425)**	INPSGGST **(SEQ ID NO: 426)**	ARELKRGDYYYYYGMDV **(SEQ ID NO: 427)**
E2-D4	GYTFITDY **(SEQ ID NO: 428)**	LIPSDGST **(SEQ ID NO: 429)**	ARDGSHYDFDN **(SEQ ID NO: 430)**
E2-E5	GFTFSSYA **(SEQ ID NO: 431)**	ITGNGGST **(SEQ ID NO: 432)**	AREEGITGTGFDY **(SEQ ID NO: 433)**
E2-F1	GYIFTSYG **(SEQ ID NO: 434)**	ISSYNGNT **(SEQ ID NO: 435**	ARGPQMDV **(SEQ ID NO: 436)**

Sequence ID	V_H CDR1	V_H CDR2	V_H CDR3
E2-G5	GYTFTSYG (SEQ ID NO: 437)	ISAYNGNT (SEQ ID NO: 438)	ATDLWPIYCSGGSCYETSYYGMDV (SEQ ID NO: 439)
E2-G9	GYTFITDY (SEQ ID NO: 440)	LIPSDGST (SEQ ID NO: 441)	ARDGSHYDFDN (SEQ ID NO: 442)
E2-H5	GYTFTSYY (SEQ ID NO: 443)	INPSGGST (SEQ ID NO: 444)	AREEMAPFLSNYGMDV (SEQ ID NO: 445)
E2-H8	GFTVSSEY (SEQ ID NO: 446)	IYTSGPT (SEQ ID NO: 447)	ARVGNGGGYNL (SEQ ID NO: 448)
E2-H9	GFTFSSYA (SEQ ID NO: 449)	ISGSGTNT (SEQ ID NO: 450)	VREFGGPSNY (SEQ ID NO: 451)
E2-H10	GDTFSRYG (SEQ ID NO: 452)	MSTVTGNT (SEQ ID NO: 453)	ARGLCRDSSCLTPYYYYGMDV (SEQ ID NO: 454)
E1-D7	GFTFSSYG (SEQ ID NO: 58)	ISYSGNT (SEQ ID NO: 59)	ARLPYCSGGNCYDMDV (SEQ ID NO: 60)
T1-E6	GFTFSSYG (SEQ ID NO: 857)	ISYSGNT (SEQ ID NO: 858)	ARLPYCSGGNCYDMDV (SEQ ID NO: 859)
E4-F2	GFTFGDYA (SEQ ID NO: 860)	ITAKAHGGVT (SEQ ID NO: 861)	SNQRWLSSPL (SEQ ID NO: 862)
T1-A3	GFTFGDYA (SEQ ID NO: 863)	IRAKAHGGVT (SEQ ID NO: 864)	SNQRWLSSPL (SEQ ID NO: 865)
T1-A6	GFTFSSYS (SEQ ID NO: 866)	ISSSSSYI (SEQ ID NO: 867)	ARGVGGTMKMDV (SEQ ID NO: 868)
T1-A10	GFGFKNYW (SEQ ID NO: 869)	IKKDGSEK (SEQ ID NO: 870)	ARGHFGMDV (SEQ ID NO: 871)
E2-D5	GFTFVSYA (SEQ ID NO: 872)	ISGSGGDT (SEQ ID NO: 873)	VKSKGGIRKYMEV (SEQ ID NO: 874)
E2-G6	GFTFVNYA (SEQ ID NO: 875)	IIGSGGDT (SEQ ID NO: 876)	VKSKGGIRKYMEV (SEQ ID NO: 877)
E2-H3	GYTFSTYG (SEQ ID NO: 878)	VSAYRRNA (SEQ ID NO: 1000)	ARKRYGAFDV (SEQ ID NO: 879)
E2-H12	GFTVSSEY (SEQ ID NO: 880)	IYTSGPT (SEQ ID NO: 881)	ARVGNGGGYNL (SEQ ID NO: 882)
E2-H2	GYIFTSYG (SEQ ID NO: 883)	ISSYNGNT (SEQ ID NO: 884)	ARGPQMDV (SEQ ID NO: 885)
E2-D10	GDTFSRYG (SEQ ID NO: 886)	MSTVTGNT (SEQ ID NO: 887)	ARGLCRDSSCLTPYYYYGMDV (SEQ ID NO: 888)
E2-D11	GYTFTSYY (SEQ ID NO: 889)	INPSGGST (SEQ ID NO: 890)	ARELKRGDYYYYYGMDV (SEQ ID NO: 891)

Table 53B. Light chain (V_L) complementary determining regions (CDRs) of the CTLA-4 antibodies

Sequence ID	V_L CDR1	V_L CDR2	V_L CDR3
E1-A4	SSDVGGSDY (SEQ ID NO: 61)	EVS (SEQ ID NO: 62)	CSYAGSSTFV (SEQ ID NO: 63)

Sequence ID	V_L CDR1	V_L CDR2	V_L CDR3
E1-A8	QDISNS **(SEQ ID NO: 64)**	GAS **(SEQ ID NO: 65)**	QQGNSFPIT **(SEQ ID NO: 66)**
E1-A9	GGSFADNY **(SEQ ID NO: 67)**	EHH **(SEQ ID NO: 68)**	QSYDSSTPVV **(SEQ ID NO: 69)**
E1-A10	NIGSKS **(SEQ ID NO: 70)**	DDS **(SEQ ID NO: 71)**	QVWANSTVV **(SEQ ID NO: 72)**
E1-A12	TGAVTTGHY **(SEQ ID NO: 73)**	DAT **(SEQ ID NO: 74)**	LLSYSGARV **(SEQ ID NO: 75)**
E1-B6	SSNIGAGYD **(SEQ ID NO: 76)**	GNS **(SEQ ID NO: 77)**	LSWDESLNAYV **(SEQ ID NO: 78)**
E1-B10	SGSVSTSYY **(SEQ ID NO: 79)**	TT.....N **(SEQ ID NO: 80)**	VLYMGSGIWV **(SEQ ID NO: 81)**
E1-B11	SGSIASYF **(SEQ ID NO: 82)**	DDN **(SEQ ID NO: 83)**	QSYHSSTFYV **(SEQ ID NO: 84)**
E1-B12	TGAVTTGHY **(SEQ ID NO: 85)**	DAT **(SEQ ID NO: 86)**	LLSYSGARV **(SEQ ID NO: 87)**
T2-C10	SGHSSYI **(SEQ ID NO: 88)**	LEGSGSY **(SEQ ID NO: 89)**	ETWDSNLPSWV **(SEQ ID NO: 90)**
E1-C12	SSNIGAGYD **(SEQ ID NO: 91)**	GNS **(SEQ ID NO: 92)**	LSWDESLNAYV **(SEQ ID NO: 93)**
E1-D7	SGSIASNY **(SEQ ID NO: 94)**	EDN **(SEQ ID NO: 95)**	QSYDSTNVV **(SEQ ID NO: 96)**
E2-A4	QDISNS **(SEQ ID NO: 455)**	GAS **(SEQ ID NO: 456)**	QQGNSFPIT **(SEQ ID NO: 457)**
E2-A7	SSDVGGYKY **(SEQ ID NO: 458)**	DVS **(SEQ ID NO: 459)**	SSYAGSNSHFV **(SEQ ID NO: 460)**
E2-A10	SGSVSSNYH **(SEQ ID NO: 461)**	NTD **(SEQ ID NO: 462)**	ALYMGSGISI **(SEQ ID NO: 463)**
E2-A12	SGSVSTSYY **(SEQ ID NO: 464)**	TTN **(SEQ ID NO: 465)**	VLYMGSGIWV **(SEQ ID NO: 466)**
E2-C4	GGSFADNY **(SEQ ID NO: 467)**	EHH **(SEQ ID NO: 468)**	QSYDSSTPVV **(SEQ ID NO: 469)**
E2-D4	SSDVGGYNY **(SEQ ID NO: 470)**	EVN **(SEQ ID NO: 471)**	SSYSSSSTLV **(SEQ ID NO: 472)**
E2-E5	SGSISTSYY **(SEQ ID NO: 473)**	TTN **(SEQ ID NO: 474)**	VLYMGSGIWV **(SEQ ID NO: 475)**
E2-F1	SSNIGAGYD **(SEQ ID NO: 476)**	GNS **(SEQ ID NO: 477)**	LSWDESLNAYV **(SEQ ID NO: 478)**
E2-G5	SSNIGSNY **(SEQ ID NO: 479)**	SNN **(SEQ ID NO: 480)**	AAWDDSLSGWV **(SEQ ID NO: 481)**
E2-G9	SSDVGGYNY **(SEQ ID NO: 482)**	EVN **(SEQ ID NO: 483)**	SSYSSSSTLV **(SEQ ID NO: 484)**
E2-H5	SDSLASNY **(SEQ ID NO: 485)**	ENN **(SEQ ID NO: 486)**	QSYDGTPV **(SEQ ID NO: 487)**
E2-H8	SGDVGAHDY **(SEQ ID NO: 488)**	EGS **(SEQ ID NO: 489)**	SSFAGTNNYV **(SEQ ID NO: 490)**

Sequence ID	V_L CDR1	V_L CDR2	V_L CDR3
E2-H9	SSNIGAPYD **(SEQ ID NO: 491)**	ANK **(SEQ ID NO: 492)**	AAWDDSLGGLYV **(SEQ ID NO: 493)**
E2-H10	TGAVTTGHY **(SEQ ID NO: 494)**	DAT **(SEQ ID NO: 495)**	LLSYSGARV **(SEQ ID NO: 496)**
T1-E6	SGSIASNY **(SEQ ID NO: 892)**	EDN **(SEQ ID NO: 893)**	HSYDSTNVV **(SEQ ID NO: 894)**
E4-F2	SSNIGSNT **(SEQ ID NO: 895)**	SNN **(SEQ ID NO: 896)**	AAWDDSLSGQV **(SEQ ID NO: 897)**
T1-A3	SSNIGSNT **(SEQ ID NO: 898)**	SNN **(SEQ ID NO: 899)**	AAWDDSLSGQV **(SEQ ID NO: 900)**
T1-A6	DSNIGSNY **(SEQ ID NO: 901)**	RNN **(SEQ ID NO: 902)**	AAWDDSLSGPV **(SEQ ID NO: 903)**
T1-A10	SLRRYY **(SEQ ID NO: 904)**	GKD **(SEQ ID NO: 905)**	GSRDSSGTRVV **(SEQ ID NO: 906)**
E2-D5	SNNVGNQG **(SEQ ID NO: 907)**	RNG **(SEQ ID NO: 908)**	SAWDRSLVAWV **(SEQ ID NO: 909)**
E2-G6	SNNVGNQG **(SEQ ID NO: 910)**	ING **(SEQ ID NO: 911)**	TAWDRSLVAWV **(SEQ ID NO: 912)**
E2-H3	SNNVGNQG **(SEQ ID NO: 913)**	RNN **(SEQ ID NO: 914)**	SAWDSSLSAVI **(SEQ ID NO: 915)**
E2-H12	SGDVGAHDY **(SEQ ID NO: 916)**	EGS **(SEQ ID NO: 917)**	SSFAGTNNYV **(SEQ ID NO: 918)**
E2-H2	SSNIGAGYD **(SEQ ID NO: 919)**	GNS **(SEQ ID NO: 920)**	LSWDESLNAYV **(SEQ ID NO: 921)**
E2-D10	TGAVTSGHY **(SEQ ID NO: 922)**	DTT **(SEQ ID NO: 923)**	LLSYSGDRV **(SEQ ID NO: 924)**
E2-D11	GGSFADNY **(SEQ ID NO: 925)**	EHH **(SEQ ID NO: 926)**	QSYDSSTPVV **(SEQ ID NO: 927)**

[00194] The nucleic acid sequences of the heavy and light chain complementary determining regions of the CTLA-4 antibodies are shown in Table 54A-B below:

Table 54A. Heavy chain (V_H) complementary determining regions (CDRs) of the CTLA-4 antibodies

Sequence ID	V_H CDR1	V_H CDR2	V_H CDR3
E1-A4	ggaggcacttttag cacctatcct **(SEQ ID NO: 217)**	attatccctatt cttggaacacca **(SEQ ID NO: 218)**	gctcaagacaatggtgctttt gatacc **(SEQ ID NO: 219)**
E1-A8	ggattcacgtttag cagctatgtc **(SEQ ID NO: 220)**	attagtggtagt ggtggtagcaca **(SEQ ID NO: 221)**	gcgagaggaggcagtgcctgg tcgcttgatatc **(SEQ ID NO: 222)**

Sequence ID	V_H CDR1	V_H CDR2	V_H CDR3
E1-A9	ggatacaccttcac cagctactat **(SEQ ID NO: 223)**	atcaaccctagt ggtggtagcaca **(SEQ ID NO: 224)**	gcgagagaactaaaacgcggg gattactactactacggt atggacgtc **(SEQ ID NO: 225)**
E1-A10	ggattcaccttcag tggctacgac **(SEQ ID NO: 226)**	attggtatacgt ggtgacaca **(SEQ ID NO: 227)**	gtaagagatccgtccggccac ggtatggacgtc **(SEQ ID NO: 228)**
E1-A12	ggtgacacctttag caggtatggg **(SEQ ID NO: 229)**	atgagcaccgtc actggaaacaca **(SEQ ID NO: 230)**	gcgagaggactatgtcgtgat agcagctgcctaacccccctac tactattacggtatggacgtc **(SEQ ID NO: 231)**
E1-B6	ggttacatctttac gagttatggt **(SEQ ID NO: 232)**	atcagttcttac aatggtaacaca **(SEQ ID NO: 233)**	gcgagaggtccgcaaatggac gtc **(SEQ ID NO:234)**
E1-B10	ggattcacctttag cagctatgcc **(SEQ ID NO: 235)**	attagtggtagt ggtggtagcaca **(SEQ ID NO: 236)**	gcgagagaagagggtataact ggaactggctttgactac **(SEQ ID NO: 237)**
E1-B11	ggattcacctttag tgaccactac **(SEQ ID NO: 238)**	agtagaaacaaa gctaacagttac accaca **(SEQ ID NO:239)**	gcgagagcgaggggctacatg gacgtc **(SEQ ID NO: 240)**
E1-B12	ggtgacacctttag caggtatggg **(SEQ ID NO: 241)**	atgagcaccgtc actggaaacaca **(SEQ ID NO: 242)**	gcgagaggactatgtcgtgat agcagctgcctaacccccctac tactattacggtatggacgtc **(SEQ ID NO: 243)**
T2-C10	ggattcaccttcag tagctatgct **(SEQ ID NO: 244)**	atatcatatgat ggaagcaataaa **(SEQ ID NO: 245)**	gcgagagatttcagcagctcg ttcctccttggtggctac **(SEQ ID NO: 246)**
E1-C12	ggttacatctttac gagttatggt **(SEQ ID NO: 247)**	atcagttcttac aatggtaacaca **(SEQ ID NO: 248)**	gcgagaggtccgcaaatggac gtc **(SEQ ID NO: 249)**
E1-D7	ggattcaccttcag cagctatggc **(SEQ ID NO: 250)**	atctcttacagt ggcaacact **(SEQ ID NO: 251)**	gccagactgccatattgtagt ggtggtaactgctacgatatg gacgtc **(SEQ ID NO: 252)**
E2-A4	ggattcacgtttag cagctatgtc **(SEQ ID NO: 637)**	attagtggtagt ggtggtagcaca **(SEQ ID NO: 638)**	gcgagaggaggcagtgcctgg tcgcttgatatc **(SEQ ID NO: 639)**
E2-A7	ggattcactttcag gagttacgct **(SEQ ID NO: 640)**	atatcatatgat ggagacaacact **(SEQ ID NO: 641)**	gcgaaactcggggtgactacg tatgcttttgatatc **(SEQ ID NO: 642)**
E2-A10	ggaggcaccttcag cagctatgct **(SEQ ID NO: 643)**	atcatccctatc cttggtatagca **(SEQ ID NO: 644)**	gcgagagattgggactac **(SEQ ID NO: 645)**
E2-A12	ggattcacctttag cagctatgcc **(SEQ ID NO: 646)**	attagtggtagt ggtggtagcaca **(SEQ ID NO: 647)**	gcgagagaagagggtataact ggaactggctttgactac **(SEQ ID NO: 648)**

Sequence ID	V_H CDR1	V_H CDR2	V_H CDR3
E2-C4	ggatacaccttcac cagctactat **(SEQ ID NO: 649)**	atcaaccctagt ggtggtagcaca **(SEQ ID NO: 650)**	gcgagagaactaaaacgcggg gattactactactacggt atggacgtc **(SEQ ID NO: 651)**
E2-D4	ggatacaccttcat caccgactat **(SEQ ID NO: 652)**	ctcatccccagt gatggaagtaca **(SEQ ID NO: 653)**	gcgagagatggtagtcattac gactttgacaac **(SEQ ID NO:654)**
E2-E5	ggattcacctttag cagctatgcc **(SEQ ID NO: 655)**	attactggtaat ggtggtagcaca **(SEQ ID NO: 656)**	gcgagagaagagggtataact ggaactggctttgactac **(SEQ ID NO: 657)**
E2-F1	ggttacatctttac gagttatggt **(SEQ ID NO: 658)**	atcagttcttac aatggtaacaca **(SEQ ID NO:659)**	gcgagaggtccgcaaatggac gtc **(SEQ ID NO: 660)**
E2-G5	ggttacacctttac cagctatggt **(SEQ ID NO: 661)**	atcagcgcttac aatggtaacaca **(SEQ ID NO: 662)**	gcaacagatctatggcccata tattgtagtggtggtagctgc tacgaaacgagctactacggt atggacgtc **(SEQ ID NO: 663)**
E2-G9	ggatacaccttcat caccgactat **(SEQ ID NO: 664)**	ctcatccccagt gatggaagtaca **(SEQ ID NO: 665)**	gcgagagatggtagtcattac gactttgacaac **(SEQ ID NO: 666)**
E2-H5	ggatacaccttcac cagctactat **(SEQ ID NO: 667)**	atcaaccctagt ggtggtagcaca **(SEQ ID NO: 668)**	gcgagagaggagatggccccg ttcctttcgaactacggtatg gacgtc **(SEQ ID NO: 669)**
E2-H8	gggttcaccgtcag cagcgagtac **(SEQ ID NO: 670)**	atttatacaagt ggtcccacc **(SEQ ID NO: 671)**	gcgagagtagggaatggaggt ggctacaatttg **(SEQ ID NO: 672)**
E2-H9	ggattcacgtttag cagctatgcc **(SEQ ID NO: 673)**	ataagtggtagt ggcactaataca **(SEQ ID NO: 674)**	gttagagagttcggtggtccc tcaaactac **(SEQ ID NO: 675)**
E2-H10	ggtgacacctttag caggtatggg **(SEQ ID NO: 676)**	atgagcaccgtc actggaaacaca **(SEQ ID NO: 677)**	gcgagaggactatgtcgtgat agcagctgcctaacccctac tactattacggtatggacgtc **(SEQ ID NO: 678)**
T1-E6	ggattcaccttcag cagctatggc **(SEQ ID NO: 928)**	atctcttacagt ggcaacact **(SEQ ID NO: 929)**	gccagactgccatattgtagt ggtggtaactgctacgatatg gacgtc **(SEQ ID NO: 930)**
E4-F2	ggattcacctttgg tgattatgct **(SEQ ID NO: 931)**	attacagccaag gctcacggtggg gtaaca **(SEQ ID NO: 932)**	agtaatcaacgatggttgtcg tcgcctctc **(SEQ ID NO: 933)**
T1-A3	ggattcacctttgg tgattatgct **(SEQ ID NO: 934)**	attagagccaag gctcacggtggg gtaaca **(SEQ ID NO: 935)**	agtaatcaacgatggttgtcg tcgcctctc **(SEQ ID NO: 936)**

Sequence ID	V_H CDR1	V_H CDR2	V_H CDR3
T1-A6	ggattcacctttag tagctatagc **(SEQ ID NO: 937)**	attagtagtagt agtagttacata **(SEQ ID NO: 938)**	gcgagaggtgtcgggggtact atgaagatggacgtc **(SEQ ID NO: 939)**
T1-A10	ggattcgggtttaa gaactactgg **(SEQ ID NO: 940)**	ataaagaaagat ggaagtgagaaa **(SEQ ID NO: 941)**	gcgaggggtcatttcggtatg gacgtc **(SEQ ID NO: 942)**
E2-D5	ggattcacctttgt cagctatgcc **(SEQ ID NO: 943)**	attagtggtagt ggtggtgacaca **(SEQ ID NO: 944)**	gtgaagtcaaaaggggaata cgaaagtatatggaggtc **(SEQ ID NO: 945)**
E2-G6	ggattcacctttgt caactatgcc **(SEQ ID NO: 946)**	attattggtagt ggtggtgacaca **(SEQ ID NO: 947)**	gtgaagtcaaaaggggaata cgaaagtatatggaggtc **(SEQ ID NO: 948)**
E2-H3	ggttacaccttctc cacttatggt **(SEQ ID NO: 949)**	gtcagcgcttac agacgtaacgca **(SEQ ID NO: 950)**	gcgagaaagcgctacggtgct tttgatgtc **(SEQ ID NO: 951)**
E2-H12	gggttcaccgtcag cagcgagtac **(SEQ ID NO: 952)**	atttatacaagt ggtcccacc **(SEQ ID NO: 953)**	gcgagagtagggaatggaggt ggctacaatttg **(SEQ ID NO: 954)**
E2-H2	ggttacatctttac gagttatggt **(SEQ ID NO: 955)**	atcagttcttac aatggtaacaca **(SEQ ID NO: 956)**	gcgagaggtccgcaaatggac gtc **(SEQ ID NO: 957)**
E2-D10	ggtgacacctttag caggtatggg **(SEQ ID NO: 958)**	atgagcaccgtc actggaaacaca **(SEQ ID NO: 959)**	gcgagaggactatgtcgtgat agcagctgcctaacccctac tactattacggtatggacgtc **(SEQ ID NO: 960)**
E2-D11	ggatacaccttcac cagctactat **(SEQ ID NO: 961)**	atcaaccctagt ggtggtagcaca **(SEQ ID NO: 962)**	gcgagagaactaaaacgcggg gattactactactacggt atggacgtc **(SEQ ID NO: 963)**

Table 54B. Light chain (V_L) complementary determining regions (CDRs) of the CTLA-4 antibodies

Sequence ID	V_L CDR1	V_L CDR2	V_L CDR3
E1-A4	agcagtgatgttggt ggttctgactat **(SEQ ID NO: 253)**	gaggtcagt **(SEQ ID NO: 254)**	tgttcatatgctggaagtag tacttttgtc **(SEQ ID NO: 255)**
E1-A8	caggatattagcaac tcg **(SEQ ID NO: 256)**	ggtgcatcc **(SEQ ID NO: 257)**	caacagggtaacagtttccc gatcacc **(SEQ ID NO: 258)**
E1-A9	ggtggcagctttgcc gacaactat **(SEQ ID NO: 259)**	gaacatcac **(SEQ ID NO: 260)**	cagtcttatgatagcagcac tcccgtggta **(SEQ ID NO: 261)**
E1-A10	aacattggaagtaaa agt **(SEQ ID NO: 262)**	gatgacagc **(SEQ ID NO: 263)**	caggtgtgggccaacagcac tgtggtc **(SEQ ID NO: 264)**

Sequence ID	V_L CDR1	V_L CDR2	V_L CDR3
E1-A12	actggagctgtcacc actggtcattat **(SEQ ID NO: 265)**	gatgcaact **(SEQ ID NO: 266)**	ctgctctcctatagtggtgc tcgggtg **(SEQ ID NO: 267)**
E1-B6	agctccaacatcggg gcaggttatgat **(SEQ ID NO: 268)**	ggtaacagc **(SEQ ID NO: 269)**	ctatcatgggatgaaagcct gaatgcttatgtc **(SEQ ID NO: 270)**
E1-B10	tctggctcagtctct actagttactac **(SEQ ID NO: 271)**	accacaaac **(SEQ ID NO: 272)**	gtcctatatatgggtagtgg catttgggtg **(SEQ ID NO: 273)**
E1-B11	agtggcagcattgcc agctacttt **(SEQ ID NO: 274)**	gacgataac **(SEQ ID NO: 275)**	cagtcttatcatagcagcac cttttatgtc **(SEQ ID NO: 276)**
E1-B12	actggagctgtcacc actggtcattat **(SEQ ID NO: 277)**	gatgcaact **(SEQ ID NO: 278)**	ctgctctcctatagtggtgc tcgggtg **(SEQ ID NO: 279)**
T2-C10	agtgggcacagtagc tacatc **(SEQ ID NO: 280)**	cttgaaggtagt ggaagctac **(SEQ ID NO: 281)**	gagacctgggacagtaacct cccttcttgggtg **(SEQ ID NO: 282)**
E1-C12	agctccaacatcggg gcaggttatgat **(SEQ ID NO: 283)**	ggtaacagc **(SEQ ID NO: 284)**	ctatcatgggatgaaagcct gaatgcttatgtc **(SEQ ID NO: 285)**
E1-D7	agtggcagcattgcc agcaactat **(SEQ ID NO: 286)**	gaggataac **(SEQ ID NO: 287)**	cagtcttatgatagcaccaa tgtggta **(SEQ ID NO: 288)**
E2-A4	caggatattagcaac tcg **(SEQ ID NO: 679)**	ggtgcatcc **(SEQ ID NO: 680)**	caacagggtaacagtttccc gatcacc **(SEQ ID NO: 681)**
E2-A7	agcagtgatgttggt ggttataagtat **(SEQ ID NO: 682)**	gatgtcagt **(SEQ ID NO: 683)**	agctcatatgcaggcagcaa cagtcattttgtc **(SEQ ID NO: 684)**
E2-A10	tctggctcggtctct agtaactatcac **(SEQ ID NO: 685)**	aatacagac **(SEQ ID NO: 686)**	gctctctatatgggtagcgg catttcgata **(SEQ ID NO: 687)**
E2-A12	tctggctcagtctct actagttactac **(SEQ ID NO: 688)**	accacaaac **(SEQ ID NO: 689)**	gtcctatatatgggtagtgg catttgggtg **(SEQ ID NO: 690)**
E2-C4	ggtggcagctttgcc gacaactat **(SEQ ID NO: 691)**	gaacatcac **(SEQ ID NO: 692)**	cagtcttatgatagcagcac tcccgtggta **(SEQ ID NO: 693)**
E2-D4	agcagtgatgttggt ggttataactat **(SEQ ID NO: 694)**	gaggtcaat **(SEQ ID NO: 695)**	agctcatattcgagcagcag cactttggtc **(SEQ ID NO: 696)**
E2-E5	tctggctcaatctct actagttactac **(SEQ ID NO: 697)**	accacaaac **(SEQ ID NO: 698)**	gtcctatatatgggtagtgg catttgggtg **(SEQ ID NO: 699)**
E2-F1	agctccaacatcggg gcaggttatgat	ggtaacagc **(SEQ ID NO: 701)**	ctatcatgggatgaaagcct gaatgcttatgtc

Sequence ID	V_L CDR1	V_L CDR2	V_L CDR3
	(SEQ ID NO: 700)		**(SEQ ID NO: 702)**
E2-G5	agctccaacatcggaagtaattat **(SEQ ID NO: 703)**	agtaataat **(SEQ ID NO: 704)**	gcagcatgggatgacagcctgagtggttgggtg **(SEQ ID NO: 705)**
E2-G9	agcagtgatgttggtggttataactat **(SEQ ID NO: 706)**	gaggtcaat **(SEQ ID NO: 707)**	agctcatattcgagcagcagcactttggtc **(SEQ ID NO: 708)**
E2-H5	agtgacagccttgccagcaactat **(SEQ ID NO: 709)**	gaaaataac **(SEQ ID NO: 710)**	cagtcctatgatggcaccccggtg **(SEQ ID NO: 711)**
E2-H8	agcggtgacgttggtgcgcatgactat **(SEQ ID NO: 712)**	gagggcagt **(SEQ ID NO: 713)**	agctcatttgcaggaaccaacaattacgtc **(SEQ ID NO: 714**
E2-H9	agctccaacatcggggcaccttatgat **(SEQ ID NO: 715)**	gctaacaag **(SEQ ID NO: 716)**	gcagcctgggatgacagcctgggtggtctttatgtc **(SEQ ID NO: 717)**
E2-H10	actggagctgtcaccactggtcattat **(SEQ ID NO: 718)**	gatgcaact **(SEQ ID NO: 719)**	ctgctctcctatagtggtgctcgggtg **(SEQ ID NO: 720)**
T1-E6	agtggcagcattgccagcaactat **(SEQ ID NO: 964)**	gaggataac **(SEQ ID NO: 965)**	cattcttatgatagcaccaatgtggta **(SEQ ID NO: 966)**
E4-F2	agctccaacatcggaagtaatact **(SEQ ID NO: 967)**	agtaataat **(SEQ ID NO: 968)**	gcagcatgggatgacagcctgagtggtcaagtg **(SEQ ID NO: 969)**
T1-A3	agctccaacatcggaagtaatact **(SEQ ID NO: 970)**	agtaataat **(SEQ ID NO: 971)**	gcagcatgggatgacagcctgagtggtcaagtg **(SEQ ID NO: 972)**
T1-A6	gactccaacatcggaagtaattat **(SEQ ID NO: 973)**	aggaataat **(SEQ ID NO: 974)**	gcagcatgggatgacagcctgagtggtccggtg **(SEQ ID NO: 975)**
T1-A10	agcctcagaaggtattat **(SEQ ID NO: 976)**	ggcaaagac **(SEQ ID NO: 977)**	ggctcacgggacagcagtggcacccgtgtggtc **(SEQ ID NO: 978)**
E2-D5	agcaacaatgttggcaaccaagga **(SEQ ID NO: 979)**	agaaatggc **(SEQ ID NO: 980)**	tcagcatgggacaggagcctcgtagcttgggtg **(SEQ ID NO: 981)**
E2-G6	agcaacaatgttggcaaccaagga **(SEQ ID NO: 982)**	ataaatggc **(SEQ ID NO: 983)**	acagcatgggacaggagcctcgtagcttgggtg **(SEQ ID NO: 984)**
E2-H3	agcaacaatgttggcaaccaagga **(SEQ ID NO: 985)**	aggaataac **(SEQ ID NO: 986)**	tcagcatgggacagcagcctcagtgctgtgata **(SEQ ID NO: 987)**
E2-H12	agcggtgacgttggtgcgcatgactat **(SEQ ID NO: 988)**	gagggcagt **(SEQ ID NO: 989)**	agctcatttgcaggaaccaacaattacgtc **(SEQ ID NO: 990)**

Sequence ID	V_L CDR1	V_L CDR2	V_L CDR3
E2-H2	caggatattagcaactcg **(SEQ ID NO: 991)**	ggtgcatcc **(SEQ ID NO: 992)**	caacagggtaacagtttcccgatcacc **(SEQ ID NO: 993)**
E2-D10	actggagctgtcaccagtggtcattat **(SEQ ID NO: 994)**	gatacaacc **(SEQ ID NO: 995)**	ttgctctcctatagtggtgatcgagta **(SEQ ID NO: 996)**
E2-D11	ggtggcagctttgccgacaactat **(SEQ ID NO: 997)**	gaacatcac **(SEQ ID NO: 998)**	cagtcttatgatagcagcactcccgtggta **(SEQ ID NO:999)**

[00195] The amino acid sequences of the heavy and light chain framework regions of the CTLA4 antibodies are shown in Table 55A-B below:

Table 55A. Heavy chain (V_H) framework regions (FRs) of the CTLA-4 antibodies

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
E1-A4	QVQLVQSGAEVKKPGSSVKVSCKAS **(SEQ ID NO: 97)**	ISWVRQAPGQGLEWMGG **(SEQ ID NO: 98)**	KYAQKFQDRVTITADESTSTAYMELSSLRSDDTAAYYC **(SEQ ID NO: 99)**	WGQGTMVTVSS **(SEQ ID NO: 100)**
E1-A8	QVQLVQSGGGLVQPGGSLRLSCAAS **(SEQ ID NO: 101)**	MSWVRQAPGKGLEWVSS **(SEQ ID NO: 102)**	DYADSVKGRFPISRDNSKNTLYLEMNSLRAEDTAVYYC **(SEQ ID NO: 103)**	WGQGTTVTVSS **(SEQ ID NO: 104)**
E1-A9	EVQLVQSGAEVKKPGASVKVSCKAS **(SEQ ID NO: 105)**	MHWVRQAPGQGLEWMGI **(SEQ ID NO: 106)**	SYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC **(SEQ ID NO: 107)**	WGQGTTVTVSS **(SEQ ID NO: 108)**
E1-A10	QVQLVQSGGGLVQSGGSLRLSCAAS **(SEQ ID NO: 109)**	MHWVRQAAGKGLEWVSN **(SEQ ID NO: 110)**	YYSDSVKGRFIISRENAKSSLYLQMNSLRAGDTAVYYC **(SEQ ID NO: 111)**	WGKGTTVTVSS **(SEQ ID NO: 112)**
E1-A12	QVQLVQSGGEVKKPGASVKVSCKAS **(SEQ ID NO: 113)**	ITWVRQAPGQGLEWMGW **(SEQ ID NO: 114)**	NSAQKFQGRVFLTRDTSTSTAYLELRSLRPDDTAVYYC **(SEQ ID NO: 115)**	WGKGTLVTVSS **(SEQ ID NO: 116)**
E1-B6	QVQLQQSGTEVKKPGASVKVSCKAS	FTWVRQAPGQGLEWMGW **(SEQ ID NO: 118)**	DYAQKFEGRVTMTTDTSTTTAYMELRGLKSDDTAMYYC	WGQGTTVTVSS **(SEQ ID NO: 120)**

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
	(SEQ ID NO: 117)		**(SEQ ID NO: 119)**	
E1-B10	QVQLVQSGGGLVQPGGSLRLSCAAS **(SEQ ID NO: 121)**	MSWVRQAPGKGLEWVSA **(SEQ ID NO: 122)**	YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC **(SEQ ID NO: 123)**	WGQGTLVTVSS **(SEQ ID NO: 124)**
E1-B11	EVQLVQSGGGLVQPGGSLRLSCAAS **(SEQ ID NO: 125)**	MDWVRQAPGKGLEWVGR **(SEQ ID NO: 126)**	EYAASVKGRFTISRDESENSLYLQMNSLRAEDTAVYYC **(SEQ ID NO: 127)**	WGKGTTVTVSS **(SEQ ID NO:128)**
E1-B12	QVQLVQSGGEVKKPGASVKVSCKAS **(SEQ ID NO: 129)**	ITWVRQAPGQGLEWMGW **(SEQ ID NO: 130)**	NSAQKFQGRVFLTRDTSTSTAYLELRSLRPDDTAVYYC **(SEQ ID NO: 131)**	WGKGTLVTVSS **(SEQ ID NO: 132)**
T2-C10	EVQLVQSGGGVVQPGRSLRLSCAAS **(SEQ ID NO: 133)**	MHWVRQAPGKGLEWVAV **(SEQ ID NO: 134)**	YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC **(SEQ ID NO: 135)**	WGQGTLVTVSS **(SEQ ID NO: 136)**
E1-C12	QVQLVQSGAEVKKPGASVKVSCKAS **(SEQ ID NO: 137)**	FTWVRQAPGQGLEWMGW **(SEQ ID NO: 138)**	DYAQKFEGRVTMTTDTSTTTAYMELRGLKSDDTAMYYC **(SEQ ID NO: 139)**	WGQGTTVTVSS **(SEQ ID NO: 140)**
E1-D7	QVQLQESGGGVVQPGRSLRLSCAAS **(SEQ ID NO: 141)**	MHWVRQPPGEGLEWIGH **(SEQ ID NO: 142)**	YYNPSLRSRFSISKDTSKNQFSLHLRSVTAADTAVYYC **(SEQ ID NO: 143)**	WGQGTLVTVSS **(SEQ ID NO: 144)**
E2-A4	QVQLVQSGGGLVQPGGSLRLSCAAS **(SEQ ID NO: 497)**	MSWVRQAPGKGLEWVSS **(SEQ ID NO: 498)**	DYADSVKGRFPISRDNSKNTLYLEMNSLRAEDTAVYYC **(SEQ ID NO: 499)**	WGQGTTVTVSS **(SEQ ID NO: 500)**
E2-A7	QVQLVQSGGSVVRPGRSLRLACAAS **(SEQ ID NO: 501)**	MHWVRQTPGKGLEWVAV **(SEQ ID NO: 502)**	FYADAVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC **(SEQ ID NO: 503)**	WGQGTLVTVSS **(SEQ ID NO: 504)**
E2-A10	QVQLQQSGAEVKKPGSSVKVSCKAS **(SEQ ID NO: 505)**	ISWVRQAPGQGLEWMGR **(SEQ ID NO: 506)**	NYAQKFQGRVTITADESTSTAYMELSSLRSEDTAVYYC **(SEQ ID NO: 507)**	WGQGTLVTVSS **(SEQ ID NO: 508)**

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
E2-A12	QVQLVQSGGGLVQPGGSLRLSCAAS **(SEQ ID NO: 509)**	MSWVRQAPGKGLEWVSA **(SEQ ID NO: 510)**	YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC **(SEQ ID NO: 511)**	WGQGTLVTVSS **(SEQ ID NO: 512)**
E2-C4	EVQLVQSGAEVKKPGASVKVSCKAS **(SEQ ID NO: 513)**	MHWVRQAPGQGLEWMGI **(SEQ ID NO: 514)**	SYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC **(SEQ ID NO: 515)**	WGQGTTVTVSS **(SEQ ID NO: 516)**
E2-D4	QVQLVQSGAEVKKPGASVKLSCKGS **(SEQ ID NO: 517)**	IHWVRQAPGQGLEWMGR **(SEQ ID NO: 518)**	IYAQKFRGRVTMTRDTSTRTVYMELSSLRSEDTALYYC **(SEQ ID NO: 519)**	WGQGTLVTVSS **(SEQ ID NO: 520)**
E2-E5	QVQLVQSGGGLVQPGGSLRLSCAAS **(SEQ ID NO: 521)**	MSWVRQAPGKGLEWVSS **(SEQ ID NO: 522)**	YYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC **(SEQ ID NO: 523)**	WGQGTLVTVSS **(SEQ ID NO: 524)**
E2-F1	QVQLVQSGAEVKKPGASVKVSCKAS **(SEQ ID NO: 525)**	FTWVRQAPGQGLEWMGW **(SEQ ID NO: 526)**	DYAQKFEGRVTMTTDTSTTTAYMELRGLKSDDTAMYYC **(SEQ ID NO: 527)**	WGQGTTVTVSS **(SEQ ID NO:528)**
E2-G5	EVQLVESGA.EVRKPGESLTISCKAS **(SEQ ID NO: 529)**	ISWVRQAPGQGLEWMGW **(SEQ ID NO: 530)**	NYAQKLQ.GRVTMTTDTSTSTAYMELRSLRSDDTAVYYC **(SEQ ID NO: 531)**	WGQGTLVTVSS **(SEQ ID NO: 532)**
E2-G9	QVQLVQSGAEVKKPGASVKLSCKGS **(SEQ ID NO: 533)**	IHWVRQAPGQGLEWMGR **(SEQ ID NO: 534)**	IYAQKFRGRVTMTRDTSTRTVYMELSSLRSEDTALYYC **(SEQ ID NO: 535)**	WGQGTLVTVSS **(SEQ ID NO: 536)**
E2-H5	EVQLVESGAEVKKPGASVKVSCKAS **(SEQ ID NO: 537)**	MHWVRQAPGQGLEWMGI **(SEQ ID NO: 538)**	SYAQKFQGRVTMTRDMSTSTVYMELSSLRSEDTAVYYC **(SEQ ID NO: 539)**	WGQGTMVTVSS **(SEQ ID NO: 540)**
E2-H8	EVQLVQSGGGLIQPGGSLRLSCAAS **(SEQ ID NO: 541)**	MTWVRQAPGKGLEWVSN **(SEQ ID NO: 542)**	YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC **(SEQ ID NO: 543)**	WGQGTLVTVSS **(SEQ ID NO: 544)**
E2-H9	EVQLVESGGGLVQPGGSLRLPCAAS	MSWVRQAPGKGLEWVSV	HYADSVKGRFTISRDNFKNTVYLQ	WGQGTLVTVSS **(SEQ ID NO: 548)**

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
	(SEQ ID NO: 545)	**(SEQ ID NO: 546)**	VNSPRAEDTAVY YC **(SEQ ID NO: 547)**	
E2-H10	QVQLVQSGGEV KKPGASVKVSC KAS **(SEQ ID NO: 549)**	ITWVRQAPGQ GLEWMGW **(SEQ ID NO: 550)**	NSAQKFQGRVFL TRDTSTSTAYLE LRSLRPDDTAVY YC **(SEQ ID NO: 551)**	WGKGTLVTVSS **(SEQ ID NO: 552)**
T1-E6	QVQLQESGG.G VVQPGRSLRLS CAAS **(SEQ ID NO: [ ])**	MHWVRQPPGE GLEWIGH **(SEQ ID NO: [ ])**	YYNPSLRSRFSI SKDTSKNQFSLH LRSVTAADTAVY YC **(SEQ ID NO: [ ])**	WGQGTLVTVSS **(SEQ ID NO: [ ])**
E4-F2	QVQLVQSGG.G LVQPGRSLRLS CRGS **(SEQ ID NO: [ ])**	MSWVRQAPGK GLEWIAF **(SEQ ID NO: [ ])**	EYAASVKGRFTI SRDDSKNTAYLQ MNSLKTEDTAVY YC **(SEQ ID NO: [ ])**	WGQGTTVTVSS **(SEQ ID NO: [ ])**
T1-A3	QVQLVQSGG.G LVQPGRSLRLS CRGS **(SEQ ID NO: [ ])**	MSWVRQAPGK GLEWIAF **(SEQ ID NO: [ ])**	EYAASVKGRFTI SRDDSKNTAYLQ MNSLKTEDTAVY YC **(SEQ ID NO: [ ])**	WGQGTTVTVSS **(SEQ ID NO: [ ])**
T1-A6	QVQLVQSGGGL VQPGGSLRLSC AAS **(SEQ ID NO: [ ])**	MNWVRQAPGK GLEWVSS **(SEQ ID NO: [ ])**	YYADSVKGRFTI SRDNAKNSLYLQ MNSLRDEDTAVY YC **(SEQ ID NO: [ ])**	WGQGTLVTVSS **(SEQ ID NO: [ ])**
T1-A10	QVQLVQSGGGL VQPGGSLRLSC AAS **(SEQ ID NO: [ ])**	MTWVRQAPGK GLEWVAN **(SEQ ID NO: [ ])**	YYVDSVKGRFTS SRDNAKNSLYLQ MNSLRAEDTAVY YC **(SEQ ID NO: [ ])**	WGPGTTVTVSS **(SEQ ID NO: [ ])**
E2-D5	QVQLVQSGGGL VQPGGSLRLSC AAS **(SEQ ID NO: [ ])**	MSWVRQAPGK GLEWVSS **(SEQ ID NO: [ ])**	YYADSVKGRFTI SRDNSESRLYLQ MNSLGPEDTALY YC **(SEQ ID NO: [ ])**	WGQGTMVTVSS **(SEQ ID NO: [ ])**
E2-G6	QVPWCVWGRLG PAWGVPDTLLC AS **(SEQ ID NO: [ ])**	MTWIRQAPGK GLEWVSC **(SEQ ID NO: [ ])**	YYAHSVKGRITI SKDNSQSRLYLL MNMLGPEDSVLY YC **(SEQ ID NO: [ ])**	WGQGTMVTVSS **(SEQ ID NO: [ ])**
E2-H3	EVQLVQSGPEV KKPGDSVKVPC KAS **(SEQ ID NO: [ ])**	ISWVRQAPGQ GLEWMGW **(SEQ ID NO: [ ])**	NYAQKFQDRVTM TTDTSTNTAYME LKSLRSDDTAIY FC **(SEQ ID NO: [ ])**	WGQGTMVTVSS **(SEQ ID NO: [ ])**

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
E2-H12	EVQLVQSGGGLIQPGGSLRLSCAAS **(SEQ ID NO: [ ])**	MTWVRQAPGKGLEWVSN **(SEQ ID NO: [ ])**	YYADSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYC **(SEQ ID NO: [ ])**	WGQGTLVTVSS **(SEQ ID NO: [ ])**
E2-H2	QVQLQQSGTEVKKPGASVKVSCKAS **(SEQ ID NO: [ ])**	FTWVRQAPGQGLEWMGW **(SEQ ID NO: [ ])**	DYAQKFEGRVTMTTDTSTTTAYMELRGLKSDDTAMYYC **(SEQ ID NO: [ ])**	WGQGTTVTVSS **(SEQ ID NO: [ ])**
E2-D10	QVQLVQSGGEVKKPGASVKVSCKAS **(SEQ ID NO: [ ])**	ITWVRQAPGQGLEWMGW **(SEQ ID NO: [ ])**	NSAQKFQGRVFLTRDTSTSTAYLELRSLRPDDTAVYYC **(SEQ ID NO: [ ])**	WGKGTLVTVSS **(SEQ ID NO: [ ])**
E2-D11	EVQLVQSGAEVKKPGASVKVSCKAS **(SEQ ID NO: [ ])**	MHWVRQAPGQGLEWMGI **(SEQ ID NO: [ ])**	SYAQKFQGRVTMTRDTSTSTVYMELSSLRSEDTAVYYC **(SEQ ID NO: [ ])**	WGQGTTVTVSS **(SEQ ID NO: [ ])**

Table 55B. Light chain (V_L) framework regions (FRs) of the CTLA-4 antibodies

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
E1-A4	QSALTQPRSVSGSPGQSVTISCTGT **(SEQ ID NO: 145)**	VSWYQQHPGKAPKLIIY **(SEQ ID NO: 146)**	KRPSGVSDRFSGSKSGNTASLRISGLQAQDEADYYC **(SEQ ID NO: 147)**	FGSGTEVTVL **(SEQ ID NO: 148)**
E1-A8	DIQMTQSPSSVSASIGDRVTITCRAS **(SEQ ID NO: 149)**	LAWYQQKPGKAPKLLIY **(SEQ ID NO: 150)**	NLRSGVPSRFSGGGSGTYFTLTISSLQPEDFATYYC **(SEQ ID NO: 151)**	FGQGTRLEIK **(SEQ ID NO: 152)**
E1-A9	QPVLTQPHSVSESPGKTVTISCTRS **(SEQ ID NO: 153)**	VQWYQQRPGSAPTLMIY **(SEQ ID NO: 154)**	QRPFGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYC **(SEQ ID NO: 155)**	FGGGTKLTVL **(SEQ ID NO: 156)**
E1-A10	QPVLTQPPSVSVAPGQTARITCGGN **(SEQ ID NO: 157)**	VHWYQQKPGQAPVLVVY **(SEQ ID NO: 158)**	DRPSGIPERFSGSNSGNTATLTISRVEAGDEADYYC **(SEQ ID NO: 159)**	FGGGTKVTVL **(SEQ ID NO: 160)**
E1-A12	QTVVTQEPSLTVSPGGTVTLTCGSS	PYWFQQKPGQAPTTLIY **(SEQ ID NO: 162)**	HKHSWTPARFSGSVLGGKAALTLSGAQPEDEADYYC **(SEQ ID NO: 163)**	FGGGTKLTVL

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
	(SEQ ID NO: 161)			**(SEQ ID NO: 164)**
E1-B6	QSVLTQPPSVSGAPGQRVTISCTGS **(SEQ ID NO: 165)**	VHWYQQLPGTAPKLLIY **(SEQ ID NO: 166)**	SRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYC **(SEQ ID NO: 167)**	FGSGTKVTVL **(SEQ ID NO: 168)**
E1-B10	QTVVTQEPSFSVSPGGTVTLTCGLS **(SEQ ID NO: 169)**	PSWYQQTPGQAPRTLIY **(SEQ ID NO: 170)**	TRSSGVPDRFSGSILGNKAALTITGAQADDESDYYC **(SEQ ID NO: 171)**	FGGGTKLTVL **(SEQ ID NO: 172)**
E1-B11	NFMLTHPHSVSESPGKTVTISCTRS **(SEQ ID NO: 173)**	VQWYQQRPGSSPTTVIY **(SEQ ID NO:174)**	QRPSGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYC **(SEQ ID NO: 175)**	FGTGTKVTVL **(SEQ ID NO:176)**
E1-B12	QTVVTQEPSLTVSPGGTVTLTCGSS **(SEQ ID NO: 177)**	PYWFQQKPGQAPTTLIY **(SEQ ID NO:178)**	HKHSWTPARFSGSVLGGKAALTLSGAQPEDEADYYC **(SEQ ID NO: 179)**	FGGGTKLTVL **(SEQ ID NO:180)**
T2-C10	LPVLTQSSSASASLGSSVKLTCTLS **(SEQ ID NO: 181)**	IAWHQQQPGKAPRYLMK **(SEQ ID NO: 182)**	NKGSGVPDRFSGSSSGADRYLTISNLQSEDEADYYC **(SEQ ID NO: 183)**	FGGGTKLTVL **(SEQ ID NO: 184)**
E1-C12	QSVLTQPPSVSGAPGQRVTISCTGS **(SEQ ID NO: 185)**	VHWYQQLPGTAPKLLIY **(SEQ ID NO: 186)**	SRPSGVPDRFSGSKSGTSPSLAISGLQSEDEADYYC **(SEQ ID NO: 187)**	FGSGTKVTVL **(SEQ ID NO: 188)**
E1-D7	NFMLTQPHSMSESPGKTVTISCTRS **(SEQ ID NO: 189)**	VQWFQQRPGSAPTTVIY **(SEQ ID NO:190)**	QRPSGVPDRFSGSIDRSSNSASLIISGLKTEDEADYYC **(SEQ ID NO: 191)**	FGGGTKLTVL **(SEQ ID NO:192)**
E2-A4	DIQMTQSPSSVSASIGDRVTITCRAS **(SEQ ID NO: 553)**	LAWYQQKPGKAPKLLIY **(SEQ ID NO: 554)**	NLRSGVPSRFSGGGSGTYFTLTISSLQPEDFATYYC **(SEQ ID NO: 555)**	FGQGTRLEIK **(SEQ ID NO: 556)**
E2-A7	QSALTQPRSVSGSPGQSVTISCTGT **(SEQ ID NO: 557)**	VSWYQHHPGKAPKLMIY **(SEQ ID NO: 558)**	ERPSGVPDRFSGSKSGNTASLTISGLQAEDEADYYC **(SEQ ID NO: 559)**	FGTGTKVTVL **(SEQ ID NO: 560)**

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
E2-A10	QTVVTQEPSFSVAPGGTVTLTCALS **(SEQ ID NO: 561)**	PSWFQQTPGQAPRTLIY **(SEQ ID NO: 562)**	IRSHGVPDRFSGSLLGNKAALTITGAQPNDESEYYC **(SEQ ID NO: 563)**	FGGGTKVTVL **(SEQ ID NO: 564)**
E2-A12	QTVVTQEPSFSVSPGGTVTLTCGLS **(SEQ ID NO: 565)**	PSWYQQTPGQAPRTLIY **(SEQ ID NO: 566)**	TRSSGVPDRFSGSILGNKAALTITGAQADDESDYYC **(SEQ ID NO: 567)**	FGGGTKLTVL **(SEQ ID NO: 568)**
E2-C4	QPVLTQPHSVSESPGKTVTISCTRS **(SEQ ID NO: 569)**	VQWYQQRPGSAPTLMIY **(SEQ ID NO: 570)**	QRPFGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYC **(SEQ ID NO: 571)**	FGGGTKLTVL **(SEQ ID NO: 572)**
E2-D4	QPVLTQPRSVSGSPGQSVTISCTGT **(SEQ ID NO: 573)**	VSWYQQHPGKAPKLIIY **(SEQ ID NO: 574)**	KRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYC **(SEQ ID NO: 575)**	FGGGTKLTVL **(SEQ ID NO: 576)**
E2-E5	HTVVTQEPSFSVTPGGTVTLTCGLS **(SEQ ID NO: 577)**	PIWYQHTPGQAPRTLIY **(SEQ ID NO: 578)**	TPSSGVPDRFSGSILGNKAALTITGAQEDDESDYYC **(SEQ ID NO: 579)**	FGGRTKLTVL **(SEQ ID NO: 580)**
E2-F1	QSVLTQPPSVSGAPGQRVTISCTGS **(SEQ ID NO: 581)**	VHWYQQLPGTAPKLLIY **(SEQ ID NO:582)**	SRPSGVPDRFSGSKSGTSASLAISGLQSEDEADYYC **(SEQ ID NO: 583)**	FGSGTKVTVL **(SEQ ID NO:584)**
E2-G5	QPGLTQPPSASGTPGQRVTLSCSGS **(SEQ ID NO: 585)**	VFWYQQLPGTAPKLLIY **(SEQ ID NO:586)**	QRPSGVPDRFSASKSGTSASLAISGLRSEDEADYYC **(SEQ ID NO: 587)**	FGGGTKLTVL **(SEQ ID NO:588)**
E2-G9	QPVLTQPRSVSGSPGQSVTISCTGT **(SEQ ID NO: 589)**	VSWYQQHPGKAPKLIIY **(SEQ ID NO: 590)**	KRPSGVPDRFSGSKSGNTASLTVSGLQAEDEADYYC **(SEQ ID NO: 591)**	FGGGTKLTVL **(SEQ ID NO: 592)**
E2-H5	NFMLTHPHSVSESPGKTVTISCTGS **(SEQ ID NO: 593)**	VQWYQQRPGSAPTTVIY **(SEQ ID NO:594])**	QRPSGVPDRFSGSIDGSSNSASLTISALETEDEADYYC **(SEQ ID NO: 595)**	FGTGTKLTVL **(SEQ ID NO: 596)**
E2-H8	QSALTQPASVSGSPGQSITISCTGT	VSWYQQHPGKAPKLMIY	KRPSGVSNRFSGSKSGNTASLTVSGLQAEDEADYYC	FGTGTKVAVL **(SEQ ID NO: 600)**

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
	(SEQ ID NO: 597)	**(SEQ ID NO: 598)**	**(SEQ ID NO: 599)**	
E2-H9	QSVLTHPPSVS GAPGQRVTISC TGN **(SEQ ID NO: 601)**	VHWYQQLPGT APKLLIY **(SEQ ID NO: 602)**	YRPSGVPDRFSG SKSGTSASLAIS GLRSKDEADYYC **(SEQ ID NO: 603)**	FGTGTKVTVL **(SEQ ID NO: 604)**
E2-H10	QTVVTQEPSLT VSPGGTVTLTC GSS **(SEQ ID NO: 605)**	PYWFQQKPGQ APTTLIY **(SEQ ID NO: 606)**	HKHSWTPARFSG SVLGGKAALTLS GAQPEDEADYYC **(SEQ ID NO: 607)**	FGGGTKLTVL **(SEQ ID NO: 608)**
T1-E6	NFMLTQPHSMS ESPGKTVTISC TRS **(SEQ ID NO: [ ])**	VQWFQQRPGS APTTVIY **(SEQ ID NO: [ ])**	QRPSGVPDRFSG SIDRSSNSASLI ISGLKTEDEADY YC **(SEQ ID NO: [ ])**	FGGGTKLTVL **(SEQ ID NO: [ ])**
E4-F2	LPVLTQAPSAS GTPGQRVTISC SGS **(SEQ ID NO: [ ])**	VNWYQHLPGT APKLLIY **(SEQ ID NO: [ ])**	QRPSGVPDRFSG SKSGTSASLAIS GLRSEDEADYYC **(SEQ ID NO: [ ])**	FGGGTKLTVL **(SEQ ID NO: [ ])**
T1-A3	LPVLTQAPSAS GTPGQRVTISC SGS **(SEQ ID NO: [ ])**	VNWYQHLPGT APKLLIY **(SEQ ID NO: [ ])**	QRPSGVPDRFSG SKSGTSASLAIS GLRSEDEADYYC **(SEQ ID NO: [ ])**	FGGGTKLTVL **(SEQ ID NO: [ ])**
T1-A6	QSVLTQPPSAS GTPGQTVTITC SGS **(SEQ ID NO: [ ])**	VYWYQQLPGT APKLLIY **(SEQ ID NO: [ ])**	QRPSGVPDRFSG SKSGTSASLAIS GLRSEDEADYYC **(SEQ ID NO: [ ])**	FGGGTKLTVL **(SEQ ID NO: [ ])**
T1-A10	SSELTQDPAVS VALGQTVRITC QGD **(SEQ ID NO: [ ])**	ASWYQQKPGQ APLVVIF **(SEQ ID NO: [ ])**	KRPSGIPDRFSG SRSGNTASLTIT ATQAEDEADYYC **(SEQ ID NO: [ ])**	FGGGTKVTRP **(SEQ ID NO: [ ])**
E2-D5	QPGLTQPPSVS KGLRQTATLTC TGN **(SEQ ID NO: [ ])**	AAWLQQHQGH PPKLLFF **(SEQ ID NO: [ ])**	KRPSGISERFSA SRSGSTASLTIT ELQPDDEADYYC **(SEQ ID NO: [ ])**	FGGGTRVTVL **(SEQ ID NO: [ ])**
E2-G6	HPGLTHPPSES KGLIHTATLTC TGN **(SEQ ID NO: [ ])**	APWLHHHHGH PPKLLFF **(SEQ ID NO: [ ])**	KRPSWISKRFSA SKSRSTASLTIT ELQPDDDADYYC **(SEQ ID NO: [ ])**	FGGGTRVTVL **(SEQ ID NO: [ ])**
E2-H3	SYELTQPPSVS EGLRQTATLTC TGN **(SEQ ID NO: [ ])**	AAWLQQHQGH PPKLLSY **(SEQ ID NO: [ ])**	NRPSGISERLSA SRSGNTASLTIT GLQPEDEADYYC **(SEQ ID NO: [ ])**	FGGGTKLTVL **(SEQ ID NO: [ ])**
E2-H12	QSALTQPASVS GSPGQSITISC TGT	VSWYQQHPGK APKLMIY **(SEQ ID NO: [ ])**	KRPSGVSNRFSG SKSGNTASLTVS GLQAEDEADYYC	FGTGTKVAVL **(SEQ ID NO: [ ])**

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
	(SEQ ID NO: [ ])		**(SEQ ID NO: [ ])**	
E2-H2	QSVLTQPPSVSGAPGQRVTISCTGS **(SEQ ID NO: [ ])**	VHWYQQLPGTAPKLLIY **(SEQ ID NO: [ ])**	SRPSGVPDRFSGSKSGTSPSLAISGLQSEDEADYYC **(SEQ ID NO: [ ])**	FGSGTKVTVL **(SEQ ID NO: [ ])**
E2-D10	QTVVTQEPSLTVSPGGTVTLTCGSS **(SEQ ID NO: [ ])**	PYWFQQKPGQAPRTLIY **(SEQ ID NO: [ ])**	NRHSWTPARFSGSLLGAKAALTLSGVQPEDEADYYC **(SEQ ID NO: [ ])**	FGGETKLTVL **(SEQ ID NO: [ ])**
E2-D11	QPVLTQPHSVSESPGKTVTISCTRS **(SEQ ID NO: [ ])**	VQWYQQRPGSAPTLMIY **(SEQ ID NO: [ ])**	QRPFGVPDRFSGSIDSSSNSASLTISGLKTEDEADYYC **(SEQ ID NO: [ ])**	FGGGTKLTVL **(SEQ ID NO: [ ])**

[00196] The nucleic acid sequences of the heavy and light chain framework regions of the CTLA-4 antibodies are shown in Table 56A-B below:

Table 56A. Heavy chain (V_H) framework regions (FRs) of the CTLA-4 antibodies

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
E1-A4	caggtgcagctggtgcagtctggagctgaggtgaagaagcctggtcctcggtgaaagtctcctgcaaggcttct **(SEQ ID NO: 289)**	atcagctgggtgcgacaggccctggacaagggcttgagtggatgggagg **(SEQ ID NO: 290)**	aagtacgcacagaagttccaggacagagtcacgattaccgcggacgaatccacgagcacggcctacatggagctgagcagcctgagatcagacgacacggccgcctattattgt **(SEQ ID NO: 291)**	tggggccaagggacaatggtcaccgtctcttcag **(SEQ ID NO: 292)**
E1-A8	caggtgcagctggtgcagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctct **(SEQ ID NO: 293)**	atgagttgggtccgccaggctccagggaaggggctggagtgggtctcaagt **(SEQ ID NO: 294)**	gactacgcagactccgtgaagggccggttccccatctccagagacaattccaagaacacattgtatctggaaatgaacagcctgagagctgaggacacggctgtatattactgt **(SEQ ID NO: 295)**	tggggccaagggaccacggtcaccgtctcctcag **(SEQ ID NO: 296)**
E1-A9	gaggtgcagctggtgcagtctggggctgaggtgaagaagcctgg	atgcactgggtgcgacaggccctggacaagggcttgagt	agctacgcacagaagttccagggcagagtcaccatgaccagggacacg	tggggccaagggaccacggtcaccgtctcctca

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
	ggcctcagtgaaggtttcctgcaaggcatct **(SEQ ID NO: 297)**	ggatgggaata **(SEQ ID NO: 298)**	tccacgagcacagtctacatggagctgagcagcctgagatctgaggacacggccgtgtattactgt **(SEQ ID NO: 299)**	**(SEQ ID NO: 300)**
E1-A10	caggtgcagctggtgcagtctgggggaggcttggtacagtctgggggtccctgagactctcctgtgcagcctct **(SEQ ID NO: 301)**	atgcactgggtccgccaagcagcaggaaaaggtctagagtgggtctcaaat **(SEQ ID NO: 302)**	tactattcagactccgtgaagggccgattcatcatctccagagaaaatgccaagagctccttgtatcttcaaatgaacagcctgagagccggggacacggctgtgtattattgt **(SEQ ID NO: 303)**	tggggcaaagggaccacggtcaccgtctcctcag **(SEQ ID NO: 304)**
E1-A12	caggtgcagctggtgcagtctggaggtgaggtgaagaagcctgggcctcagtgaaggtctcctgcaaggcttct **(SEQ ID NO: 305)**	atcacctgggtgcgtcaggcccctggacaagggcttgagtggatgggatgg **(SEQ ID NO: 306)**	aactccgcgcagaagttccagggcagagtcttcttgacccgagacacatccacgagcacagcctacttggagctgaggagcctgagacctgacgacacggccgtctattactgt **(SEQ ID NO: 307)**	tggggcaaaggcaccctggtcaccgtctcctcag **(SEQ ID NO: 308)**
E1-B6	caggtacagctgcagcagtcaggaactgaggtgaagaagcctgggcctcagtgaaagtctcctgcaaggcttct **(SEQ ID NO: 309)**	ttcacttgggtgcggcaggccccggacaaggccttgagtggatgggatgg **(SEQ ID NO: 310)**	gactatgcacaaaagttcgagggcagagtcaccatgaccacagacacatccacgaccacagcctatatggagttgaggggtctgaaatctgacgacacggccatgtattattgt **(SEQ ID NO: 311)**	tggggccaagggaccacggtcaccgtctcctca **(SEQ ID NO: 312)**
E1-B10	caggtgcagctggtgcagtctggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctct **(SEQ ID NO: 313)**	atgagctgggtccgccaggctccagggaaggggctggagtgggtctcagct **(SEQ ID NO: 314)**	tactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagctgaggac	tggggccagggcaccctggtcaccgtctcctcag **(SEQ ID NO: 316)**

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
			acggctgtgtat tactgt **(SEQ ID NO: 315)**	
E1-B11	gaggtgcagct ggtgcagtctg ggggaggcttg gtccagcctgg agggtccctga gactctcctgt gcagcctct **(SEQ ID NO: 317)**	atggactggg tccgccaggc tccagggaag gggctggagt gggttggccg t **(SEQ ID NO: 318)**	gaatacgccgcg tctgtgaaaggc agattcaccatc tcaagagatgaa tcagagaactca ctgtatctgcaa atgaacagcctg agagccgaggac acggctgtgtat tactgt **(SEQ ID NO: 319)**	tggggcaaagg gaccacggtca ccgtctcctca **(SEQ ID NO:320)**
E1-B12	caggtgcagct ggtgcagtctg gaggtgaggtg aagaagcctgg ggcctcagtga aggtctcctgc aaggcttct **(SEQ ID NO: 321)**	atcacctggg tgcgtcaggc ccctggacaa gggcttgagt ggatgggatg g **(SEQ ID NO:322)**	aactccgcgcag aagttccagggc agagtcttcttg acccgagacaca tccacgagcaca gcctacttggag ctgaggagcctg agacctgacgac acggccgtctat tactgt **(SEQ ID NO: 323)**	tggggcaaagg caccctggtca ccgtctcctca g **(SEQ ID NO:324)**
T2-C10	gaggtgcagct ggtgcagtctg ggggaggcgtg gtccagcctgg gaggtccctga gactctcctgt gcagcctct **(SEQ ID NO: 325)**	atgcactggg tccgccaggc tccaggcaag gggctggagt gggtggcagt t **(SEQ ID NO: 326)**	tactacgcagac tccgtgaagggc cgattcaccatc tccagagacaat tccaagaacacg ctgtatctgcaa atgaacagcctg agagctgaggac acggctgtgtat tactgt **(SEQ ID NO: 327)**	tggggccaggg aaccctggtca ccgtctcctca g **(SEQ ID NO: 328)**
E1-C12	caggtgcagct ggtgcagtctg gggctgaggtg aagaagcctgg ggcctcagtga aggtctcctgc aaggcttct **(SEQ ID NO: 329)**	ttcacttggg tgcggcaggc ccccggacaa ggccttgagt ggatgggatg g **(SEQ ID NO: 330)**	gactatgcacaa aagttcgagggc agagtcaccatg accacagacaca tccacgaccaca gcctatatggag ttgaggggtctg aaatctgacgac acggccatgtat tattgt **(SEQ ID NO: 331)**	tggggccaagg gaccacggtca ccgtctcctca **(SEQ ID NO: 332)**

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
E1-D7	caggtgcagctgcaggagtcgggggaggcgtggtccagcctgggaggtctctgagactcctcctgtgcagcctct **(SEQ ID NO: 333)**	atgcactgggtccgccagcccccaggggaggcctggagtggattgggcac **(SEQ ID NO:334)**	tactacaacccgtcgctcagaagtcgatttagtatttcaaaagacacgtccaagaatcagttctccctgcacctgaggtctgtgactgccgcagacacggccgtttattactgt **(SEQ ID NO: 335)**	tggggccaaggcaccctggtcaccgtctcctca **(SEQ ID NO: 336)**
E2-A4	caggtgcagctggtgcagtctggggaggcttggtacagcctgggggtccctgagactcctcctgtgcagcctct **(SEQ ID NO: 721)**	atgagttgggtccgccaggctccagggaaggggctggagtgggtctcaagt **(SEQ ID NO: 722)**	gactacgcagactccgtgaagggccggttccccatctccagagacaattccaagaacacattgtatctggaaatgaacagcctgagagctgaggacacggctgtatattactgt **(SEQ ID NO: 723)**	tggggccaagggaccacggtcaccgtctcctcag **(SEQ ID NO: 724)**
E2-A7	caggtgcagctggtgcagtctggggaagtgtggtccggcctgggaggtccctgcgactcgcctgtgcagcctct **(SEQ ID NO: 725)**	atgcactgggtccgccagactccaggcaaggggctggagtgggtggcagtt **(SEQ ID NO: 726)**	ttttatgcagacgccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagctgaggacacggctgtgtattactgt **(SEQ ID NO: 727)**	tggggccaaggaaccctggtcaccgtctcctcag **(SEQ ID NO: 728)**
E2-A10	caggtacagctgcagcagtcagggctgaggtgaagaagcctggtcctcggtgaaggtctcctgcaaggcttct **(SEQ ID NO: 729)**	atcagctgggtgcgacaggcccctggacaagggcttgagtggatgggaagg **(SEQ ID NO: 730)**	aactacgcacagaagttccagggcagagtcacgattaccgcggacgaatccacgagcacagcctacatggagctgagcagcctgagatctgaggacacggccgtgtattactgt **(SEQ ID NO: 731)**	tggggccagggcaccctggtcaccgtctcctcag **(SEQ ID NO: 732)**
E2-A12	caggtgcagctggtgcagtctggggaggcttggtacagcctgggggtccctga	atgagctgggtccgccaggctccagggaaggggctggagt	tactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacg	tggggccagggcaccctggtcaccgtctcctcag

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
	gactctcctgtgcagcctct **(SEQ ID NO: 733)**	gggtctcagct **(SEQ ID NO: 734)**	ctgtatctgcaaatgaacagcctgagagctgaggacacggctgtgtattactgt **(SEQ ID NO: 735)**	**(SEQ ID NO: 736)**
E2-C4	gaggtgcagctggtgcagtctgggctgaggtgaagaagcctggggcctcagtgaaggtttcctgcaaggcatct **(SEQ ID NO: 737)**	atgcactgggtgcgacaggccctggacaagggcttgagtggatgggaata **(SEQ ID NO: 738)**	agctacgcacagaagttccagggcagagtcaccatgaccagggacacgtccacgagcacagtctacatggagctgagcagcctgagatctgaggacacggccgtgtattactgt **(SEQ ID NO: 739)**	tggggccaagggaccacggtcaccgtctcctca **(SEQ ID NO: 740)**
E2-D4	caggtgcagctggtgcagtctggagctgaggtgaagaagcctggggcctcagtgaagctttcctgcaagggatct **(SEQ ID NO: 741)**	atacactgggtgcggcaggcccctggacaagggcttgagtggatgggaaga **(SEQ ID NO: 742)**	atttacgcacagaagttccggggcagagtcaccatgaccagggacacgtccacgagaacggtctacatggagctgagcagcctgcgatcagaggacacggccctatattattgt **(SEQ ID NO: 743)**	tggggccagggcaccctggtcaccgtctcctcag **(SEQ ID NO: 744)**
E2-E5	caggtgcagctggtgcagtctgggggaggcttggtacagcctgggggtccctgagactctcctgtgcagcctct **(SEQ ID NO: 745)**	atgagctgggtccgccaggctccagggaaggggctggagtgggtctcatct **(SEQ ID NO: 746)**	tactacgcagactccgtgaagggccggttcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagctgaggacacggctgtgtattactgt **(SEQ ID NO: 747)**	tggggccagggcaccctggtcaccgtctcctcag **(SEQ ID NO: 748)**
E2-F1	caggtacagctgcagcagtcaggaactgaggtgaagaagcctggggcctcagtgaaagtctcctgcaaggcttct **(SEQ ID NO: 749)**	ttcacttgggtgcggcaggccccggacaaggccttgagtggatgggatgg **(SEQ ID NO: 750)**	gactatgcacaaaagttcgagggcagagtcaccatgaccacagacacatccacgaccacagcctatatggagttgaggggtctgaaatctgacgacacggccatgtattattgt	tggggccaagggaccacggtcaccgtctcctca **(SEQ ID NO: 752)**

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
			(SEQ ID NO: 751)	
E2-G5	gaggtgcagct ggtggagtctg gagccgaggtg agaaagcccgg agagtctctga cgatctcctgc aaggcttct **(SEQ ID NO: 753)**	atcagctggg tgcgacaggc ccctggacaa gggcttgagt ggatgggatg g **(SEQ ID NO: 754)**	aactatgcacag aagctccagggc agagtcaccatg accacagacaca tccacgagcaca gcctacatggag ctgaggagcctg agatctgacgac acggccgtgtat tactgt **(SEQ ID NO: 755)**	tggggccaagg caccctggtca ccgtctcttca **(SEQ ID NO: 756)**
E2-G9	caggtgcagct ggtgcagtctg gagctgaggtg aagaagcctgg ggcctcagtga agctttcctgc aagggatct **(SEQ ID NO: 757)**	atacactggg tgcggcaggc ccctggacaa gggcttgagt ggatgggaag a **(SEQ ID NO: 758)**	atttacgcacag aagttccggggc agagtcaccatg accagggacacg tccacgagaacg gtctacatggag ctgagcagcctg cgatcagaggac acggccctatat tattgt **(SEQ ID NO: 759)**	tggggccaggg caccctggtca ccgtctcctca g **(SEQ ID NO: 760)**
E2-H5	gaggtgcagct ggtggagtctg gggctgaggtg aagaagcctgg ggcctcagtga aggtttcctgc aaggcatct **(SEQ ID NO: 761)**	atgcactggg tgcgacaggc ccctggacaa gggcttgagt ggatgggaat a **(SEQ ID NO: 762)**	agctacgcacag aagttccagggc agagtcaccatg accagggacatg tccacgagcaca gtctacatggag ctgagcagcctg agatctgaggac acggctgtgtat tactgt **(SEQ ID NO: 763)**	tggggccaagg gacaatggtca ccgtctcttca **(SEQ ID NO: 764)**
E2-H8	gaggtgcagct ggtgcagtctg gaggaggcttg atccagccggg ggggtccctga gactctcctgc gcagcctct **(SEQ ID NO: 765)**	atgacctggg tccgccaggc tccagggaag gggctggagt gggtctcaaa t **(SEQ ID NO: 766)**	tactacgcagac tctgtgaagggc cgattcaccatc tccagggacaac gccaagaactca ctgtatctgcaa atgaacagcctg agagccgaggac acggccgtgtat tactgt **(SEQ ID NO: 767)**	tggggccaggg caccctggtca ccgtctcctca g **(SEQ ID NO: 768)**
E2-H9	gaggtgcagct ggtggagtctg ggggaggcttg gttcagccggg	atgagctggg tccgccaggc tccagggaag gggctggagt	cactacgcagac tccgtgaagggc cggttcaccatc tccagagacaat	tggggccaggg caccctggtca ccgtctcctca g

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
	ggggtccctaa gactgccctgt gcagcctct **(SEQ ID NO: 769)**	gggtctctgt t **(SEQ ID NO: 770)**	ttcaagaacacg gtatatctgcaa gtgaacagcccg agagccgaggac acggccgtctat tattgt **(SEQ ID NO: 771)**	**(SEQ ID NO: 772)**
E2-H10	caggtgcagct ggtgcagtctg gaggtgaggtg aagaagcctgg ggcctcagtga aggtctcctgc aaggcttct **(SEQ ID NO: 773)**	atcacctggg tgcgtcaggc ccctggacaa gggcttgagt ggatgggatg g **(SEQ ID NO:774)**	aactccgcgcag aagttccag... ggcagagtcttc ttgacccgagac acatccacgagc acagcctacttg gagctgaggagc ctgagacctgac gacacggccgtc tattactgt **(SEQ ID NO: 775)**	tggggcaaagg caccctggtca ccgtctcctca g **(SEQ ID NO: 776)**
T1-E6	caggtgcagct gcaggagtcgg ggggaggcgtg gtccagcctgg gaggtctctga gactctcctgt gcagcctct **(SEQ ID NO: [ ])**	atgcactggg tccgccagcc cccaggggag ggcctggagt ggattgggca c **(SEQ ID NO: [ ])**	tactacaacccg tcgctcagaagt cgatttagtatt tcaaaagacacg tccaagaatcag ttctccctgcac ctgaggtctgtg actgccgcagac acggccgtttat tactgt **(SEQ ID NO: [ ])**	tggggccaagg caccctggtca ccgtctcctca **(SEQ ID NO: [ ])**
E4-F2	caggtgcagct ggtgcagtctg ggggaggcttg gtacagccagg gcggtccctga gactctcctgt agaggttct **(SEQ ID NO: [ ])**	atgagctggg tccgccaggc tccagggaag gggctggaat ggatagcttt c **(SEQ ID NO: [ ])**	gaatatgccgcg tctgtgaaaggc agattcaccatc tcaagagatgat tcaaagaacacg gcgtatctgcaa atgaacagcctg aaaaccgaggac acggccgtgtat tactgc **(SEQ ID NO: [ ])**	tggggccaagg gaccacggtca ccgtctcctca g **(SEQ ID NO: [ ])**
T1-A3	caggtgcagct ggtgcagtctg ggggaggcttg gtacagccagg gcggtccctga gactctcctgt agaggttct **(SEQ ID NO: [ ])**	atgagctggg tccgccaggc tccagggaag gggctggaat ggatagcttt c **(SEQ ID NO: [ ])**	gaatatgccgcg tctgtgaaaggc agattcaccatc tcaagagatgat tcaaagaacacg gcgtatctgcaa atgaacagcctg aaaaccgaggac	tggggccaagg gaccacggtca ccgtctcctca g **(SEQ ID NO: [ ])**

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
			acggccgtgtat tactgc **(SEQ ID NO: [ ])**	
T1-A6	caggtgcagct ggtgcagtctg ggggaggcttg gtacagcctgg ggggtccctga gactctcctgt gcagcctct **(SEQ ID NO: [ ])**	atgaactggg tccgccaggc tccagggaag gggctggagt gggtctcatc c **(SEQ ID NO: [ ])**	tactacgcagac tcagtgaagggc cgattcaccatc tccagagacaac gccaagaactca ctgtatctgcaa atgaacagcctg agagacgaggac acggctgtgtat tactgt **(SEQ ID NO: [ ])**	tggggccaagg caccctggtca ccgtctcctca g **(SEQ ID NO: [ ])**
T1-A10	caggtgcagct ggtgcagtctg gggaggcttg gtccagccggg ggggtccctgc gactctcctgt gcagcctct **(SEQ ID NO: [ ])**	atgacctggg tccgccaggc cccagggaag gggctggagt gggtggccaa t **(SEQ ID NO: [ ])**	tactatgtggac tctgtgaagggc cgattcaccagc tccagagacaac gccaagaactca ctgtatctccaa atgaacagcctg agagccgaggac acggccgtatat tactgt **(SEQ ID NO: [ ])**	tggggcccagg gaccacggtca ccgtctcctca **(SEQ ID NO: [ ])**
E2-D5	caggtgcagct ggtgcagtctg gggaggcttg gtccagcctgg ggggtccctga gactctcctgt gcagcctct **(SEQ ID NO: [ ])**	atgagctggg tccgccaggc tccagggaag gggctggagt gggtctcaag t **(SEQ ID NO: [ ])**	tactacgcagac tccgtgaagggc cggttcaccatc tccagagacaat tccgagagcagg ctgtatttgcaa atgaacagcctg ggacctgaggac acggcccttat tactgt **(SEQ ID NO: [ ])**	tggggccaagg gacaatggtca ccgtctcttca g **(SEQ ID NO: [ ])**
E2-G6	caggtgccctg gtgcgtctggg ggaggcttggt ccagcctgggg ggtccctgata ctctcctgtgc gcctct **(SEQ ID NO: [ ])**	atgacctgga tccgccaggc tccagggaag gggctggagt gggtctcatg t **(SEQ ID NO: [ ])**	tactacgcacac tccgtgaagggg cggatcaccatc tccaaagacaat tcccagagcagg ctgtatttgcta atgaacatgctg ggacctgaggac tcggtcctttat tactgt **(SEQ ID NO: [ ])**	tggggccaagg gacaatggtca ccgtctcttca g **(SEQ ID NO: [ ])**
E2-H3	gaggtgcagct ggtgcagtctg	atcagttggg tgcgacaggc	aactatgcacag aaattccaggac	tggggccaagg gacaatggtca

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
	ggcctgaggtg aagaagcctgg ggactcagtga aggtcccctgc aaggcttct **(SEQ ID NO: [ ])**	ccctggacaa gggcttgagt ggatgggatg g **(SEQ ID NO: [ ])**	agagtcaccatg accacagacaca tccacgaacaca gcctacatggag ctgaagagcctg agatctgacgac acggccatatat ttctgt **(SEQ ID NO: [ ])**	ccgtctcttca g **(SEQ ID NO: [ ])**
E2-H12	gaggtgcagct ggtgcagtctg gaggaggcttg atccagccggg ggggtccctga gactctcctgc gcagcctct **(SEQ ID NO: [ ])**	atgacctggg tccgccaggc tccagggaag gggctggagt gggtctcaaa t **(SEQ ID NO: [ ])**	tactacgcagac tctgtgaagggc cgattcaccatc tccagggacaac gccaagaactca ctgtatctgcaa atgaacagcctg agagccgaggac acggccgtgtat tactgt **(SEQ ID NO: [ ])**	tggggccaggg caccctggtca ccgtctcctca **(SEQ ID NO: [ ])**
E2-H2	caggtacagct gcagcagtcag gaactgaggtg aagaagcctgg ggcctcagtga aagtctcctgc aaggcttct **(SEQ ID NO: [ ])**	ttcacttggg tgcggcaggc ccccggacaa ggccttgagt ggatgggatg g **(SEQ ID NO: [ ])**	gactatgcacaa aagttcgagggc agagtcaccatg accacagacaca tccacgaccaca gcctatatggag ttgaggggtctg aaatctgacgac acggccatgtat tattgt **(SEQ ID NO: [ ])**	tggggccaagg gaccacggtca ccgtctcctca **(SEQ ID NO: [ ])**
E2-D10	caggtgcagct ggtgcagtctg gaggtgaggtg aagaagcctgg ggcctcagtga aggtctcctgc aaggcttct **(SEQ ID NO: [ ])**	atcacctggg tgcgtcaggc ccctggacaa gggcttgagt ggatgggatg g **(SEQ ID NO: [ ])**	aactccgcgcag aagttccagggc agagtcttcttg accagagacaca tccacgagcaca gcctacttggag ctgaggagcctg agacctgacgac acggccgtctat tactgt **(SEQ ID NO: [ ])**	tggggcaaagg caccctggtca ccgtctcctca **(SEQ ID NO: [ ])**
E2-D11	gaggtgcagct ggtgcagtctg gggctgaggtg aagaagcctgg ggcctcagtga aggtttcctgc aaggcatct	atgcactggg tgcgacaggc ccctggacaa gggcttgagt ggatgggaat a **(SEQ ID NO: [ ])**	agctacgcacag aagttccagggc agagtcaccatg accagggacacg tccacgagcaca gtctacatggag ctgagcagcctg	tggggccaagg gaccacggtca ccgtctcctca **(SEQ ID NO: [ ])**

Seq ID	VH FR1	VH FR2	VH FR3	VH FR4
	(SEQ ID NO: [ ])		agatctgaggac acggccgtgtat tactgt **(SEQ ID NO: [ ])**	

Table 56B. Light chain (V_L) framework regions (FRs) of the CTLA-4 antibodies

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
E1-A4	cagtctgcc ctgactcag cctcgctca gtgtccggg tctcctgga cagtcagtc accatctcc tgcactgga acc **(SEQ ID NO: 337)**	gtctcctggtac caacagcaccca ggcaaagccccc aaactcataatt tat **(SEQ ID NO:338)**	aagcggccctcaggggt ttctgatcgcttctctg gctccaagtctggcaac acggcctccctgagaat ctcggggctccaggctc aggacgaggctgattat tactgc **(SEQ ID NO: 339)**	ttcggtag tgggaccg aggtcacc gtcctgg **(SEQ ID NO:340)**
E1-A8	gacatccag atgacccag tctccatct tctgtgtct gcatctata ggagacaga gtcaccatc acttgtcgg gcgagt **(SEQ ID NO:341)**	ttagcctggtat cagcagaaacca gggaaagccccct aaactcctgatc tat **(SEQ ID NO:342)**	aatttgcgaagtggggt cccttcaaggttcagcg gcggtggatctgggacg tatttcactctcactat cagtagcctacagcctg aagattttgcgacttac tattgt **(SEQ ID NO: 343)**	ttcggcca agggacgc gactggag attaaac **(SEQ ID NO:344)**
E1-A9	cagcctgtg ctgactcag ccgcactct gtgtcggag tctccgggg aagacggtc accatctcc tgcacccgc agc **(SEQ ID NO: 345)**	gtgcagtggtac caacagcgcccg ggcagtgccccc acccttatgatc tat **(SEQ ID NO: 346)**	caaagacccttttggggt ccctgatcgattctctg gctccatcgacagctcc tccaactctgcctccct caccatctctggactga agactgaggacgaggct gactactactgt **(SEQ ID NO: 347)**	ttcggcgg agggacca agctgacc gtcctag **(SEQ ID NO: 348)**
E1-A10	cagcctgtg ctgactcag ccaccctca gtgtcagtg gccccagga cagacggcc aggattacc	gtgcactggtac cagcagaagcca ggccaggccccct gtgttggtcgtc tat **(SEQ ID NO: 350)**	gaccggccctcagggat ccct...gagcgattct ctggctccaactctggg aacacggccaccctgac catcagcagggtcgaag ccggggatgaggccgac tattactgt	ttcggcgg agggacca aggtgacc gtcctgg **(SEQ ID NO: 352)**

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
	tgtgggggaaac **(SEQ ID NO: 349)**		**(SEQ ID NO: 351)**	
E1-A12	cagactgtggtgactcaggagccctcactgactgtgtccccaggagggacagtcactctcacctgtggctccagc **(SEQ ID NO: 353)**	ccctactggttccagcagaagcctggccaggccccacgacactgattat **(SEQ ID NO: 354)**	cacaaacactcctggacccctgcccggttctcaggctccgtccttgggggcaaagctgccctgaccctttcgggtgcgcagcctgaagatgaggctgactattactgc **(SEQ ID NO: 355)**	ttcggcgggagggaccaagctgaccgtcctca **(SEQ ID NO: 356)**
E1-B6	cagtctgtgctgactcagccaccctcagtgtctggggccccagggcagagggtcaccatctcctgcactgggagc **(SEQ ID NO: 357)**	gtacactggtaccagcagcttccaggaacagccccaaactcctcatctat **(SEQ ID NO: 358)**	agtcggccctcaggggtccctgaccgattctctggctccaagtctggcacctcagcctccctggccatcagtgggctccagtctgaagatgaggctgattattattgt **(SEQ ID NO: 359)**	tttggatctgggaccaaggtcaccgtcctgg **(SEQ ID NO: 360)**
E1-B10	cagactgtggtgactcaggagccatcgttctcagtgtcccctggagggacagtcacactcactgtggcttgagc **(SEQ ID NO: 361)**	cccagctggtaccagcagacccccaggccaggctccacgcacactcatctac **(SEQ ID NO: 362)**	actcgctcttctggggtccctgatcgcttctctggctccatccttgggaacaaagctgccctcaccatcacgggggcccaggcagatgatgaatctgattattactgt **(SEQ ID NO: 363)**	ttcggcgggagggaccaagctgaccgtcctag **(SEQ ID NO: 364)**
E1-B11	aattttatgctgactcaccccactctgtgtcggagtctccgggggaagacggtaaccatctcctgcacccgcagc **(SEQ ID NO: 365)**	gtgcagtggtaccagcagcgcccgggcagttccccaccactgtgatctat **(SEQ ID NO: 366)**	caaagaccctctggggtccctgatcggttctctggctccatcgacagctcctccaactctgcctccctcaccatctctggactgaagactgaggacgaggctgactattactgt **(SEQ ID NO: 367)**	ttcggaactgggaccaaggtcaccgtcctag **(SEQ ID NO: 368)**

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
E1-B12	cagactgtg gtgactcag gagccctca ctgactgtg tccccagga gggacagtc actctcacc tgtggctcc agc **(SEQ ID NO: 369)**	ccctactggttc cagcagaagcct ggccaggccccc acgacactgatt tat **(SEQ ID NO: 370)**	cacaaacactcctggac ccctgcccggttctcag gctccgtccttgggggc aaagctgccctgaccct ttcgggtgcgcagcctg aagatgaggctgactat tactgc **(SEQ ID NO: 371)**	ttcggcgg agggacca agctgacc gtcctca **(SEQ ID NO: 372)**
T2-C10	ctgcctgtg ctgactcaa tcatcctct gcctctgct tccctggga tcctcggtc aagctcacc tgcactctg agc **(SEQ ID NO: 373)**	atcgcatggcat cagcagcagcca gggaaggcccct cggtacttgatg aag **(SEQ ID NO: 374)**	aacaaggggagcggagt tcctgatcgcttctcag gctccagctctggggct gaccgctacctcaccat ctccaacctccagtctg aggatgaggctgattat tactgt **(SEQ ID NO: 375)**	ttcggcgg agggacca agctgacc gtccta **(SEQ ID NO: 376)**
E1-C12	cagtctgtg ctgactcag ccaccctca gtgtctggg gccccaggg cagagggtc accatctcc tgcactggg agc **(SEQ ID NO: 377)**	gtacactggtac cagcagcttcca ggaacagccccc aaactcctcatc tat **(SEQ ID NO: 378)**	agtcggccctcaggggt ccctgaccgattctctg gctccaagtctggcacc tcaccctccctggccat cagtgggctccagtctg aagatgaggctgattat tattgt **(SEQ ID NO: 379)**	tttggatc tgggacca aggtcacc gtcctgg **(SEQ ID NO: 380)**
E1-D7	aattttatg ctgactcag ccccactct atgtcggag tctccgggg aagacggtg accatctcc tgcacccgc agc **(SEQ ID NO: 381)**	gtgcagtggttc cagcagcgcccg ggcagtgccccc accactgtgatc tat **(SEQ ID NO: 382)**	caacgaccctctggggt ccctgatcggttctctg gctccatcgacaggtcc tccaactctgcctccct catcatctctggactga agactgaggacgaggct gactactactgt **(SEQ ID NO: 383)**	ttcggcgg agggacca agctgacc gtcctg **(SEQ ID NO: 384)**
E2-A4	gacatccag atgacccag tctccatct tctgtgtct gcatctata	ttagcctggtat cagcagaaacca gggaaagcccct aaactcctgatc tat	aatttgcgaagtggggt cccttcaaggttcagcg gcggtggatctgggacg tatttcactctcactat cagtagcctacagcctg	ttcggcca agggacgc gactggag attaaac

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
	ggagacaga gtcaccatc acttgtcgg gcgagt **(SEQ ID NO: 777)**	**(SEQ ID NO: 778)**	aagattttgcgacttac tattgt **(SEQ ID NO: 779)**	**(SEQ ID NO:780)**
E2-A7	cagtctgcc ctgactcag cctcgctca gtgtccggg tctcctgga cagtcagtc accatctcc tgcactgga acc **(SEQ ID NO:781)**	gtctcctggtac caacaccaccca ggcaaagccccc aaactcatgatt tat **(SEQ ID NO: 782)**	gagcggccctcaggggt ccctgatcgcttctctg gctccaagtctggcaac acggcctccctgaccat ctctgggctccaggcgg aggatgaggctgattat tactgc **(SEQ ID NO: 783)**	ttcggcac tgggacca aagtcacc gtcctag **(SEQ ID NO:784)**
E2-A10	cagactgtg gtgactcag gagccatcg ttctcagtg gcccctggg gggacagtc acactcact tgtgccttg agc **(SEQ ID NO: 785)**	cccagctggttc cagcagacccca ggccaggcgcca cgcacactcatc tac **(SEQ ID NO:786)**	atacgttctcatggggt ccctgatcggttctctg gctctctccttggaaac aaagcagccctcaccat cacgggggcccagccaa atgatgaatctgaatac tactgt **(SEQ ID NO: 787)**	ttcggcgg agggacca aggtgacc gtcctag **(SEQ ID NO:788)**
E2-A12	cagactgtg gtgactcag gagccatcg ttctcagtg tcccctgga gggacagtc acactcact tgtggcttg agc **(SEQ ID NO: 789)**	cccagctggtac cagcagacccca ggccaggctcca cgcacactcatc tac **(SEQ ID NO: 790)**	actcgctcttctggggt ccctgatcgcttctctg gctccatccttgggaac aaagctgccctcaccat cacgggggcccaggcag atgatgaatctgattat tactgt **(SEQ ID NO: 791)**	ttcggcgg agggacca agctgacc gtcctag **(SEQ ID NO:792)**
E2-C4	cagcctgtg ctgactcag ccgcactct gtgtcggag tctccgggg aagacggtc accatctcc tgcacccgc agc	gtgcagtggtac caacagcgcccg ggcagtgccccc acccttatgatc tat **(SEQ ID NO: 794)**	caaagacccttggggt ccctgatcgattctctg gctccatcgacagctcc tccaactctgcctccct caccatctctggactga agactgaggacgaggct gactactactgt **(SEQ ID NO: 795)**	ttcggcgg agggacca agctgacc gtcctag **(SEQ ID NO:796)**

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
	(SEQ ID NO: 793)			
E2-D4	cagcctgtg ctgactcag cctcgctca gtgtccggg tctcctgga cagtcagtc accatctcc tgcactgga acc **(SEQ ID NO: 797)**	gtctcctggtac caacaacaccca ggcaaggccccc aaactcatcatt tat **(SEQ ID NO: 798)**	aagcggccctcaggggt ccctgatcgcttctctg gctccaagtctggcaac acggcctccctgaccgt ctctgggctccaggctg aggatgaggctgattat tactgc **(SEQ ID NO: 799)**	ttcggcgg ggggacca agttgacc gtcctag **(SEQ ID NO:800)**
E2-E5	catactgtg gtgactcag gagccatcc ttctcagtg acccctgga gggacagtc acactcact tgtggcttg agc **(SEQ ID NO: 801)**	cccatctggtac cagcacacccca ggccaggctcca cgcacactcatc tac **(SEQ ID NO:802)**	actccctcttctggggt ccctgatcgcttctctg gctccatccttgggaac aaagctgccctcaccat cacgggggcccaggaag atgatgaatctgattat tactgt **(SEQ ID NO: 803)**	ttcggcgg aaggacca aactgacc gtcctag **(SEQ ID NO:804)**
E2-F1	cagtctgtg ctgactcag ccaccctca gtgtctggg gccccaggg cagagggtc accatctcc tgcactggg agc **(SEQ ID NO: 805)**	gtacactggtac cagcagcttcca ggaacagccccc aaactcctcatc tat **(SEQ ID NO:806)**	agtcggccctcaggggt ccctgaccgattctctg gctccaagtctggcacc tcagcctccctggccat cagtgggctccagtctg aagatgaggctgattat tattgt **(SEQ ID NO: 807)**	tttggatc tgggacca aggtcacc gtcctgg **(SEQ ID NO: 808)**
E2-G5	cagcctggg ctgactcag ccaccctca gcgtctggg acccccggg cagagggtc accctctct tgttctgga agc **(SEQ ID NO: 809)**	gtattctggtac cagcagctccca ggaacggccccc aaactcctcatc tat **(SEQ ID NO: 810)**	cagaggccctcaggggt ccctgaccgattctctg cctccaagtctggcacc tcagcctccctggccat cagtgggctccggtccg aggatgaggctgattat tactgt **(SEQ ID NO: 811)**	ttcggcgg agggacca agctgacc gtcctag **(SEQ ID NO: 812)**
E2-G9	cagcctgtg ctgactcag cctcgctca	gtctcctggtac caacaacaccca ggcaaggccccc	aagcggccctcaggggt ccctgatcgcttctctg gctccaagtctggcaac	ttcggcgg ggggacca

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
	gtgtccgggtctcctggacagtcagtcaccatctcctgcactggaacc **(SEQ ID NO: 813)**	aaactcatcattat **(SEQ ID NO: 814)**	acggcctccctgaccgtctctgggctccaggctgaggatgaggctgattattactgc **(SEQ ID NO: 815)**	agttgaccgtcctag **(SEQ ID NO: 816)**
E2-H5	aattttatgctgactcaccccactctgtgtcggagtctccggggaagacggtaaccatctcctgcaccggcagc **(SEQ ID NO: 817)**	gtgcagtggtaccagcagcgcccgggcagtgccccaccactgtgatctat **(SEQ ID NO: 818)**	caaagaccctctggggtccctgatcgattctctggctccatcgacggctcctccaactctgcctccctcaccatctctgcactggagactgaggacgaggctgactactactgt **(SEQ ID NO: 819)**	ttcggcacagggaccaaactgaccgtcctcc **(SEQ ID NO: 820)**
E2-H8	cagtctgccctgactcagcctgcctccgtgtcagggtctcctggacagtcgatcaccatctcctgcactggaacc **(SEQ ID NO: 821)**	gtctcgtggtaccaacaacacccgggcaaagccccaaactcatgattat **(SEQ ID NO: 822)**	aagcggccctcaggggtttctaatcgcttctctggctccaagtctggcaacacggcctccctgaccgtctctgggctccaggctgaggatgaggctgattactactgc **(SEQ ID NO: 823)**	ttcggaactgggaccaaggtcgccgtcctag **(SEQ ID NO: 824)**
E2-H9	cagtctgtgctgactcacccaccctcagtgtctggggccccaggcagagggtcaccatctcctgcactgggaac **(SEQ ID NO: 825)**	gtacactggtaccagcagcttccaggaacagccccaaactcctcattat **(SEQ ID NO: 826)**	tatcggccctcaggggtccctgaccgattctctggctccaagtctggcacctcagcctccctggccatcagtgggctccggtccaaagatgaggctgattattactgt **(SEQ ID NO: 827)**	ttcggaactgggaccaaggtcaccgtcctac **(SEQ ID NO: 828)**
E2-H10	cagactgtggtgactcagagccctcactgactgtgtccccaggagggacagtcactctcacc	ccctactggttccagcaaaagcctggccaggccccacgacactgattat **(SEQ ID NO:830)**	cacaaacactcctggaccccctgcccggttctcaggctccgtccttgggggcaaagctgccctgaccctttcgggtgcgcagcctgaagatgaggctgactattactgc **(SEQ ID NO: 831)**	ttcggcggagggaccaagctgaccgtcctca **(SEQ ID NO:832)**

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
	tgtggctcc agc **(SEQ ID NO: 829)**			
T1-E6	aattttatg ctgactcag ccccactct atgtcggag tctccgggg aagacggtg accatctcc tgcacccgc agc **(SEQ ID NO: [ ])**	gtgcagtggttc cagcagcgcccg ggcagtgccccc accactgtgatc tat **(SEQ ID NO: [ ])**	caacgaccctctggggt ccctgatcggttctctg gctccatcgacaggtcc tccaactctgcctccct catcatctctggactga agactgaggacgaggct gactactactgt **(SEQ ID NO: [ ])**	ttcggcgg agggacca agctgacc gtcctgg **(SEQ ID NO: [ ])**
E4-F2	ctgcctgtg ctgactcag gcaccctca gcgtctggg acccccggg cagagggtc accatctct tgttctgga agc **(SEQ ID NO: [ ])**	gtaaactggtac caacacctccca ggaacggccccc aaactcctcatc tat **(SEQ ID NO: [ ])**	caacggccctcaggggt ccctgaccgattctctg gctccaagtctggcacc tcagcctccctggccat cagtgggctccggtccg aggatgaggctgattat tactgt **(SEQ ID NO: [ ])**	ttcggcgg agggacca agctgacc gtcctag **(SEQ ID NO: [ ])**
T1-A3	ctgcctgtg ctgactcag gcaccctca gcgtctggg acccccggg cagagggtc accatctct tgttctgga agc **(SEQ ID NO: [ ])**	gtaaactggtac caacacctccca ggaacggccccc aaactcctcatc tat **(SEQ ID NO: [ ])**	cagcggccctcaggggt ccctgaccgattctctg gctccaagtctggcacc tcagcctccctggccat cagtgggctccggtccg aggatgaggctgattat tactgt **(SEQ ID NO: [ ])**	ttcggcgg agggacca agctgacc gtcctag **(SEQ ID NO: [ ])**
T1-A6	cagtctgtg ctgactcag ccaccctca gcgtctggg acccccggg cagacggtc accatcact tgttctgga agc **(SEQ ID NO: [ ])**	gtatactggtac cagcagctccca ggaacggccccc aaactcctcatc tat **(SEQ ID NO: [ ])**	cagcggccctcaggggt ccctgaccgattctctg gctccaagtctggcacc tcagcctccctggccat cagtgggctccggtccg aggatgaggctgattat tactgt **(SEQ ID NO: [ ])**	ttcggcgg agggacca agctgacc gtcctag **(SEQ ID NO: [ ])**

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
T1-A10	tcttctgag ctgactcag gaccctgct gtgtctgtg gccttggga cagacagtc aggatcaca tgccaagga gac (SEQ ID NO: [ ])	gcaagctggtac cagcagaagcca ggacaggcccct ttggttgtcatc ttt **(SEQ ID NO: [ ])**	aagcggccctcggggat ccccgaccgcttctctg gctccaggtcaggaaac acagcttccttgaccat aactgcgacccaggcgg aggatgaggctgattat tattgt **(SEQ ID NO: [ ])**	ttcggcgg agggacca aggtgacc cgtccta **(SEQ ID NO: [ ])**
E2-D5	cagcctggg ctgactcag ccaccctcg gtgtccaag ggcttgaga cagaccgcc acactcacc tgcactggg aac **(SEQ ID NO: [ ])**	gcagcttggctg cagcagcaccag ggccaccctccc aaactcctcttc ttt **(SEQ ID NO: [ ])**	aagcggccctcagggat ctcagagagattctctg catccaggtcaggaagt acagcctccctgaccat tactgaactccagcctg atgacgaggctgactat tactgc **(SEQ ID NO: [ ])**	ttcggcgg agggacca gggtgacc gtcctag **(SEQ ID NO: [ ])**
E2-G6	catcctggg ctgactcat ccaccctcg gagtccaag ggtttgata cataccgcc acactcacc tgcactggg aac **(SEQ ID NO: [ ])**	gcaccttggctg catcaccaccat ggccaccctccc aaactcctcttc ttt (SEQ ID NO: [ ])	aagcggccctcatggat ctcaaagagattctctg catccaagtcacgaagt acagcctccctgaccat tactgaactccaacctg atgacgacgctgactat tactgt (SEQ ID NO: [ ])	ttcggcgg agggacca gggtgacc gtcctag (SEQ ID NO: [ ])
E2-H3	tcctatgag ctgactcag ccaccctcg gtgtccgag ggcttgaga cagaccgcc acactcacc tgcactggg aac **(SEQ ID NO: [ ])**	gcagcttggctg cagcagcaccag ggccaccctccc aaactcctatcc tac **(SEQ ID NO: [ ])**	aaccggccctcagggat ctcagagagattatctg catccaggtcaggaaac acagcctccctgaccat tactggactccagcctg aggacgaggctgactat tactgc **(SEQ ID NO: [ ])**	ttcggcgg agggacca agctgacc gtcctag **(SEQ ID NO: [ ])**
E2-H12	cagtctgcc ctgactcag cctgcctcc gtgtcaggg tctcctgga	gtctcgtggtac caacaacacccg ggcaaagccccc aaactcatgatt tat	aagcggccctcaggggt ttctaatcgcttctctg gctccaagtctggcaac acggcctccctgaccgt ctctgggctccaggctg	ttcggaac tgggacca aggtcgcc gtcctag

Seq ID	VL FR1	VL FR2	VL FR3	VL FR4
	cagtcgatcaccatctcctgcactggaacc **(SEQ ID NO: [ ])**	**(SEQ ID NO: [ ])**	aggatgaggctgattactactgc **(SEQ ID NO: [ ])**	**(SEQ ID NO: [ ])**
E2-H2	gacatccagatgacccagtctccatcttctgtgtctgcatctataggagacagagtcaccatcacttgtcgggcgagt **(SEQ ID NO: [ ])**	ttagcctggtatcagcagaaaccagggaaagcccctaaactcctgatctat **(SEQ ID NO: [ ])**	aatttgcgaagtggggtcccttcaaggttcagcggcggtggatctgggacgtatttcactctcactatcagtagcctacagcctgaagattttgcgacttactattgt **(SEQ ID NO: [ ])**	ttcggccaagggacgcgactggagattaaac **(SEQ ID NO: [ ])**
E2-D10	cagacggtggtgactcaggagccctcactgactgtgtccccaggagggacagtcactctcacctgtggctccagc **(SEQ ID NO: [ ])**	ccctactggttccagcagaagcctggccaagccccaggacactgattat **(SEQ ID NO: [ ])**	aacagacactcctggactcctgcccggttctcaggctcccctccttggggccaaagctgccctgacactgtcaggtgtgcagcctgaggatgaggctgactattactgc **(SEQ ID NO: [ ])**	ttcggcggagagaccaaactgaccgtcctag **(SEQ ID NO: [ ])**
E2-D11	cagcctgtgctgactcagccgcactctgtgtcggagtctccggggaagacggtcaccatctcctgcacccgcagc **(SEQ ID NO: [ ])**	gtgcagtggtaccaacagcgcccgggcagtgccccaccttatgatctat **(SEQ ID NO: [ ])**	caaagacccttggggtccctgatcgattctctggctccatcgacagctcctccaactctgcctccctcaccatctctggactgaagactgaggacgaggctgactactactgt **(SEQ ID NO: [ ])**	ttcggcgggggaccaagctgaccgtcctag **(SEQ ID NO: [ ])**

[00197] The CTLA-4 antibodies described herein bind to CTLA-4. In one embodiment, the CTLA-4 antibodies have high affinity and high specificity for CTLA-4. Some embodiments also feature antibodies that have a specified percentage identity or similarity to the amino acid or nucleotide sequences of the anti- CTLA-4 antibodies described herein. For example, "homology" or "identity" or "similarity" refers to sequence similarity between two peptides or between two nucleic acid molecules. Homology can be determined by comparing a

position in each sequence, which may be aligned for purposes of comparison. When a position in the compared sequence is occupied by the same base or amino acid, then the molecules are homologous at that position. A degree of homology between sequences is a function of the number of matching or homologous positions shared by the sequences. For example, the antibodies can have 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher amino acid sequence identity when compared to a specified region or the full length of any one of the anti-CTLA-4 antibodies described herein. For example, the antibodies can have 60%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher nucleic acid identity when compared to a specified region or the full length of any one of the anti-CTLA-4 antibodies described herein. Sequence identity or similarity to the nucleic acids and proteins of the present invention can be determined by sequence comparison and/or alignment by methods known in the art, for example, using software programs known in the art, such as those described in Ausubel et al. eds. (2007) Current Protocols in Molecular Biology. For example, sequence comparison algorithms (i.e. BLAST or BLAST 2.0), manual alignment or visual inspection can be utilized to determine percent sequence identity or similarity for the nucleic acids and proteins of the present invention.

[00198] "Polypeptide" as used herein can encompass a singular "polypeptide" as well as plural "polypeptides," and refers to a molecule composed of monomers (amino acids) linearly linked by amide bonds (also known as peptide bonds). The term "polypeptide" refers to any chain or chains of two or more amino acids, and does not refer to a specific length of the product. Thus, peptides, dipeptides, tripeptides, oligopeptides, "protein," "amino acid chain," or any other term used to refer to a chain or chains of two or more amino acids, can refer to "polypeptide" herein, and the term "polypeptide" can be used instead of, or interchangeably with any of these terms. "Polypeptide" can also refer to the products of post-expression modifications of the polypeptide, including without limitation glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, or modification by non-naturally occurring amino acids. A polypeptide can be derived from a natural biological source or produced by recombinant technology, but is not necessarily translated from a designated nucleic acid sequence. It may be generated in any manner, including by chemical synthesis. As to amino acid sequences, one of skill in the art will readily recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds, deletes, or substitutes a single amino acid or a small percentage of amino acids in the encoded sequence is collectively

referred to herein as a "conservatively modified variant". In some embodiments the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants of the anti-CTLA-4 antibodies disclosed herein can exhibit increased cross-reactivity to CTLA-4 in comparison to an unmodified CTLA-4 antibody.

[00199] For example, a "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a nonessential amino acid residue in an immunoglobulin polypeptide is replaced with another amino acid residue from the same side chain family. In another embodiment, a string of amino acids can be replaced with a structurally similar string that differs in order and/or composition of side chain family members.

[00200] **Antibodies**

[00201] As used herein, an "antibody" or "antigen-binding polypeptide" can refer to a polypeptide or a polypeptide complex that specifically recognizes and binds to an antigen. An antibody can be a whole antibody and any antigen binding fragment or a single chain thereof. For example, "antibody" can include any protein or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule having biological activity of binding to the antigen. Non-limiting examples a complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework (FR) region, or any portion thereof, or at least one portion of a binding protein. As used herein, the term "antibody" can refer to an immunoglobulin molecule and immunologically active portions of an immunoglobulin (Ig) molecule, i.e., a molecule that contains an antigen binding site that specifically binds (immunoreacts with) an antigen. By "specifically binds" or "immunoreacts with" is meant that the antibody reacts with one or more antigenic determinants of the desired antigen and does not react with other polypeptides.

[00202] The terms "antibody fragment" or "antigen-binding fragment", as used herein, is a portion of an antibody such as $F_{(ab')2}$, $F_{(ab)2}$, F_{ab}', F_{ab}, Fv, scFv and the like. Regardless of structure, an antibody fragment binds with the same antigen that is recognized by the intact antibody. The term "antibody fragment" can include aptamers (such as spiegelmers), minibodies, and diabodies. The term "antibody fragment" can also include any synthetic or genetically engineered protein that acts like an antibody by binding to a specific antigen to form a complex. Antibodies, antigen-binding polypeptides, variants, or derivatives described herein include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, epitope-binding fragments, e.g., Fab, Fab' and $F(ab')_2$, Fd, Fvs, single-chain Fvs (scFv), single-chain antibodies, dAb (domain antibody), minibodies, disulfide-linked Fvs (sdFv), fragments comprising either a VL or VH domain, fragments produced by a Fab expression library, and anti-idiotypic (anti-Id) antibodies.

[00203] A "single-chain variable fragment" or "scFv" refers to a fusion protein of the variable regions of the heavy (V_H) and light chains (V_L) of immunoglobulins. A single chain Fv ("scFv") polypeptide molecule is a covalently linked VH:VL heterodimer, which can be expressed from a gene fusion including VH- and VL-encoding genes linked by a peptide-encoding linker. (*See* Huston et al. (1988) Proc Nat Acad Sci USA 85(16):5879-5883). In some aspects, the regions are connected with a short linker peptide of ten to about 25 amino acids. The linker can be rich in glycine for flexibility, as well as serine or threonine for solubility, and can either connect the N-terminus of the V_H with the C-terminus of the V_L, or vice versa. This protein retains the specificity of the original immunoglobulin, despite removal of the constant regions and the introduction of the linker. A number of methods have been described to discern chemical structures for converting the naturally aggregated, but chemically separated, light and heavy polypeptide chains from an antibody V region into an scFv molecule, which will fold into a three dimensional structure substantially similar to the structure of an antigen-binding site. *See*, e.g., U.S. Patent No. 5,091,5 13; No. 5,892,019; No. 5,132,405; and No. 4,946,778, each of which are incorporated by reference in their entireties.

[00204] Very large naive human scFv libraries have been and can be created to offer a large source of rearranged antibody genes against a plethora of target molecules. Smaller libraries can be constructed from individuals with infectious diseases in order to isolate disease-specific antibodies. (*See* Barbas et al., Proc. Natl. Acad. Sci. USA 89:9339-43 (1992); Zebedee et al, Proc. Natl. Acad. Sci. USA 89:3 175-79 (1992)).

[00205] Antibodies of the invention can also be modified to produce mosaic antibodies. A mosaic antibody is one in which the external amino acid residues of an antibody of one species are rationally replaced or "mosaicked" by the external amino acid residues of an antibody of a second species such that the antibody of the first species is not immunogenic in the second species, thereby reducing the immunogenicity of the antibody. Since the antigenicity of a protein depends primarily on its surface properties, the immunogenicity of an antibody can be reduced by substituting exposed residues that differ from those typically found in antibodies of another mammalian species. Reasonable substitution of this external residue should have little or no effect on the internal domain or on inter-domain contacts. Thus, since the changes are limited to variable region framework residues, ligand binding properties should not be affected. This process is called "mosaicism" since only the outer surface or skin of the antibody is altered and the supporting residues remain undisturbed.

[00206] The "mosaicing" process utilizes sequence data for human antibody variable domains compiled by available Kabat et al (1987) Sequences of Proteins of Immunological interest,4th ed., Bethesda, Md., National Institutes of Health, updates to this database, and other accessible U.S. and foreign databases (nucleic acids and Proteins). Non-limiting examples of methods for generating mosaic antibodies include EP 519596; U.S. Pat. No. 6,797,492; and is described in Padlan et al, 1991.

[00207] Antibody molecules obtained from humans fall into five classes of immunoglobulins: IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Those skilled in the art will appreciate that heavy chains are classified as gamma, mu, alpha, delta, or epsilon (γ, μ, α, δ, ε) with some subclasses among them (e.g., γ1-γ4). Certain classes have subclasses as well, such as IgG_1, IgG_2, IgG_3 and IgG_4 and others. The immunoglobulin subclasses (isotypes) e.g., IgG_1, IgG_2, IgG_3, IgG_4, IgG_5, etc. are well characterized and are known to confer functional specialization. With regard to IgG, a standard immunoglobulin molecule comprises two identical light chain polypeptides of molecular weight approximately 23,000 Daltons, and two identical heavy chain polypeptides of molecular weight 53,000-70,000. The four chains are typically joined by disulfide bonds in a "Y" configuration wherein the light chains bracket the heavy chains starting at the mouth of the "Y" and continuing through the variable region. Immunoglobulin or antibody molecules described herein can be of any type (e.g., IgG, IgE, IgM, IgD, IgA, and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of an immunoglobulin molecule.

[00208] Light chains are classified as either kappa or lambda (κ, λ). Each heavy chain class can be bound with either a kappa or lambda light chain. In general, the light and heavy chains are covalently bonded to each other, and the "tail" portions of the two heavy chains are bonded to each other by covalent disulfide linkages or non-covalent linkages when the immunoglobulins are generated either by hybridomas, B cells, or genetically engineered host cells. In the heavy chain, the amino acid sequences run from an N-terminus at the forked ends of the Y configuration to the C-terminus at the bottom of each chain.

[00209] Both the light and heavy chains are divided into regions of structural and functional homology. The terms "constant" and "variable" are used functionally. The variable domains of both the light (VL) and heavy (VH) chain portions determine antigen recognition and specificity. Conversely, the constant domains of the light chain (CL) and the heavy chain (CH1, CH2 or CH3) confer important biological properties such as secretion, transplacental mobility, Fc receptor binding, complement binding, and the like. The term "antigen-binding site," or "binding portion" can refer to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains, referred to as "hypervariable regions," are interposed between more conserved flanking stretches known as "framework regions," or "FRs". Thus, the term "FR" can refer to amino acid sequences which are naturally found between, and adjacent to, hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs." VH and VL regions, which contain the CDRs, as well as frameworks (FRs) of the CTLA-4 antibodies are shown in Table 1A-Table 12B.

[00210] The six CDRs present in each antigen-binding domain are short, non-contiguous sequences of amino acids that are specifically positioned to form the antigen-binding domain as the antibody assumes its three dimensional configuration in an aqueous environment. The remainder of the amino acids in the antigen-binding domains, the FR regions, show less inter-molecular variability. The framework regions largely adopt a β-sheet conformation and the CDRs form loops which connect, and in some cases form part of, the β-sheet structure. The

framework regions act to form a scaffold that provides for positioning the CDRs in correct orientation by inter-chain, non-covalent interactions. The antigen-binding domain formed by the positioned CDRs provides a surface complementary to the epitope on the immunoreactive antigen, which promotes the non-covalent binding of the antibody to its cognate epitope. The amino acids comprising the CDRs and the framework regions, respectively, can be readily identified for a heavy or light chain variable region by one of ordinary skill in the art, since they have been previously defined (*See*, "Sequences of Proteins of Immunological Interest," Kabat, E., et al., U.S. Department of Health and Human Services, (1983); and Chothia and Lesk, *J. Mol. Biol.*, 196:901-917 (1987)).

[00211] Where there are two or more definitions of a term which is used and/or accepted within the art, the definition of the term as used herein is intended to include all such meanings unless explicitly stated to the contrary. A specific example is the use of the term "complementarity determining region" ("CDR") to describe the non-contiguous antigen combining sites found within the variable region of both heavy and light chain polypeptides. This particular region has been described by Kabat et al., U.S. Dept. of Health and Human Services, "Sequences of Proteins of Immunological Interest" (1983) and by Chothia et al., *J. Mol. Biol.* 196:901-917 (1987), which are incorporated herein by reference in their entireties. The CDR definitions according to Kabat and Chothia include overlapping or subsets of amino acid residues when compared against each other. Nevertheless, application of either definition to refer to a CDR of an antibody or variants thereof is intended to be within the scope of the term as defined and used herein. The appropriate amino acid residues which encompass the CDRs as defined by each of the above cited references are set forth in the table below as a comparison. The exact residue numbers which encompass a particular CDR will vary depending on the sequence and size of the CDR. Those skilled in the art can routinely determine which residues comprise a particular CDR given the variable region amino acid sequence of the antibody.

CDR	Kabat Numbering	Chothia Numbering
VH CDR1	31-35	26-32
VH CDR2	50-65	52-58
VH CDR3	95-102	95-102
VL CDR1	24-34	26-32
VL CDR2	50-56	50-52
VL CDR3	89-97	91-96

[00212] Kabat et al. defined a numbering system for variable domain sequences that is applicable to any antibody. The skilled artisan can unambiguously assign this system of "Kabat numbering" to any variable domain sequence, without reliance on any experimental data beyond the sequence itself. As used herein, "Kabat numbering" refers to the numbering system set forth by Kabat et al., U.S. Dept. of Health and Human Services, "Sequence of Proteins of Immunological Interest" (1983).

[00213] In addition to table above, the Kabat number system describes the CDR regions as follows: CDR-H1 begins at approximately amino acid 31 (i.e., approximately 9 residues after the first cysteine residue), includes approximately 5-7 amino acids, and ends at the next tryptophan residue. CDR-H2 begins at the fifteenth residue after the end of CDR-H1, includes approximately 16-19 amino acids, and ends at the next arginine or lysine residue. CDR-H3 begins at approximately the thirty third amino acid residue after the end of CDR-H2; includes 3-25 amino acids; and ends at the sequence W-G-X-G, where X is any amino acid. CDR-L1 begins at approximately residue 24 (i.e., following a cysteine residue); includes approximately 10-17 residues; and ends at the next tryptophan residue. CDR-L2 begins at approximately the sixteenth residue after the end of CDR-L1 and includes approximately 7 residues. CDR-L3 begins at approximately the thirty third residue after the end of CDR-L2 (i.e., following a cysteine residue); includes approximately 7-11 residues and ends at the sequence F or W-G-X-G, where X is any amino acid.

[00214] As used herein, the term "epitope" can include any protein determinant that can specifically bind to an immunoglobulin, a scFv, or a T-cell receptor. The variable region allows the antibody to selectively recognize and specifically bind epitopes on antigens. For example, the VL domain and VH domain, or subset of the complementarity determining regions (CDRs), of an antibody combine to form the variable region that defines a three dimensional antigen-binding site. This quaternary antibody structure forms the antigen-binding site present at the end of each arm of the Y. Epitopic determinants can consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. For example, antibodies can be raised against N- terminal or C-terminal peptides of a polypeptide. More specifically, the antigen-binding site is defined by three CDRs on each of the VH and VL chains (i.e. CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2 and CDR-L3). In one embodiment, the antibodies can be directed to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) having Ann UniProt Reference No:

P16410 (CTLA-4_HUMAN) (223 amino acid residues in length), comprising the amino acid sequence of SEQ ID NO: [ ]:

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        10          20          30          40          50
MACLGFQRHK AQLNLATRTW PCTLLFFLLF IPVFCKAMHV AQPAVVLASS
        60          70          80          90         100
RGIASFVCEY ASPGKATEVR VTVLRQADSQ VTEVCAATYM MGNELTFLDD
       110         120         130         140         150
SICTGTSSGN QVNLTIQGLR AMDTGLYICK VELMYPPPYY LGIGNGTQIY
       160         170         180         190         200
VIDPEPCPDS DFLLWILAAV SSGLFFYSFL LTAVSLSKML KKRSPLTTGV
       210         220
YVKMPPTEPE CEKQFQPYFI
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[00215] As used herein, the terms "immunological binding," and "immunological binding properties" can refer to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. (See Nature 361 : 186-87 (1993)). The ratio of K_{off} /K_{on} enables the cancellation of all parameters not related to affinity, and is equal to the equilibrium binding constant, K_D. (See, generally, Davies et al. (1990) Annual Rev Biochem 59:439-473). An antibody of the invention can specifically bind to a CTLA4 epitope when the equilibrium binding constant (K_D) is ≤1 μM, ≤10 μM, ≤ 10 nM, ≤ 10 pM, or ≤ 100 pM to about 1 pM, as measured by kinetic assays such as radioligand binding assays or similar assays known to those skilled in the art, such as BIAcore or Octet (BLI). For example, in some embodiments, the K_D is between about 1E-12 M and a K_D about 1E-11 M. In some embodiments, the K_D is between about 1E-11 M and a K_D about 1E-10 M. In some embodiments, the K_D is between about 1E-10 M and a K_D about 1E-9 M. In some embodiments, the K_D is between about 1E-9 M and a K_D about 1E-8 M. In some

embodiments, the K_D is between about 1E-8 M and a K_D about 1E-7 M. In some embodiments, the K_D is between about 1E-7 M and a K_D about 1E-6 M. For example, in some embodiments, the K_D is about 1E-12 M while in other embodiments the K_D is about 1E-11 M. In some embodiments, the K_D is about 1E-10 M while in other embodiments the K_D is about 1E-9 M. In some embodiments, the K_D is about 1E-8 M while in other embodiments the K_D is about 1E-7 M. In some embodiments, the K_D is about 1E-6 M while in other embodiments the K_D is about 1E-5 M. In some embodiments, for example, the K_D is about 3 E-11 M, while in other embodiments the K_D is about 3E-12 M. In some embodiments, the K_D is about 6E-11 M. "Specifically binds" or "has specificity to," can refer to an antibody that binds to an epitope via its antigen-binding domain, and that the binding entails some complementarity between the antigen-binding domain and the epitope. For example, an antibody is said to "specifically bind" to an epitope when it binds to that epitope, via its antigen-binding domain more readily than it would bind to a random, unrelated epitope.

[00216] For example, the CTLA4 antibody can be monovalent or bivalent, and can comprise a single or double chain. Functionally, the binding affinity of the CTLA4 antibody is within the range of 10^{-5}M to 10^{-12} M. For example, the binding affinity of the CTLA4 antibody is from 10^{-6} M to 10^{-12} M, from 10^{-7} M to 10^{-12} M, from 10^{-8} M to 10^{-12} M, from 10^{-9} M to 10^{-12} M, from 10^{-5} M to 10^{-11} M, from 10^{-6} M to 10^{-11} M, from 10^{-7} M to 10^{-11} M, from 10^{-8} M to 10^{-11} M, from 10^{-9} M to 10^{-11} M, from 10^{-10} M to 10^{-11} M, from 10^{-5} M to 10^{-10}M, from 10^{-6} M to 10^{-10} M, from 10^{-7} M to 10^{-10} M, from 10^{-8} M to 10^{-10}M, from 10^{-9} M to 10^{-10} M, from 10^{-5} M to 10^{-9} M, from 10^{-6} M to 10^{-9}M, from 10^{-7} M to 10^{-9} M, from 10^{-8} M to 10^{-9} M, from 10^{-5} M to 10^{-8} M, from 10^{-6} M to 10^{-8} M, from 10^{-7} M to 10^{-8} M, from 10^{-5} M to 10^{-7} M, from 10^{-6} M to 10^{-7} M, or from 10^{-5} M to 10^{-6} M.

[00217] A CTLA-4 protein, or a derivative, fragment, analog, homolog or ortholog thereof, can be utilized as an immunogen in the generation of antibodies that immunospecifically bind these protein components. A CTLA-4 protein or a derivative, fragment, analog, homolog, or ortholog thereof, coupled to a proteoliposome can be utilized as an immunogen in the generation of antibodies that immunospecifically bind these protein components.

[00218] Those skilled in the art will recognize that it is possible to determine, without undue experimentation, if a human monoclonal antibody has the same specificity as a human monoclonal antibody of the invention by ascertaining whether the former prevents the latter from binding to CTLA-4. For example, if the human monoclonal antibody being tested competes with the human monoclonal antibody of the invention, as shown by a decrease in

binding by the human monoclonal antibody of the invention, then it is likely that the two monoclonal antibodies bind to the same, or to a closely related, epitope.

[00219] Another way to determine whether a human monoclonal antibody has the specificity of a human monoclonal antibody of the invention is to pre-incubate the human monoclonal antibody of the invention with the CTLA-4 protein, with which it is normally reactive, and then add the human monoclonal antibody being tested to determine if the human monoclonal antibody being tested is inhibited in its ability to bind CTLA-4. If the human monoclonal antibody being tested is inhibited then, in all likelihood, it has the same, or functionally equivalent, epitopic specificity as the monoclonal antibody of the invention. Screening of human monoclonal antibodies of the invention can be also carried out by utilizing CTLA-4 and determining whether the test monoclonal antibody is able to neutralize CTLA-4.

[00220] Various procedures known within the art can be used for the production of polyclonal or monoclonal antibodies directed against a protein of the invention, or against derivatives, fragments, analogs homologs or orthologs thereof. (*See*, for example, Antibodies: A Laboratory Manual, Harlow E, and Lane D, 1988, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, incorporated herein by reference).

[00221] Antibodies can be purified by well-known techniques, such as affinity chromatography using protein A or protein G, which provide primarily the IgG fraction of immune serum. Subsequently, or alternatively, the specific antigen which is the target of the immunoglobulin sought, or an epitope thereof, can be immobilized on a column to purify the immune specific antibody by immunoaffinity chromatography. Purification of immunoglobulins is discussed, for example, by D. Wilkinson (The Scientist, published by The Scientist, Inc., Philadelphia PA, Vol. 14, No. 8 (April 17, 2000), pp. 25-28).

[00222] The term "monoclonal antibody" or "mAb" or "Mab" or "monoclonal antibody composition", as used herein, can refer to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

[00223] Monoclonal antibodies can be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent

to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes can be immunized *in vitro*.

[00224] The immunizing agent can include the protein antigen, a fragment thereof or a fusion protein thereof. For example, peripheral blood lymphocytes can be used if cells of human origin are desired, or spleen cells or lymph node cells can be used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (*See* Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Immortalized cell lines can be transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. For example, rat or mouse myeloma cell lines are employed. The hybridoma cells can be cultured in a suitable culture medium that contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine ("HAT medium"), which substances prevent the growth of HGPRT-deficient cells.

[00225] Immortalized cell lines that are useful are those that fuse efficiently, support stable high-level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. For example, immortalized cell lines can be murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center (San Diego, California) and the American Type Culture Collection (Manassas, Virginia). Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies. (See Kozbor, J. Immunol, 133:3001 (1984); Brodeur et al, Monoclonal Antibody Production Techniques and Applications, Marcel Dekker, Inc., New York, (1987) pp. 51-63)).

[00226] The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against the antigen. For example, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., 107:220 (1980). Moreover, in

therapeutic applications of monoclonal antibodies, it is important to identify antibodies having a high degree of specificity and a high binding affinity for the target antigen.

[00227] After the desired hybridoma cells are identified, the clones can be subcloned by limiting dilution procedures and grown by standard methods. (See Goding, Monoclonal Antibodies: Principles and Practice, Academic Press, (1986) pp. 59-103). Suitable culture media for this purpose include, for example, Dulbecco's Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells can be grown *in vivo* as ascites in a mammal.

[00228] The monoclonal antibodies secreted by the subclones can be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A-Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

[00229] Monoclonal antibodies can also be made by recombinant DNA methods, such as those described in U.S. Patent No. 4,816,567 (incorporated herein by reference in its entirety). DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a source of such DNA. Once isolated, the DNA can be placed into expression vectors, which are then transfected into host cells such as 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. The DNA also can be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences (*See* U.S. Patent No. 4,816,567; Morrison, Nature 368, 812-13 (1994)) or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

[00230] Fully human antibodies, for example, are antibody molecules in which the entire sequence of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies" or "fully human antibodies". Human monoclonal antibodies, such as fully human and humanized antibodies, can be prepared by using trioma technique; the human B-cell hybridoma technique (see Kozbor, et al, 1983

Immunol Today 4: 72); and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole, et al, 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96). Human monoclonal antibodies can be utilized and can be produced by using human hybridomas (see Cote, et al, 1983. Proc Natl Acad Sci USA 80: 2026-2030) or by transforming human B-cells with Epstein Barr Virus in vitro (see Cole, et al., 1985 In: MONOCLONAL ANTIBODIES AND CANCER THERAPY, Alan R. Liss, Inc., pp. 77-96).

[00231] "Humanized antibodies" can be antibodies from a non-human species (such as mouse), whose amino acid sequences (for example, in the CDR regions) have been modified to increase their similarity to antibody variants produced in humans. Antibodies can be humanized by methods known in the art, such as CDR-grafting. See also, Safdari et al., (2013) *Biotechnol Genet Eng Rev.*; 29:175-86. In addition, humanized antibodies can be produced in transgenic plants, as an an inexpensive production alternative to existing mammalian systems. For example, the transgenic plant can be a tobacco plant, *i.e.*, *Nicotiania benthamiana*, and *Nicotiana tabaccum*. The antibodies are purified from the plant leaves. Stable transformation of the plants can be achieved through the use of *Agrobacterium tumefaciens* or particle bombardment. For example, nucleic acid expression vectors containing at least the heavy and light chain sequences are expressed in bacterial cultures, *i.e.*, *A. tumefaciens* strain BLA4404, via transformation. Infiltration of the plants can be accomplished via injection. Soluble leaf extracts can be prepared by grinding leaf tissue in a mortar and by centrifugation. Isolation and purification of the antibodies can be readily be performed by many of the methods known to the skilled artisan in the art. Other methods for antibody production in plants are described in, for example, Fischer et al., Vaccine, 2003, 21:820-5; and Ko et al, Current Topics in Microbiology and Immunology, Vol. 332, 2009, pp. 55-78. As such, the invention further provides any cell or plant comprising a vector that encodes the antibody of the invention, or produces the antibody of the invention.

[00232] Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Pat. Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489-498 (1991); Studnicka et al., *Protein Engineering* 7(6):805-814 (1994); Roguska. et al., *Proc. Natl. Sci. USA* 91:969-973 (1994)), and chain shuffling (U.S. Pat. No. 5,565,332, which is incorporated by reference in its entirety). "Humanization" (also called Reshaping or CDR-grafting) is a well-established technique understood by the skilled artisan for reducing the immunogenicity of monoclonal

antibodies (mAbs) from xenogeneic sources (commonly rodent) and for improving their activation of the human immune system (See, for example, Hou S, Li B, Wang L, Qian W, Zhang D, Hong X, Wang H, Guo Y (July 2008). "Humanization of an anti-CD34 monoclonal antibody by complementarity-determining region grafting based on computer-assisted molecular modeling". *J Biochem.* 144 (1): 115–20).

[00233] In addition, antibodies (such as human antibodies) can also be produced using other techniques, including phage display libraries. (*See* Hoogenboom and Winter, J. Mol. Biol, 227:381 (1991); Marks et al., J. Mol. Biol, 222:581 (1991)). Similarly, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al., Bio/Technology 10, 779-783 (1992); Lonberg et al., Nature 368 856-859 (1994); Morrison, Nature 368, 812-13 (1994); Fishwild et al, Nature Biotechnology 14, 845-51 (1996); Neuberger, Nature Biotechnology 14, 826 (1996); and Lonberg and Huszar, *Intern. Rev. Immunol.* 13: 65-93 (1995).

[00234] Human antibodies can additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (*See*, PCT publication no. WO94/02602 and U.S. Patent No. 6,673,986). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full complement of the modifications. A non-limiting example of such a nonhuman animal is a mouse, and is termed the Xenomouse™ as disclosed in PCT publication nos. WO96/33735 and WO96/34096. This animal produces B cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the

immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv (scFv) molecules.

[00235] Thus, using such a technique, therapeutically useful IgG, IgA, IgM and IgE antibodies can be produced. For an overview of this technology for producing human antibodies, see Lonberg and Huszar *Int. Rev. Immunol.* 73:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publication nos. WO 98/24893; WO 96/34096; WO 96/33735; U.S. Pat. Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Creative BioLabs (Shirley, NY) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described herein.

[00236] An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598. It can be obtained by a method, which includes deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

[00237] One method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771. This method includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

[00238] In a further improvement on this procedure, a method for identifying a clinically relevant epitope on an immunogen and a correlative method for selecting an antibody that binds immunospecifically to the relevant epitope with high affinity, is disclosed in PCT publication No. WO99/53049.

[00239] The antibody of interest can also be expressed by a vector containing a DNA segment encoding the single chain antibody described herein. Vectors include, but are not

limited to, chemical conjugates such as described in WO 93/64701, which has targeting moiety (e.g. a ligand to a cellular surface receptor), and a nucleic acid binding moiety (e.g. polylysine), viral vectors (e.g. a DNA or RNA viral vector), fusion proteins such as described in PCT/US 95/02140 (WO 95/22618), which is a fusion protein containing a target moiety (e.g. an antibody specific for a target cell) and a nucleic acid binding moiety (e.g. a protamine), plasmids, phage, viral vectors, etc. The vectors can be chromosomal, non-chromosomal or synthetic. Retroviral vectors can also be used, and include moloney murine leukemia viruses. DNA viral vectors can also be used, and include pox vectors such as orthopox or avipox vectors, herpesvirus vectors such as a herpes simplex I virus (HSV) vector (*See* Geller, A. I. et al, J. Neurochem, 64:487 (1995); Lim, F., et al, in DNA Cloning: Mammalian Systems, D. Glover, Ed. (Oxford Univ. Press, Oxford England) (1995); Geller, A. I. et al, Proc Natl. Acad. Sci.: U.S.A. 90:7603 (1993); Geller, A. I., et al, Proc Natl. Acad. Sci USA 87: 1149 (1990), Adenovirus Vectors (see LeGal LaSalle et al, Science, 259:988 (1993); Davidson, et al, Nat. Genet 3 :219 (1993); Yang, et al, J. Virol. 69:2004 (1995) and Adeno-associated Virus Vectors (see Kaplitt, M. G.. et al, Nat. Genet. 8: 148 (1994).

[00240] Pox viral vectors introduce the gene into the cell's cytoplasm. Avipox virus vectors result in only a short term expression of the nucleic acid. Adenovirus vectors, adeno-associated virus vectors, and herpes simplex virus (HSV) vectors can be used for introducing the nucleic acid into neural cells. The adenovirus vector results in a shorter term expression (about 2 months) than adeno-associated virus (about 4 months), which in turn is shorter than HSV vectors. The particular vector chosen will depend upon the target cell and the condition being treated. The introduction can be by standard techniques, e.g. infection, transfection, transduction or transformation. Examples of modes of gene transfer include e.g., naked DNA, $CaP0_4$ precipitation, DEAE dextran, electroporation, protoplast fusion, lipofection, cell microinjection, and viral vectors.

[00241] The vector can be employed to target essentially any desired target cell. For example, stereotaxic injection can be used to direct the vectors (e.g. adenovirus, HSV) to a desired location. Additionally, the particles can be delivered by intracerebroventricular (icv) infusion using a minipump infusion system, such as a SynchroMed Infusion System. A method based on bulk flow, termed convection, has also proven effective at delivering large molecules to extended areas of the brain and can be useful in delivering the vector to the target cell. (See Bobo et al, Proc. Natl. Acad. Sci. USA 91 :2076-2080 (1994); Morrison et al, Am. J. Physiol. 266:292-305 (1994)). Other methods that can be used include catheters,

intravenous, parenteral, intraperitoneal and subcutaneous injection, and oral or other known routes of administration.

[00242] These vectors can be used to express large quantities of antibodies that can be used in a variety of ways. For example, to detect the presence of CTLA4 in a sample. The antibody can also be used to try to bind to and disrupt a CTLA4 activity.

[00243] In embodiments, the antibodies herein can be delivered to a subject using a gene-based approach. For example, the nucleotide sequence of an anti-CTLA4 antibody as described herein can be delivered into a subject using a vector, DNA or RNA. *See,* for example, Deal, Cailin E., Andrea Carfi, and Obadiah J. Plante. "Advancements in mRNA Encoded Antibodies for Passive Immunotherapy." *Vaccines* 9.2 (2021): 108. Such methods can allow for the design and generation of more complex antibody molecules with improved and/or added functions.

[00244] Viral vectors such as adenovirus (Ad) and adeno-associated virus (AAV) have been engineered for *in vivo* mAb expression by replacing part of their genome with nucleic acid sequences encoding the antibody of interest. The term "viral vector" can refer to a nucleic acid vector construct that includes at least one element of viral origin and has the capacity to be packaged into a viral vector particle. The viral vector can contain the nucleic acid encoding an antibody, antigen-binding portion thereof, or CAR as described herein in place of non-essential viral genes. The vector and/or particle may be utilized for the purpose of transferring any nucleic acids into cells either in vitro or in vivo.

[00245] Retroviruses are a common tool for gene delivery. In embodiments, a retrovirus is used to deliver a polynucleotide encoding the antibody to a cell. The term "retrovirus" can refer to an RNA virus that reverse transcribes its genomic RNA into a linear double-stranded DNA copy and subsequently covalently integrates its genomic DNA into a host genome. Once the virus is integrated into the host genome, it is referred to as a "provirus." The provirus serves as a template for RNA polymerase II and directs the expression of RNA molecules which encode the structural proteins and enzymes needed to produce new viral particles.

[00246] Illustrative retroviruses suitable for use in particular embodiments, include, but are not limited to: Moloney murine leukemia virus (M-MuLV), Moloney murine sarcoma virus (MoMSV), Harvey murine sarcoma virus (HaMuSV), murine mammary tumor virus (MuMTV), gibbon ape leukemia virus (GaLV), feline leukemia virus (FLV), Spumavirus, Friend murine leukemia virus, Murine Stem Cell Virus (MSCV) and Rous Sarcoma Virus (RSV)) and lentivirus.

[00247] The term "lentivirus" can refer to a group (or genus) of complex retroviruses. Illustrative lentiviruses include, but are not limited to: HIV (human immunodeficiency virus; including HIV type 1, and HIV type 2); visna-maedi virus (VMV) virus; the caprine arthritis-encephalitis virus (CAEV); equine infectious anemia virus (EIAV); feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV). In one embodiment, HIV based vector backbones (i.e., HIV cis-acting sequence elements) are preferred. In particular embodiments, a lentivirus is used to deliver a polynucleotide comprising a CAR to a cell.

[00248] Gene transfer of the antibody nucleotide sequences themselves, as DNA or RNA, is an alternative option for transient *in vivo* antibody production. For example, plasmid DNA approaches can utilie an electroporation component to enhance transfection efficiency following IM delivery. Also, mRNA delivery can be used for *in vivo* expression of antibodies. In embodiments, the mRNA encoding the antibody of interest can be modified, such as optimization of the mRNA codon usage, and lipid nanoparticles can be used for mRNA delivery.

[00249] In an embodiment, the antibodies described herein can be full-length antibodies, containing an Fc region similar to wild-type Fc regions that bind to Fc receptors.

[00250] Techniques can be adapted for the production of single-chain antibodies specific to an antigenic protein of the invention (*See* e.g., U.S. Patent No. 4,946,778). In addition, methods can be adapted for the construction of F_{ab} expression libraries (*See* e.g., Huse, et al, 1989 Science 246: 1275-1281) to allow rapid and effective identification of monoclonal F_{ab} fragments with the desired specificity for a protein or derivatives, fragments, analogs or homologs thereof. Antibody fragments that contain the idiotypes to a protein antigen can be produced by techniques known in the art including, but not limited to: (i) an $F_{(ab')2}$ fragment produced by pepsin digestion of an antibody molecule; (ii) an F_{ab} fragment generated by reducing the disulfide bridges of an $F_{(ab')2}$ fragment; (iii) an F_{ab} fragment generated by the treatment of the antibody molecule with papain and a reducing agent and (iv) F_v fragments.

[00251] Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies can, for example, target immune system cells to unwanted cells (see U.S. Patent No. 4,676,980), and for treatment of HIV infection (*See* PCT Publication Nos. WO91/00360; WO92/20373). The antibodies can be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins can 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 and those disclosed, for example, in U.S. Patent No. 4,676,980.

[00252] The antibody of the invention can be modified with respect to effector function, so as to enhance, e.g., the effectiveness of the antibody in treating cancer. For example, cysteine residue(s) can be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated can have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). (*See* Caron et al, J. Exp Med., 176: 1 191-1 195 (1992) and Shopes, J. Immunol., 148: 2918-2922 (1992)). Alternatively, an antibody can be engineered that has dual Fc regions and can thereby have enhanced complement lysis and ADCC capabilities. (*See* Stevenson et al, Anti-Cancer Drug Design, 3 : 219-230 (1989)). In one embodiment, the antibody of the invention has modifications of the Fc region, such that the Fc region does not bind to the Fc receptors. For example, the Fc receptor is Fcγ receptor. Antibodies with modification of the Fc region such that the Fc region does not bind to Fcγ, but still binds to neonatal Fc receptor are useful as described herein.

[00253] In certain embodiments, an antibody of the invention can comprise an Fc variant comprising an amino acid substitution which alters the antigen-independent effector functions of the antibody, in particular the circulating half-life of the antibody. Such antibodies exhibit either increased or decreased binding to FcRn when compared to antibodies lacking these substitutions, therefore, have an increased or decreased half-life in serum, respectively. Fc variants with improved affinity for FcRn are anticipated to have longer serum half-lives, and such molecules have useful applications in methods of treating mammals where long half-life of the administered antibody is desired, *e.g.*, to treat a chronic disease or disorder. In contrast, Fc variants with decreased FcRn binding affinity are expected to have shorter halt-lives, and such molecules are also useful, for example, for administration to a mammal where a shortened circulation time can be advantageous, *e.g.*, for *in vivo* diagnostic imaging or in situations where the starting antibody has toxic side effects when present in the circulation for prolonged periods. Fc variants with decreased FcRn binding affinity are also less likely to cross the placenta and, thus, are also useful in the treatment of diseases or disorders in pregnant women. In addition, other applications in which reduced FcRn binding affinity can be desired include those applications in which localization to the brain, kidney, and/or liver is desired. In one embodiment, the Fc variant-containing antibodies can exhibit reduced transport across the epithelium of kidney glomeruli from the vasculature. In another

embodiment, the Fc variant-containing antibodies can exhibit reduced transport across the blood brain barrier (BBB) from the brain, into the vascular space. In one embodiment, an antibody with altered FcRn binding comprises an Fc domain having one or more amino acid substitutions within the "FcRn binding loop" of an Fc domain. The FcRn binding loop is comprised of amino acid residues 280-299 (according to EU numbering). Exemplary amino acid substitutions with altered FcRn binding activity are disclosed in PCT Publication No. WO05/047327 which is incorporated by reference herein. In certain exemplary embodiments, the antibodies, or fragments thereof, of the invention comprise an Fc domain having one or more of the following substitutions: V284E, H285E, N286D, K290E and S304D (EU numbering).

[00254] In some embodiments, mutations are introduced to the constant regions of the mAb such that the antibody dependent cell-mediated cytotoxicity (ADCC) activity of the mAb is altered. For example, the mutation is an LALA mutation in the CH2 domain. In one embodiment, the antibody (e.g., a human mAb, or a bispecific Ab) contains mutations on one scFv unit of the heterodimeric mAb, which reduces the ADCC activity. In another embodiment, the mAb contains mutations on both chains of the heterodimeric mAb, which completely ablates the ADCC activity. For example, the mutations introduced into one or both scFv units of the mAb are LALA mutations in the CH2 domain. These mAbs with variable ADCC activity can be optimized such that the mAbs exhibits maximal selective killing towards cells that express one antigen that is recognized by the mAb, however exhibits minimal killing towards the second antigen that is recognized by the mAb.

[00255] In other embodiments, antibodies of the invention for use in the diagnostic and treatment methods described herein have a constant region, e.g., an IgG_1 , IgG_2, or IgG_4 heavy chain constant region, which can be altered to reduce or eliminate glycosylation. For example, an antibody of the invention can also comprise an Fc variant comprising an amino acid substitution which alters the glycosylation of the antibody. For example, the Fc variant can have reduced glycosylation (e.g., N- or O-linked glycosylation). In some embodiments, the Fc variant comprises reduced glycosylation of the N-linked glycan normally found at amino acid position 297 (EU numbering). In another embodiment, the antibody has an amino acid substitution near or within a glycosylation motif, for example, an N-linked glycosylation motif that contains the amino acid sequence NXT or NXS. In a particular embodiment, the antibody comprises an Fc variant with an amino acid substitution at amino acid position 228 or 299 (EU numbering). In more particular embodiments, the antibody comprises an IgGl or IgG4 constant region comprising an S228P and a T299A mutation (EU numbering).

[00256] Exemplary amino acid substitutions which confer reduced or altered glycosylation are described in PCT Publication No, WO05/018572, which is incorporated by reference herein in its entirety. In some embodiments, the antibodies of the invention, or fragments thereof, are modified to eliminate glycosylation. Such antibodies, or fragments thereof, can be referred to as "agly" antibodies, or fragments thereof, (e.g. "agly" antibodies). While not wishing to be bound by theory "agly" antibodies, or fragments thereof, can have an improved safety and stability profile *in vivo*. Exemplary agly antibodies, or fragments thereof, comprise an aglycosylated Fc region of an IgG_4 antibody which is devoid of Fc-effector function thereby eliminating the potential for Fc mediated toxicity to the normal vital tissues and cells that express CTLA4. In yet other embodiments, antibodies of the invention, or fragments thereof, comprise an altered glycan. For example, the antibody can have a reduced number of fucose residues on an N-glycan at Asn297 of the Fc region, i.e., is afucosylated. In another embodiment, the antibody can have an altered number of sialic acid residues on the N-glycan at Asn297 of the Fc region.

[00257] The invention also is directed to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

[00258] Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas aeruginosa), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Non-limiting examples include ^{212}Bi, ^{131}I, ^{131}In, ^{90}Y, and ^{186}Re.

[00259] Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as l,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in

Vitetta et al, Science 238: 1098 (1987). Carbon- 14-labeled l-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. (*See* PCT Publication No. WO94/11026, and U.S. Patent No. 5,736,137).

[00260] Those of ordinary skill in the art understand that a large variety of possible moieties can be coupled to the resultant antibodies or to other molecules of the invention. (*See*, for example, "Conjugate Vaccines", Contributions to Microbiology and Immunology, J. M. Cruse and R. E. Lewis, Jr (eds), Carger Press, New York, (1989), the entire contents of which are incorporated herein by reference).

[00261] Coupling can be accomplished by any chemical reaction that will bind the two molecules so long as the antibody and the other moiety retain their respective activities. This linkage can include many chemical mechanisms, for instance covalent binding, affinity binding, intercalation, coordinate binding, and complexation. In one embodiment, binding is, covalent binding. Covalent binding can be achieved either by direct condensation of existing side chains or by the incorporation of external bridging molecules. Many bivalent or polyvalent linking agents are useful in coupling protein molecules, such as the antibodies of the present invention, to other molecules. For example, representative coupling agents can include organic compounds such as thioesters, carbodiimides, succinimide esters, diisocyanates, glutaraldehyde, diazobenzenes and hexamethylene diamines. This listing is not intended to be exhaustive of the various classes of coupling agents known in the art but, rather, is exemplary of the more common coupling agents. (*See* Killen and Lindstrom, Jour. Immun. 133 : 1335-2549 (1984); Jansen et al., Immunological Reviews 62: 185-216 (1982); and Vitetta et al, Science 238: 1098 (1987)). Non-limiting examples of linkers are described in the literature. (*See*, for example, Ramakrishnan, S. et al., Cancer Res. 44:201-208 (1984) describing use of MBS (M-maleimidobenzoyl-N-hydroxysuccinimide ester). *See also*, U.S. Patent No. 5,030,719, describing use of halogenated acetyl hydrazide derivative coupled to an antibody by way of an oligopeptide linker. Non-limiting examples of useful linkers that can be used with the antibodies of the invention include: (i) EDC (l-ethyl-3- (3-dimethylamino-propyl) carbodiimide hydrochloride; (ii) SMPT (4- succinimidyloxycarbonyl-alpha-methyl-alpha-(2-pridyl-dithio)-toluene (Pierce Chem. Co., Cat. (21558G); (iii) SPDP (succinimidyl-6 [3-(2-pyridyldithio) propionamido]hexanoate (Pierce Chem. Co., Cat #21651G); (iv) Sulfo-LC-SPDP (sulfosuccinimidyl 6 [3-(2- pyridyldithio)-propianamide] hexanoate (Pierce Chem. Co. Cat. #2165-G); and (v) sulfo- NHS (-hydroxysulfo-succinimide: Pierce Chem. Co., Cat. #24510) conjugated to EDC.

[00262] The linkers described herein contain components that have different attributes, thus leading to conjugates with differing physio-chemical properties. For example, sulfo- NHS esters of alkyl carboxylates are more stable than sulfo-NHS esters of aromatic carboxylates. NHS-ester containing linkers are less soluble than sulfo-NHS esters. Further, the linker SMPT contains a sterically hindered disulfide bond, and can form conjugates with increased stability. Disulfide linkages, are in general, less stable than other linkages because the disulfide linkage is cleaved in vitro, resulting in less conjugate available. Sulfo-NHS, in particular, can enhance the stability of carbodimide couplings. Carbodimide couplings (such as EDC) when used in conjunction with sulfo-NHS, forms esters that are more resistant to hydrolysis than the carbodimide coupling reaction alone.

[00263] The antibodies disclosed herein can also be formulated as immunoliposomes. Liposomes containing the antibody are 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. Patent No. 5,013,556.

[00264] Non-limiting examples of 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. Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al, J. Biol. Chem., 257: 286-288 (1982) via a disulfide-interchange reaction.

[00265] ***Multispecific Antibodies (Bispecific and Trispecific)***

[00266] Multispecific antibodies are antibodies that can recognize two or more different antigens. For example, a bi-specific antibody (bsAb) is an antibody comprising two variable domains or scFv units such that the resulting antibody recognizes two different antigens. For example, a trispecific antibody (tsAb) is an antibody comprising two variable domains or scFv units such that the resulting antibody recognizes three different antigens. This invention provides for multispecific antibodies, such as bi-specific and trispecific antibodies, that recognize CTLA-4 and a second antigen and/or a third antigen. In one embodiment, multispecific antibodies (e.g., bi-specific antibodies and trispecific antibodies) can comprise CTLA-4 specific fusion proteins encompassing the antibodies described herein. Exemplary second and.or third antigens include tumor associated antigens (e.g., LINGO1), cytokines (e.g., IL-12 (IL-12A (p35 subunit) protein sequence having NCBI Reference No.

NP_000873.2; IL-12B (p40 subunit) protein sequence having NCBI Reference No. NP_002178.2); IL-18 (protein sequence having NCBI Reference no. NP_001553.1); IL-15 (protein sequence having NCBI Reference No. NP_000576.1); IL-7 (protein sequence having NCBI Reference No. NP_000871.1); IL-2 (protein sequence having NCBI Reference No. NP_000577.2); and IL-21 (protein sequence having NCBI Reference No. NP_068575.1)), cytokine cognate receptors (eg., IL-12R), and cell surface receptors. Non-limiting examples of second and/or third antigens include CTLA-4, LAG-3, CD28, CD122, 4-1BB, TIM3, OX-40, OX40L, CD40, CD40L, LIGHT, ICOS, ICOSL, GITR, GITRL, TIGIT, CD27, VISTA, B7H3, B7H4, HEVM (or BTLA), CD47, PDL1, MICA, MICB, and CD73. In one embodiment, the bispecific and trispecific antibodies comprise CTLA-4 fusion proteins. For example, the fusion protein comprises an antibody comprising a variable domain or scFv unit and a ligand or antigen and/or a third ligand or antigen as described herein such that the resulting antibody recognizes an antigen and binds to the ligand-specific receptor. Exemplary antibody compositions (e.g., VH and/or VL sequences or fragments thereof) that are useful for the design of CTLA-4 fusion proteins as described herein include, but are not limited to, anti-CAIX antibodies described in PCT/US2006/046350 and PCT/US2015/067178; anti-CXCR4 antibodies described in PCT/US20006/005691; anti-CCR4 antibodies described in PCT/US2008/088435, PCT/US2013/039744, and PCT/US2015/054202; anti-PD-L1 antibodies described in PCT/US2008/088435 and PCT/US2020/062815; anti-PD-1 antibodies described in PCT/US2020/037791 and PCT/US2020/037781; anti-GITR antibodies described in PCT/US2017/043504; anti-claudin-4 antibodies described in PCT/US2019/022272; and anti-MUC1 antibodies described in PCT/US2020/037783 (each of the applications which are incorporated by reference in their entireties). In one embodiment, the fusion protein further comprises a constant region, and/or a linker as described herein. Different formats of multispecific antibodies (e.g., bispecific antibodies and trispecific antibodies such as a fusion protein comprises an antibody that recognizes CTLA-4 and a ligand) are described herein. Ligands can be tumor associated antigens (e.g., LINGO1, ErbB2 (HER2/neu), carcinoembryonic antigen (CEA), epithelial cell adhesion molecule (EpCAM), epidermal growth factor receptor (EGFR), MUC1, MSLN, CD19, CD20, CD30, CD40, CD22, RAGE-l, MN-CA IX, RET1, RET2 (AS), prostate specific antigen (PSA), TAG-72, PAP, p53, Ras, prostein, PSMA, survivin, 9D7, prostate-carcinoma tumor antigen-l (PCTA-1), GAGE, MAGE, mesothelin, β-catenin, TGF-βRII, BRCA1/2, SAP-1, HPV-E6, HPV-E7 (see also, PCT/US2015/067225 and PCT/US2019/022272 for additional tumor-associated surface antigens, which are incorporated by reference in their entireties)); cytokines (e.g., IL-12 (IL-

12A (p35 subunit) protein sequence having NCBI Reference No. NP_000873.2; IL-12B (p40 subunit) protein sequence having NCBI Reference No. NP_002178.2); IL-18 (protein sequence having NCBI Reference no. NP_001553.1); IL-15 (protein sequence having NCBI Reference No. NP_000576.1); IL-7 (protein sequence having NCBI Reference No. NP_000871.1); IL-2 (protein sequence having NCBI Reference No. NP_000577.2); and IL-21 (protein sequence having NCBI Reference No. NP_068575.1)); CTLA-4, LAG-3, CD28, CD122, 4-1BB, TIM3, OX-40, OX40L, CD40, CD40L, LIGHT, ICOS, ICOSL, GITR, GITRL, TIGIT, CD27, VISTA, B7H3, B7H4, HEVM (or BTLA), CD47, PDL1, MICA, MICB, and CD73. Different formats of bispecific or trispecific antibodies are also provided herein. In some embodiments, each of the anti-CTLA-4 fragment and the second antigen-specific fragment and/or the third antigen-specific fragment is each independently selected from a Fab fragment, a single-chain variable fragment (scFv), or a single-domain antibody. In some embodiments, the bispecific or trispecific antibody further includes a Fc fragment (e.g., as described in PCT/US2015/021529 and PCT/US2019/023382, each of which are incorporated by reference in their entireties). A bispecific or trispecific antibody of the invention can comprise a heavy chain and a light chain combination or scFv of the CTLA-4 antibodies described herein.

[00267] Multispecific antibodies (e.g., bispecific antibodies and trispecific antibodies) of the invention (for example, an anti-CTLA-4-scFv fusion protein) can be constructed using methods known art. In some embodiments, the bi-specific antibody is a single polypeptide wherein the two scFv fragments are joined by a long linker polypeptide, of sufficient length to allow intramolecular association between the two scFv units to form an antibody. In other embodiments, the bi-specific antibody is more than one polypeptide linked by covalent or non-covalent bonds. In some embodiments, the amino acid linker depicted herein (GGGGSGGGGS; "(G4S)2" (SEQ ID NO: [ ])) can be generated with a longer G4S linker to improve flexibility. For example, the linker can also be "(G4S)3" (e.g., GGGGSGGGGSGGGGS (SEQ ID NO: [ ])); "(G4S)4" (e.g., GGGGSGGGGSGGGGSGGGGS) (SEQ ID NO: [ ]); "(G4S)5" (e.g., GGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: [ ])); "(G4S)6" (e.g., GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: [ ])); "(G4S)7" (e.g., GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGS (SEQ ID NO: [ ])); and the like. For example, use of the (G4S)5 linker can provide more flexibility to a ligand described herein and can improve expression. In some embodiments, the linker can also be $(GS)_n$, $(GGS)_n$, $(GGGS)_n$, $(GGSG)_n$, $(GGSGG)_n$, or $(GGGGS)_n$, wherein n is 1, 2, 3, 4, 5, 6, 7, 8, 9,

or 10. Non-limiting examples of linkers known to those skilled in the art that can be used to construct the fusions described herein can be found in U.S. Patent No. 9,708,412; U.S. Patent Application Publication Nos. US 20180134789 and US 20200148771; and PCT Publication No. WO2019051122 (each of which are incorporated by reference in their entireties).

[00268] In another embodiment, the multispecific antibodies (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) can be constructed using the "knob into hole" method (Ridgway et al, Protein Eng 7:617-621 (1996)). In this method, the Ig heavy chains of the two different variable domains are reduced to selectively break the heavy chain pairing while retaining the heavy-light chain pairing. The two heavy-light chain heterodimers that recognize two different antigens/ligands or three different antigens/ligands are mixed to promote heteroligation pairing, which is mediated through the engineered "knob into holes" of the CH3 domains.

[00269] In another embodiment the multispecific antibodies (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) can be constructed through exchange of heavy-light chain dimers from two or more different antibodies to generate a hybrid antibody where the first heavy-light chain dimer recognizes CTLA-4 and the second heavy-light chain dimer recognizes a second antigen and/or third antigen. The mechanism for heavy-light chain dimer is similar to the formation of human IgG_4, which also functions as a bispecific molecule. Dimerization of IgG heavy chains is driven by intramolecular force, such as the pairing the CH3 domain of each heavy chain and disulfide bridges. Presence of a specific amino acid in the CH3 domain (R409) has been shown to promote dimer exchange and construction of the IgG_4 molecules. Heavy chain pairing is also stabilized further by interheavy chain disulfide bridges in the hinge region of the antibody. Specifically, in IgG_4, the hinge region contains the amino acid sequence Cys-Pro-Ser-Cys (in comparison to the stable IgGl hinge region which contains the sequence Cys-Pro-Pro-Cys) at amino acids 226-230. This sequence difference of Serine at position 229 has been linked to the tendency of IgG_4 to form intrachain disulfides in the hinge region (Van der Neut Kolfschoten, M. et al, 2007, Science 317: 1554-1557 and Labrijn, A.F. et al, 2011, Journal of Immunol 187:3238-3246).

[00270] The multispecific antibodies (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) of the invention can be created through introduction of the R409 residue in the CH3 domain and the Cys-Pro-Ser-Cys sequence in the hinge region of antibodies that recognize CTLA-4 or a second and/or third antigen, so that the heavy-light chain dimers exchange to produce an antibody molecule with one heavy-light chain dimer

recognizing CTLA-4 and the second heavy-light chain dimer recognizing a second and/or third antigen, wherein the second and/or third antigen (or ligand) is any antigen (or ligand) disclosed herein. Known IgG_4 molecules can also be altered such that the heavy and light chains recognize CTLA-4 or a second and/or third antigen, as disclosed herein. Use of this method for constructing the multispecific antibodies (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) of the invention can be beneficial due to the intrinsic characteristic of IgG_4 molecules wherein the Fc region differs from other IgG subtypes in that it interacts poorly with effector systems of the immune response, such as complement and Fc receptors expressed by certain white blood cells. This specific property makes these IgG_4-based multispecific antibodies (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) attractive for therapeutic applications, in which the antibody is required to bind the target(s) and functionally alter the signaling pathways associated with the target(s), however not trigger effector activities.

[00271] The multispecific antibodies (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) described herein can be engineered with a non-depleting heavy chain isotype, such as IgG1-LALA or stabilized IgG4 or one of the other non-depleting variants. In some embodiments, mutations are introduced to the constant regions of the bsAb such that the antibody dependent cell-mediated cytotoxicity (ADCC) activity of the bsAb is altered. For example, the mutation is a LALA mutation in the CH2 domain. In one aspect, the multispecific antibody (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) contains mutations on one scFv unit of the heterodimeric multispecific antibody, which reduces the ADCC activity. In another aspect, the multispecific antibody (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) contains mutations on both chains of the heterodimeric multispecific antibody, which completely ablates the ADCC activity. For example, the mutations introduced in one or both scFv units of the multispecific antibody (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) are LALA mutations in the CH2 domain. These multispecific antibodies (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) with variable ADCC activity can be optimized such that the multi-specific antibodies exhibit maximal selective killing towards cells that express one antigen that is recognized by the multispecific antibody, however, exhibits minimal killing towards the second antigen that is recognized by the multispecific antibody.

[00272] The multispecific antibodies (e.g., bispecific antibodies) described herein can be engineered as modular tetrameric bispecific antibodies (tBsAb). See, for example, WO

2018/071913, which is incorporated by reference herein in its entirety. For example, the tetravalent antibody can be a dimer of a bispecific scFv fragment including a first binding site for a first antigen, and a second binding site for a second antigen. In embodiments, the anti-CTLA-4 antibody can be the first binding site for a first antigen. In embodiments, the anti-CTLA-4 antibody can be the second binding site for a second antigen. The two binding sites can be joined together via a linker domain. In embodiments, the scFv fragment is a tandem scFv, the linker domain includes an immunoglobulin hinge region (e.g., an IgGl, an IgG2, an IgG3, or an IgG4 hinge region) amino acid sequence. In embodiments, the immunoglobulin hinge region amino acid sequence can be flanked by a flexible linker amino acid sequence, e.g., having the linker amino acid sequence $(GGGS)_{x1-6}$, $(GGGGS)_{x1-6}$, or GSAGSAAGSGEF. In embodiments, the linker domain includes at least a portion of an immunoglobulin Fc domain, e.g., an IgGl, an IgG2, an IgG3, or an IgG4 Fc domain. In embodiments, the at least a portion of the immunoglobulin Fc domain does not include a CH2 domain. In embodiments, the at least a portion of the immunoglobulin Fc domain can be a CH2 domain. An exemplary CH2 domain amino acid sequence includes APELLGGPDVFLF (SEQ ID NO: [ ]). The Fc domain can be linked to the C-terminus of an immunoglobulin hinge region (e.g., an IgGl, an IgG2, an IgG3, or an IgG4 hinge region) amino acid sequence. The linker domain can include a flexible linker amino acid sequence (e.g., $(GGGS)_{x1-6}$, $(GGGGS)_{x1-6}$, or GSAGSAAGSGEF (SEQ ID NO: [ ])) at one terminus or at both termini.

[00273] In embodiments, the multispecific antibodies (e.g., bispecific antibodies) described herein can be engineered with a wild type Fc region, or a modified Fc region. For example, embodiments can comprise an IgG_3 CH2 domain. In other embodiments, the multispecific antibodies (e.g., bispecific antibodies) are engineered without an Fc domain and/or Fc fragment.

[00274] In embodiments, the tBsAb can be specific for CTLA-4, and also a target selected from the group consisting of B7H3, B7H4, CD27, CD28, CD40, CD40L, CD47, CD122, CCR4, CTLA-4, GITR, GITRL, ICOS, ICOSL, LAG-3, LIGHT, OX-40, OX40L, PD-L1, PD-1, TIM3, 4-1BB, TIGIT, VISTA, HEVM, BTLA, MICA, MICB, and KIR.

[00275] The multispecific antibodies (e.g., bispecific antibodies and trispecific antibodies such as anti-CTLA-4-scFv fusions) disclosed herein can be useful in treatment of chronic infections, diseases, or medical conditions, for example, cancer.

[00276] ***Use of Antibodies Against CTLA-4***

[00277] Antibodies of the invention specifically binding a CTLA-4 protein, or a fragment thereof, can be administered for the treatment of a CTLA-4 associated disease or disorder. A "CTLA-4-associated disease or disorder" includes disease states and/or symptoms associated with a disease state, where increased levels of CTLA-4 and/or activation of cellular signaling pathways involving CTLA-4 are found. In some embodiments, the cancer can be lung cancer, kidney cancer, ovarian cancer, prostate cancer, colon cancer, breast cancer, cervical cancer, uterine cancer, brain cancer, skin cancer, liver cancer, pancreatic cancer, glioblastoma multiforme, cutaneous squamous cell carcinoma, melanoma, renal cancer, such as clear cell renal cell carcinoma, or stomach cancer.

[00278] Antibodies of the invention, including bi-specific, polyclonal, monoclonal, humanized and fully human antibodies, can be used as therapeutic agents. Such agents will generally be employed to treat cancer in a subject, increase vaccine efficiency or augment a natural immune response. An antibody preparation, for example, one having high specificity and high affinity for its target antigen, is administered to the subject and will generally have an effect due to its binding with the target. Administration of the antibody can abrogate or inhibit or interfere with an activity of the CTLA-4 protein.

[00279] ***Pharmaceutical Compositions***

[00280] Antibodies of the invention specifically binding a CTLA-4 protein or fragment thereof can be administered for the treatment of a cancer in the form of pharmaceutical compositions. Principles and considerations involved in preparing therapeutic pharmaceutical compositions comprising the antibody, as well as guidance in the choice of components are provided, for example, in: Remington: The Science And Practice Of Pharmacy 20th ed. (Alfonso R. Gennaro, et al, editors) Mack Pub. Co., Easton, Pa., 2000; Drug Absorption Enhancement: Concepts, Possibilities, Limitations, And Trends, Harwood Academic Publishers, Langhorne, Pa., 1994; and Peptide And Protein Drug Delivery (Advances In Parenteral Sciences, Vol. 4), 1991, M. Dekker, New York.

[00281] A specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the particular antibodies, variant or derivative thereof used, the patient's age, body weight, general health, sex, and diet, and the time of administration, rate of excretion, drug combination, and the severity of the particular disease being treated. Judgment of such factors by medical caregivers is within the ordinary skill in the art. The amount will also depend on the individual patient to be treated, the route of administration, the type of formulation, the characteristics of the compound used, the severity

of the disease, and the desired effect. The amount used can be determined by pharmacological and pharmacokinetic principles well known in the art.

[00282] A therapeutically effective amount of an antibody of the invention can be the amount needed to achieve a therapeutic objective. As noted herein, this can be a binding interaction between the antibody and its target antigen that, in certain cases, interferes with the functioning of the target. The amount required to be administered will furthermore depend on the binding affinity of the antibody for its specific antigen, and will also depend on the rate at which an administered antibody is depleted from the free volume other subject to which it is administered. The dosage administered to a subject (e.g., a patient) of the antigen-binding polypeptides described herein is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight, between 0.1 mg/kg and 20 mg/kg of the patient's body weight, or 1 mg/kg to 10 mg/kg of the patient's body weight. Human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the disclosure may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation. Common ranges for therapeutically effective dosing of an antibody or antibody fragment of the invention can be, by way of nonlimiting example, from about 0.1 mg/kg body weight to about 50 mg/kg body weight. Common dosing frequencies can range, for example, from twice daily to once a week.

[00283] Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. (See, e.g., Marasco et al, Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993)). The formulation can also contain more than one active compound as necessary for the particular indication being treated, for example, those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition can comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine (e.g. IL-15), chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[00284] The active ingredients can 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.

[00285] The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

[00286] Sustained-release preparations can be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g. , films, or microcapsules. Examples of sustained-release matrices 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 γ 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), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods.

[00287] The antibodies or agents of the invention (also referred to herein as "active compounds"), and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Such pharmaceutical compositions can comprise the antibody or agent and a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable carrier" can include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Non-limiting examples of such carriers or diluents include water, saline, ringer's solutions, dextrose solution, and 5% human serum albumin. Liposomes and non-aqueous vehicles such as fixed oils can also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[00288] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (i.e., topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00289] Pharmaceutical compositions suitable for injectable use can include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™(BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In embodiments, the composition is sterile and is fluid to the extent that easy syringeability exists. It can be stable under the conditions of manufacture and storage and can be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, isotonic agents can be included, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00290] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients

enumerated above, as required, followed by filtered sterilization. For example, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00291] Oral compositions can include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00292] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[00293] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00294] The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[00295] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release

formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations are apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

[00296] Oral or parenteral compositions can be formulated in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[00297] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[00298] ***Diagnostics***

[00299] An antibody according to the invention can be used as an agent for detecting the presence of CTLA-4 (or a protein fragment thereof) in a sample. For example, the antibody can contain a detectable label. Antibodies can be polyclonal or monoclonal. An intact antibody, or a fragment thereof (e.g., F_{ab}, scFv, or $F_{(ab)2}$) can be used. The term "labeled", with regard to the probe or antibody, can encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin. The term "biological sample" can include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. Included within the usage of the term "biological

sample", therefore, is blood and a fraction or component of blood including blood serum, blood plasma, or lymph. That is, the detection method of the invention can be used to detect an analyte mRNA, protein, or genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of an analyte mRNA includes Northern hybridizations and in situ hybridizations. *In vitro* techniques for detection of an analyte protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, and immunofluorescence. In vitro techniques for detection of an analyte genomic DNA include Southern hybridizations.

[00300] Procedures for conducting immunoassays are described, for example in "ELISA: Theory and Practice: Methods in Molecular Biology", Vol. 42, J. R. Crowther (Ed.) Human Press, Totowa, NJ, 1995; "Immunoassay", E. Diamandis and T. Christopoulus, Academic Press, Inc., San Diego, CA, 1996; and "Practice and Theory of Enzyme Immunoassays", P. Tijssen, Elsevier Science Publishers, Amsterdam, 1985. Furthermore, *in vivo* techniques for detection of an analyte protein include introducing into a subject a labeled anti-analyte protein antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

[00301] Antibodies directed against a CTLA-4 protein (or a fragment thereof) can be used in methods known within the art relating to the localization and/or quantitation of a CTLA-4 protein (e.g., for use in measuring levels of the CTLA-4 protein within appropriate physiological samples, for use in diagnostic methods, for use in imaging the protein, and the like). In a given embodiment, antibodies specific to a CTLA-4 protein, or derivative, fragment, analog or homolog thereof, that contain the antibody derived antigen binding domain, are utilized as pharmacologically active compounds (referred to herein as "therapeutics").

[00302] An antibody of the invention specific for a CTLA-4 protein can be used to isolate a CTLA-4 polypeptide by standard techniques, such as immunoaffinity, chromatography or immunoprecipitation. Antibodies directed against a CTLA-4 protein (or a fragment thereof) can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, e.g., to, for example, determine the efficacy of a given treatment regimen.

[00303] Detection can be facilitated by coupling (i.e., physically linking) the antibody to a detectable substance. Examples of detectable substances include, but are not limited to, various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Non-limiting examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or

acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S, ^{32}P or ^{3}H.

[00304] ***Cellular therapies***

[00305] Cellular therapies are also provided here. For example, cellular therapies can include cells, such as T cells NK cells, or B cells, genetically engineered to express an anti-CTLA4 antibody as described herein. A "genetically engineered cell" can refer to any cell of any organism that is modified, transformed, or manipulated by addition or modification of a gene, a DNA or RNA sequence, or protein or polypeptide. Isolated cells, host cells, and genetically engineered cells can include isolated immune cells, such as NK cells, T cells, and B cells, that contain the DNA or RNA sequences encoding an antibody as described herein, and/or a chimeric receptor or chimeric receptor complex that is expressed on the cell surface.

[00306] A "T cell" is a cell of the immune system that matures in the thymus and produces T cell receptors (TCR). T cells can be naive cells (not in contact with the antigen; increased expression of CD62L, CCR7, CD28, CD3, CD127 and CD45RA and reduced expression of CD45RO compared to T_{CM}), memory T cells (T_M) (contacted with antigen and long-living) and effector cells (in contact with the antigen, cytotoxic). T_M can be further subdivided into subpopulations of central memory T cells (T_{CM}, increased expression of CD62L, CCR7, CD28, CD127, CD45RO and CD95 and decreased expression of CD54RA compared to naive T cells) and effector memory T cells (T_{EM}, reduced expression of CD62L, CCR7, CD28, CD45RA and increased expression of CD127 compared to naive T cells or T_{CM}). Effector T cells (T_E) can refer to CD8 + antigen-contacted cytotoxic T lymphocytes that have reduced expression of CD62L, CCR7, CD28 and are positive for granzyme and perforin compared to T_{CM}.

[00307] T-cells can be obtained from a number of sources, including peripheral blood mononuclear cells (PBMCs), bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue and tumours. In certain embodiments, T-cells can be obtained from a unit of blood collected from a subject using any number of techniques known to the skilled person, such as FICOLL™ separation. In one embodiment, cells from the circulating blood of a subject are obtained by apheresis. The

apheresis product typically contains lymphocytes, including T-cells, monocytes, granulocytes, B-cells, other nucleated white blood cells, red blood cells and platelets. In one embodiment, the cells collected by apheresis can be washed to remove the plasma fraction and placed in an appropriate buffer or media for subsequent processing. In one embodiment of the invention, the cells are washed with PBS. In an alternative embodiment, the washed solution lacks calcium and/or magnesium or can lack many if not all divalent cations. As would be appreciated by those of ordinary skill in the art, a washing step can be accomplished by methods known to those in the art, such as by using a semi-automated flow-through centrifuge, for example, the Cobe 2991 cell processor, the Baxter CytoMate, or the like. After washing, the cells can be resuspended in a variety of biocompatible buffers or other saline solution with or without buffer. In certain embodiments, the undesirable components of the apheresis sample can be removed and the cell directly resuspended in culture media.

[00308] In embodiments, T-cells are isolated from PBMCs. PBMCs may be isolated from buffy coats obtained by density gradient centrifugation of whole blood, for instance centrifugation through a LYMPHOPREP™ gradient, a PERCOLL™ gradient or a FICOLL™ gradient. T-cells may be isolated from PBMCs by depletion of the monocytes, for instance by using CD14 DYNABEADS®. In some embodiments, red blood cells may be lysed prior to the density gradient centrifugation.

[00309] An "NK cell" is a large granular lymphocyte, being a cytotoxic lymphocyte derived from the common lymphoid progenitor which does not naturally comprise an antigen-specific receptor (e.g. a T-cell receptor or a B-cell receptor). NK cells can be characterised by their CD3-, CD56+ phenotype. In embodiments, NK cell can refer to any known NK cell or any NK-like cell or any cell having the characteristics of an NK cell. Thus primary NK cells can be used or, in another embodiment, a NK cell known in the art that has previously been isolated and cultured can be used. Thus an NK cell-line can be used. A number of different NK cells are known and reported in the literature and any of these could be used, or a cell-line may be prepared from a primary NK cell, for example by viral transformation (Vogel et al. 2014, Leukemia 28:192-195). Suitable NK cells include (but are by no means limited to), in addition to NK-92, the NK-YS, NK-YT, MOTN-1 , NKL, KHYG-1 , HANK-1 , or NKG cell lines. Variants of other cell lines may also be used.

[00310] A “B-cell” is a B lymphocyte that, subsequent to activation, can produce antibody molecules. Activation of a B cell can be, without limitation, by recognition of an antigen by an antigen specific immunoglobulin receptor on the B cell surface or by a non-specific

stimulus, e.g., a B cell mitogen such as lipopolysaccharide or pokeweed mitogen. Thus, a B cell can be a "virgin" B lymphocyte that has never previously been activated or a "memory" B lymphocyte that has previously been activated or the progeny of such a B lymphocyte.

[00311] Cellular therapies, such as chimeric antigen receptor (CAR) T-cell therapies or chimeric antigen receptor (CAR) NK-cell therapies, are also provided herein. CAR T-cell therapies redirect a patient's T-cells and NK cells to kill tumor cells by the exogenous expression of a CAR on a T-cell or NK cell, for example. For example, when expressed in a T or NK cell, CARs have the ability to redirect T or NK cell specificity and reactivity toward a selected target in a non-MHC-restricted manner, exploiting the antigen-binding properties of monoclonal antibodies. The non-MHC-restricted antigen recognition gives T or NK cells expressing CARs the ability to recognize an antigen independent of antigen processing, thus bypassing a major mechanism of tumor escape.

[00312] A CAR can be a membrane spanning fusion protein that links the antigen recognition domain of an antibody to the intracellular signaling domains of the T-cell receptor and co-receptor. A suitable cell can be used, for example, that can secrete an anti-CTLA-4 antibody of the invention (or alternatively engineered to express an anti-CTLA-4 antibody as described herein to be secreted). The anti- CTLA-4 "payloads" to be secreted, can be, for example, minibodies, scFvs, IgG molecules, bispecific fusion molecules, and other antibody fragments as described herein. Upon contact or engineering, the cell described herein can then be introduced to a patient in need of a treatment by infusion therapies known to one of skill in the art. The patient can have a CTLA-4-associated disease or disorder as described herein, such as chronic infections or cancer. The cell (e.g., a T cell or NK cell) can be, for instance, T lymphocyte, a CD4+ T cell, a CD8+ T cell, or the combination thereof, without limitation. Exemplary CARs and CAR factories useful in aspects of the invention include those disclosed in, for example, PCT/US2015/067225 and PCT/US2019/022272, each of which are hereby incorporated by reference in their entireties. In one embodiment, the CTLA-4 antibodies discussed herein can be used in the construction of multi-specific antibodies or as the payload for a genetically engineered cell, such as a CAR-T cell, a CAR NK cell, or a genetically engineered B cell. For example, in one embodiment, the anti-CTLA-4 antibodies discussed herein can be used for the targeting of the CARS (i.e., as the targeting moiety). In another embodiment, the anti- CTLA-4 antibodies discussed herein can be used as the targeting moiety, and a different CTLA-4 antibody that targets a different epitope can be used as the payload. In another embodiment, the payload can be an immunomodulatory antibody payload.

[00313] ***Methods of Treatment***

[00314] As used herein, the terms "treat" or "treatment" refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder, such as the progression of cancer. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can refer to prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder or those in which the condition or disorder is to be prevented.

[00315] The invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a cancer (for example, if an early detection cancer biomarker is identified in such a subject), or other cell proliferation-related diseases or disorders. Such diseases or disorders include but are not limited to, e.g., those diseases or disorders associated with aberrant expression of CTLA-4. For example, the methods are used to treat, prevent or alleviate a symptom of cancer. In an embodiment, the methods are used to treat, prevent or alleviate a symptom of a solid tumor. Non-limiting examples of other tumors that can be treated by compositions described herein comprise lung cancer (e.g., non-small cell lung cancer or lung adenocarcinoma), gastric cancer, colorectal cancer, bladder cancer, breast cancer, ovarian cancer, prostate cancer, colon cancer, cervical cancer, brain cancer, skin cancer, liver cancer, pancreatic cancer, esophageal squamous cell carcinoma, nasopharyngeal carcinoma, glioblastoma multiforme, squamous cell carcinoma, melanoma, renal cell carcinoma, urothelial carcinoma, hepatocellular carcinoma, malignant pleural mesothelioma, and liquid tumors or stomach cancer. Additionally, the methods of the invention can be used to treat hematologic cancers such as leukemia and lymphoma. Alternatively, the methods can be used to treat, prevent or alleviate a symptom of a cancer that has metastasized. For example, cancers that can be treated or prevented or for which symptons can be alleviated include B-cell chronic lymphocytic leukemia (CLL), non-small-cell lung cancer, melanoma, ovarian cancer, lymphoma, or renal-cell cancer. Cancers that can also be treated or prevented or for which symptons can be alleviated include those solid tumors with a high mutation burden and WBC in filtrate.

[00316] Accordingly, in one aspect, the invention provides methods for preventing, treating or alleviating a symptom cancer or a cell proliferative disease or disorder in a subject by administering to the subject a monoclonal antibody, scFv antibody or bi- specific antibody of the invention. For example, an anti- CTLA-4 antibody can be administered in therapeutically effective amounts.

[00317] Subjects at risk for cancer or cell proliferation-related diseases or disorders can include patients who have a family history of cancer or a subject exposed to a known or suspected cancer-causing agent. Administration of a prophylactic agent can occur prior to the manifestation of cancer such that the disease is prevented or, alternatively, delayed in its progression.

[00318] In another aspect, tumor cell growth is inhibited by contacting a cell with an anti-CTLA4 antibody of the invention. The cell can be any cell that expresses CTLA-4.

[00319] Also included in the invention are methods of increasing or enhancing an immune response to an antigen. An immune response is increased or enhanced by administering to the subject a monoclonal antibody, scFv antibody, or bi-specific antibody of the invention. The immune response is augmented for example by augmenting antigen specific T effector function. The antigen is a viral (e.g. HIV), bacterial, parasitic or tumor antigen. The immune response is a natural immune response. By natural immune response is meant an immune response that is a result of an infection. The infection is a chronic infection. Increasing or enhancing an immune response to an antigen can be measured by a number of methods known in the art. For example, an immune response can be measured by measuring any one of the following: T cell activity, T cell proliferation, T cell activation, production of effector cytokines, and T cell transcriptional profile. Alternatively, the immune response is a response induced due to a vaccination.

[00320] Accordingly, in another aspect the invention provides a method of increasing vaccine efficiency by administering to the subject a monoclonal antibody or scFv antibody of the invention and a vaccine. The antibody and the vaccine are administered sequentially or concurrently. The vaccine is a tumor vaccine a bacterial vaccine or a viral vaccine.

[00321] ***Combinatory Methods***

[00322] Compositions of the invention as described herein can be administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the compositions of the disclosure include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens

(e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephalen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

[00323] In additional embodiments, the compositions of the invention as described herein can be administered in combination with cytokines. Cytokines that may be administered with the compositions include, but are not limited to, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-10, IL-12, IL-13, IL-15, anti-CD40, CD40L, and TNF-α.

[00324] In additional embodiments, the compositions described herein can be administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

[00325] In some embodiments, the compositions described herein can be administered in combination with other immunotherapeutic agents. Non-limiting examples of immunotherapeutic agents include simtuzumab, abagovomab, adecatumumab, afutuzumab, alemtuzumab, altumomab, amatuximab, anatumomab, arcitumomab, bavituximab, bectumomab, bevacizumab, bivatuzumab, blinatumomab, brentuximab, cantuzumab, catumaxomab, cetuximab, citatuzumab, cixutumumab, clivatuzumab, conatumumab, daratumumab, drozitumab, duligotumab, dusigitumab, detumomab, dacetuzumab, dalotuzumab, ecromeximab, elotuzumab, ensituximab, ertumaxomab, etaracizumab, farletuzumab, ficlatuzumab, figitumumab, flanvotumab, futuximab, ganitumab, gemtuzumab, girentuximab, glembatumumab, ibritumomab, igovomab, imgatuzumab, indatuximab, inotuzumab, intetumumab, ipilimumab, iratumumab, labetuzumab, lexatumumab, lintuzumab, lorvotuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, minretumomab, mitumomab, moxetumomab, narnatumab, naptumomab, necitumumab, nimotuzumab, nofetumomab, ocaratuzumab, ofatumumab, olaratumab, onartuzumab, oportuzumab, oregovomab, panitumumab, parsatuzumab, patritumab, pemtumomab, pertuzumab, pintumomab, pritumumab, racotumomab, radretumab, rilotumumab, rituximab, robatumumab, satumomab, sibrotuzumab, siltuximab, solitomab, tacatuzumab,

taplitumomab, tenatumomab, teprotumumab, tigatuzumab, tositumomab, trastuzumab, tucotuzumab, ublituximab, veltuzumab, vorsetuzumab, votumumab, zalutumumab, CC49, and 3F8.

[00326] The invention provides for methods of treating cancer in a patient by administering two antibodies that bind to the same epitope of the CTLA-4 protein or, alternatively, two different epitopes of the CTLA-4 protein. Alternatively, the cancer can be treated by administering a first antibody that binds to CTLA-4 and a second antibody that binds to a protein other than CTLA-4. In other embodiments, the cancer can be treated by administering a bispecific antibody that binds to CTLA-4 and that binds to a protein other than CTLA-4. For example, the other protein other than CTLA-4 can include, but is not limited to, IL-12, IL-12R, IL-2, IL-2R, IL-15, IL-15R, IL-7, IL-7R, IL-21, or IL-21R. For example, the other protein other than CTLA-4 is a tumor- associated antigen; the other protein other than CTLA-4 can also be a cytokine.

[00327] In some embodiments, the invention provides for the administration of an anti-PD-1 antibody alone or in combination with an additional antibody that recognizes another protein other than CTLA-4, with cells that are capable of effecting or augmenting an immune response. For example, these cells can be peripheral blood mononuclear cells (PBMC), or any cell type that is found in PBMC, e.g., cytotoxic T cells, macrophages, and natural killer (NK) cells.

[00328] Additionally, the invention provides administration of an antibody that binds to the CTLA4 protein and an anti-neoplastic agent, such as a small molecule, a growth factor, a cytokine or other therapeutics including biomolecules such as peptides, peptidomimetics, peptoids, polynucleotides, lipid-derived mediators, small biogenic amines, hormones, neuropeptides, and proteases. Small molecules include, but are not limited to, inorganic molecules and small organic molecules. Suitable growth factors or cytokines include an IL-2, GM-CSF, IL-12, and TNF-alpha. Small molecule libraries are known in the art. (See, Lam, Anticancer Drug Des., 12: 145, 1997.)

[00329] ***Chimeric antigen receptor (CAR) T-cell therapies***

[00330] Cellular therapies, such as chimeric antigen receptor (CAR) T-cell therapies, are also provided herein. CAR T-cell therapies redirect a patient's T-cells to kill tumor cells by the exogenous expression of a CAR on a T-cell, for example. A CAR can be a membrane spanning fusion protein that links the antigen recognition domain of an antibody to the intracellular signaling domains of the T-cell receptor and co-receptor. A suitable cell can be

used, for example, that can secrete an anti-CTLA-4 antibody of the present invention (or alternatively engineered to express an anti-CTLA-4 antibody as described herein to be secreted). The anti-CTLA-4 "payloads" to be secreted, can be, for example, minibodies, ScFvs, IgG molecules, bispecific fusion molecules, and other antibody fragments as described herein.

[00331] Solid tumors offer unique challenges for CAR-T therapies. Some barriers to CAR-T effectiveness in solid tumors include heterogeneous antigen expression, insufficient tissue homing, activation, persistence, and the immunosuppressive tumor microenvironment. Unlike blood cancers, tumor-associated target proteins are overexpressed between the tumor and healthy tissue resulting in on-target/off-tumor T-cell killing of healthy tissues. Furthermore, immune repression in the tumor microenvironment (TME) limits the activation of CAR-T cells towards killing the tumor. Upon such contact or engineering, the cell can then be introduced to a cancer patient in need of a treatment by infusion therapies known to one of skill in the art. The cancer patient may have a cancer of any of the types as disclosed herein. The cell (e.g., a T cell) can be, for instance, a tumor-infiltrating T lymphocyte, a CD4+ T cell, a CD8+ T cell, or the combination thereof, without limitation.

[00332] Exemplary CARs and CAR factories useful in aspects of the invention include those disclosed in, for example, PCT/US2015/067225 and PCT/US2019/022272, each of which are hereby incorporated by reference in their entireties. For example, CAR-T cells can be generated according to methods known in the art using lentivirus systems (via transduction), retrovirus systems (via transfection (electroporation)), and transposon systems (via PiggyBac). Useful for promoters for payloads that can be used in the generating of CAR-Ts or CAR NKs include, for example, constitutive promoters (where the promoter is the same as for CAR-T or CAR NK, such as EF1a then IRES or 2A); inducible promoters (where the promoter is different from the promoter for CAR-T, such as NFAT, IL-2 prom); and genetically engineered promoters (such as a CTLA-4 locus "knock in" of cytokine and/or a promoter that is under the control of an endogenous promoter). In one embodiment, the CTLA-4 antibodies or the CTLA-4 fusion proteins discussed herein can be used in the construction of multi-specific antibodies or as the payload for a genetically engineered cell, such as a CAR-T cell, CAR NK cell, or genetically engineered B cell. For example, in one embodiment, the anti-CTLA-4 antibodies or the CTLA-4 fusion proteins discussed herein can be used for the targeting of the CARS (i.e., as the targeting moiety). In one embodiment, the anti-CTLA-4 antibodies or the CTLA-4 fusion proteins discussed herein can be used as a payload to be secreted by a genetically engineered cell, such as a CAR-T cell, a CAR NK

cell, or a genetically engineered B cell. In another embodiment, the anti-CTLA-4 antibodies or the CTLA-4 fusion proteins discussed herein can be used as the targeting moiety, and a different CTLA-4 antibody that targets a different epitope can be used as the payload. In another embodiment, the payload can be an immunomodulatory antibody payload. In some embodiments, the CTLA-4 antibodies or the CTLA-4 fusion proteins as described herein for use in CAR-T compositions are not high-affinity CTLA-4 antibodies (for example, so that the antibody does not bind strongly to its CTLA-4 target). For example, the CTLA-4 antibodies or the CTLA-4 fusion proteins described herein can be used as a payload secreted by the genetically engineered cell, such as a CAR-T cell, a CAR-NK cell, or a genetically engineered B cell, with the two targeting moieties (for example, tumor-associated surface antigens) selected for a specific cancer (i.e. MSLN and MUC1 for ovarian cancer). Non-limiting examples of a tumor-associated surface antigen include ErbB2 (HER2/neu), carcinoembryonic antigen (CEA), epithelial cell adhesion molecule (EpCAM), epidermal growth factor receptor (EGFR), MUC1, MSLN, CD19, CD20, CD30, CD40, CD22, RAGE-l, MN-CA IX, RET1, RET2 (AS), prostate specific antigen (PSA), TAG-72, PAP, p53, Ras, prostein, PSMA, survivin, 9D7, prostate-carcinoma tumor antigen-l (PCTA-1), GAGE, MAGE, mesothelin, β-catenin, TGF-βRII, BRCA1/2, SAP-1, HPV-E6, HPV-E7 (see also, PCT/US2015/067225 and PCT/US2019/022272 for additional tumor-associated surface antigens, which are incorporated by reference in their entireties). Exemplary armored CAR-T cells are listed in the table below.

CART	Payload	Format	Promoter	Publication
PSMA	DN-TGFb			Molecular Therapy **26:** 1855 (2018)
GD2	cJun	cDNA		Nature **576:** 293(2019)
Fibronectin PD-L1	CD47 PD-L1 CTLA-4	VHH		Cancer Immunol Res. **8**:518-529 (2020)
GPC3	IL-12			J Immunol 2019; 203:198
CD20	PD-1			Cancer Science. 2019;110:3079
CD19 Muc16	PD-1			nature biotechnology 36:847 (2018)
CD19 Muc16	IL-18			Cell Reports 23:2130 (2018)
CD19	IL-12	fusion	IRES	Scientific REPOrTS 7: 10541 (2017)

Muc16				
CD19	PD-1	scFv	P2A	Clin Cancer Res 23:6982 (2017)
CAE	IL-18 IL-12		NFAT IL-2	Cell Reports 21:3205 (2017)
VEGF2	IL-12			Clin Cancer Res 18:1672 (2012)

[00333] In one embodiment, bispecific (or dual-targeted) CAR-Ts are provided. In another embodiment, the CAR-T is an engineered cell comprising a chimeric antigen receptor, wherein the chimeric antigen receptor comprises an extracellular ligand binding domain that is specific for a first antigen and a second antigen on the surface of a cancer cell, wherein the first antigen comprises CXCR4 and the second antigen comprises CLDN4, or the first antigen comprises CAIX and the second antigen comprises CD70, or the first antigen comprises MUC1 and the second antigen comprises Msln. For example, the anti-CTLA-4 antibodies or the CTLA-4 fusion proteins described herein can be used as a payload for a genetically engineered cell, such as a CAR-T, CAR-NK cell or genetically engineered B cell as described herein. In one embodiment, a CXCR4/CLDN4 dual targeting CAR-T with an anti-CTLA-4 fusion payload can be used for breast cancer. In one embodiment, a CAIX/CD70 dual targeting CAR-T with an anti-CTLA-4 fusion payload can be used for clear cell renal cell carcinoma (ccRCC). In one embodiment, a MUC1/Msln dual targeting CAR-T with an anti-CTLA-4 fusion payload can be used for ovarian cancer.

[00334] ***Diagnostic Assays***

[00335] The anti-CTLA-4 antibodies can be used diagnostically to, for example, monitor the development or progression of cancer as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment and/or prevention regimen.

[00336] In some embodiments, for diagnostic purposes, the anti-CTLA-4 antibody of the invention is linked to a detectable moiety, for example, so as to provide a method for detecting a cancer cell in a subject at risk of or suffering from a cancer.

[00337] The detectable moieties can be conjugated directly to the antibodies or fragments, or indirectly by using, for example, a fluorescent secondary antibody. Direct conjugation can be accomplished by standard chemical coupling of, for example, a fluorophore to the antibody or antibody fragment, or through genetic engineering. Chimeras, or fusion proteins can be constructed which contain an antibody or antibody fragment coupled to a fluorescent

or bioluminescent protein. For example, Casadei, et al, (Proc Natl Acad Sci U S A. 1990 Mar;87(6):2047-51) describe a method of making a vector construct capable of expressing a fusion protein of aequorin and an antibody gene in mammalian cells.

[00338] As used herein, the term "labeled", with regard to the probe or antibody, can encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject (such as a biopsy), as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect cells that express CTLA-4 in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of CTLA-4 include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, and immunofluorescence. Furthermore, *in vivo* techniques for detection of CTLA-4 include introducing into a subject a labeled anti-CTLA-4 antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

[00339] In the case of "targeted" conjugates, that is, conjugates which contain a targeting moiety— a molecule or feature designed to localize the conjugate within a subject or animal at a particular site or sites, localization can refer to a state when an equilibrium between bound, "localized", and unbound, "free" entities within a subject has been essentially achieved. The rate at which such equilibrium is achieved depends upon the route of administration. For example, a conjugate administered by intravenous injection can achieve localization within minutes of injection. On the other hand, a conjugate administered orally can take hours to achieve localization. Alternatively, localization can simply refer to the location of the entity within the subject or animal at selected time periods after the entity is administered. By way of another example, localization is achieved when an moiety becomes distributed following administration.

[00340] It is understood that a reasonable estimate of the time to achieve localization can be made by one skilled in the art. Furthermore, the state of localization as a function of time can be followed by imaging the detectable moiety (e.g., a light-emitting conjugate) according to the methods of the invention, such as with a photodetector device. The "photodetector

device" used should have a high enough sensitivity to enable the imaging of faint light from within a mammal in a reasonable amount of time, and to use the signal from such a device to construct an image.

[00341] In cases where it is possible to use light-generating moieties which are extremely bright, and/or to detect light-generating fusion proteins localized near the surface of the subject or animal being imaged, a pair of "night- vision" goggles or a standard high-sensitivity video camera, such as a Silicon Intensified Tube (SIT) camera (e.g., from Hammamatsu Photonic Systems, Bridgewater, N.J.), can be used. More typically, however, a more sensitive method of light detection is required.

[00342] In extremely low light levels the photon flux per unit area becomes so low that the scene being imaged no longer appears continuous. Instead, it is represented by individual photons which are both temporally and spatially distinct form one another. Viewed on a monitor, such an image appears as scintillating points of light, each representing a single detected photon. By accumulating these detected photons in a digital image processor over time, an image can be acquired and constructed. In contrast to conventional cameras where the signal at each image point is assigned an intensity value, in photon counting imaging the amplitude of the signal carries no significance. The objective is to simply detect the presence of a signal (photon) and to count the occurrence of the signal with respect to its position over time.

[00343] At least two types of photodetector devices, described below, can detect individual photons and generate a signal which can be analyzed by an image processor. Reduced-Noise Photodetection devices achieve sensitivity by reducing the background noise in the photon detector, as opposed to amplifying the photon signal. Noise is reduced primarily by cooling the detector array. The devices include charge coupled device (CCD) cameras referred to as "backthinned", cooled CCD cameras. In the more sensitive instruments, the cooling is achieved using, for example, liquid nitrogen, which brings the temperature of the CCD array to approximately -120°C. "Backthinned" refers to an ultra- thin backplate that reduces the path length that a photon follows to be detected, thereby increasing the quantum efficiency. A particularly sensitive backthinned cryogenic CCD camera is the "TECH 512", a series 200 camera available from Photometries, Ltd. (Tucson, Ariz.).

[00344] "Photon amplification devices" amplify photons before they hit the detection screen. This class includes CCD cameras with intensifiers, such as microchannel intensifiers. A microchannel intensifier typically contains a metal array of channels perpendicular to and co-extensive with the detection screen of the camera. The microchannel array is placed

between the sample, subject, or animal to be imaged, and the camera. Most of the photons entering the channels of the array contact a side of a channel before exiting. A voltage applied across the array results in the release of many electrons from each photon collision. The electrons from such a collision exit their channel of origin in a "shotgun" pattern, and are detected by the camera.

[00345] Even greater sensitivity can be achieved by placing intensifying microchannel arrays in series, so that electrons generated in the first stage in turn result in an amplified signal of electrons at the second stage. Increases in sensitivity, however, are achieved at the expense of spatial resolution, which decreases with each additional stage of amplification. An exemplary microchannel intensifier-based single-photon detection device is the C2400 series, available from Hamamatsu.

[00346] Image processors process signals generated by photodetector devices which count photons in order to construct an image which can be, for example, displayed on a monitor or printed on a video printer. Such image processors are typically sold as part of systems which include the sensitive photon-counting cameras described above, and accordingly, are available from the same sources. The image processors are usually connected to a personal computer, such as an IBM-compatible PC or an Apple Macintosh (Apple Computer, Cupertino, Calif), which may or may not be included as part of a purchased imaging system. Once the images are in the form of digital files, they can be manipulated by a variety of image processing programs (such as "ADOBE PHOTOSHOP", Adobe Systems, Adobe Systems, Mt. View, Calif.) and printed.

[00347] In an embodiment, the biological sample contains protein molecules from the test subject. One exemplary biological sample is a peripheral blood leukocyte sample isolated by conventional means from a subject.

[00348] The invention also encompasses kits for detecting the presence of CTLA-4 or a CTLA-4-expressing cell in a biological sample. For example, the kit can comprise: a labeled compound or agent capable of detecting a cancer or tumor cell (e.g., an anti-CTLA-4 scFv or monoclonal antibody) in a biological sample; means for determining the amount of CTLA-4 in the sample; and means for comparing the amount of CTLA-4 in the sample with a standard. The standard is, in some embodiments, a non-cancer cell or cell extract thereof. The compound or agent can be packaged in a suitable container. The kit can further comprise instructions for using the kit to detect cancer in a sample.

[00349] ***Other Embodiments***

[00350] While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

[00351] The invention is further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

[00352] Examples are provided below to facilitate a more complete understanding of the invention. The following examples illustrate the exemplary modes of making and practicing the invention. However, the scope of the invention is not limited to specific embodiments disclosed in these Examples, which are for purposes of illustration only, since alternative methods can be utilized to obtain similar results.

EXAMPLE 1

[00353] Described herein are anti-CTLA-4 antibodies identified via phage display that block CTLA-4/CD80 binding. Further, a yeast display library was also generated from this panning campaign to further interrogate the results of the 2nd and 3rd rounds of panning. After sorting clones that bound higher than the bulk, clones were sequenced and additional clones were identified that demonstrate an improved binding curve compared to the original ones found in the ELISA screens of the third round.

[00354] Embodiments herein can have commercial applications as a stand-alone antibody therapy or in combination with other therapies.

EXAMPLE 2 – aCTLA-4 abs from PMPL panning (first group)

[00355] As shown in FIG. 1, anti-CTLA-4 phage binding assay was performed. Assay performed was medium-scale phagemid rescue using PEG + NaCl to precipitate out the phages and purify them.

[00356] With the purified phage, a binding curve from ELISA data was created. We diluted each of the 9 phage PMPL candidates + E1-D7 starting at 2E13 phagemid particles/mL and decreasing 5 fold. We added these phages in triplicates for CTLA-4 Fc-coated plate and CAIX Fc coated plate.

[00357] As shown in FIG. 2, FACS confirm that CTLA-4 phages can bind to CTLA-4 expressing 1G5 Jurkat cells. The negative control was cells + secondary antibody (red box), and the positive comparison/control was current E1-D7 candidate (green box).

[00358] For the purposes of filtering out candidates, we will consider any CTLA-4 phage candidate that has over 25% positive cells as positive. Out of our 9 possible phage candidates, there was only one comparable candidate B10 (circled in blue) as it is over 75%

positive. There were also some partial positives, these are circled in orange and are B6 and C12, which are over 25% positive.

EXAMPLE 3

[00359] Soluble proteins utilized herein include:

[00360] Human CTLA-4 Human CTLA-4, His Tag (CT4-H5229) is expressed from human 293 cells (HEK293). It contains AA Ala 37 - Phe 162 (Accession # NP_005205.2)

```
1   maclgfqrhk aqlnlatrtw pctllffllf ipvfckamhv aqpavvlass rgiasfvcey
61  aspgkatevr vtvlrqadsq vtevcaatym mgneltfldd sictgtssgn qvnltiqglr
121 amdtglyick velmypppyy lgignqtqiy vidpepcpds dfllwilaav ssglffysfl
181 ltavslskml kkrspllttgv yvkmpptepe cekqfqpyfi pin
```

[00361] Mouse CTLA-4, His Tag (CT4-M52H5) is expressed from human 293 cells (HEK293). It contains AA Glu 36 - Phe 162 (Accession # NP_033973).

```
1   maclglrryk aqlqlpsrtw pfvalltllf ipvfseaiqv tqpsvvlass hgvasfpcey
61  spshntdevr vtvlrqtndq mtevcattft ekntvgfldy pfcsgtfnes rvnltiqglr
121 avdtglylck velmypppyf vgmgngtqiy vidpepcpds dfllwilvav slglffysfl
181 vtavslskml kkrspllttgv yvkmpptepe cekqfqpyfi pin
```

[00362]

[00363] Full length CTLA4 was cloned using cDNA from Transomic (BC074893)

EXAMPLE 4 – aCTLA-4

[00364] **CTLA4 Overview:**

[00365] -Protein receptor that functions as an immune checkpoint

[00366] -Overall structure: Extracellular V domain, Transmembrane domain, cytoplasmic tail

[00367] -Homodimer when membrane-bound: Monomer in soluble form

[00368] **CTLA4 Binding:**

[00369] -CD28 homolog

[00370] -binds to CD-80/86 (B7-1/2)

[00371] -highly conserved MYPPY motif involved in binding

[00372] Mechanisms to Suppress Immune Response (Fig. 15)

[00373] -Still much debate: Ligand competition, negative signaling, ligand removal, effects on T cell mobility

[00374] **Background (Fig. 23):**

[00375] - T cells are important mediators to anti-tumor immunity

[00376] - They express inhibitory immune checkpoints: these immune checkpoints serve to limit T cell activation, preventing collateral damage to the body by unrestrained T cell activity

[00377] - PD1 protein is expressed on the surface of T cells: Upon ligation to its ligands PDL-1 and PDL-2, a negative pathway is promoted to inhibit T cell function

[00378] - Upon ligation to its ligands PDL-1 and PDL-2, a negative pathway is promoted to inhibit T cell function: Tumor cells also express PDL1 which can facilitate tumor escape.

[00379] **MLR Assay (Fig. 24):**

[00380] - Co-culture of CD4+ T cells with monocyte-derived DCs each from different donors: Allorecognition of the dendritic cells leads to activation of T cells

[00381] - DCs expressing PDL1 can suppress T cell activation: Addition of immune checkpoint inhibitors can recover T cell from suppression

[00382] - Investigate whether anti-PD1 enhances T cell activation

[00383] - Measure IFNy and IL2 cytokine production, indicators of T cell activation

[00384] **Protocol:**

[00385] -Isolate CD14+ monocytes using Miltenyi CD14+ microbeads

[00386] - Culture in Miltenyi Mo-DC media (pre-prepared media with GM-CSF + IL4)

[00387] - Culture for 5 days, then add: TNF-α (1000 U/ml), IL-1β (5 ng/ml), IL-6 (10 ng/ml) and prostaglandin E2 (PGE2) (1 μM) and culture for 2 days to mature DC

[00388] - mMo-DCs express various DC markers that are involved in the formation of immunological synapses between DCs and naive T cells, including CD80, CD86, and MHC II (HLA-DR). Mature Mo-DCs also expressed DC activation markers CD83, CD40, and CCR7

[00389] **Protocol Continued:**

[00390] - Isolate T cells day of MLR experiment (CD4+ negative selection kit StemCell)

[00391] - 100,000 T cells and 10,000 MoDC cells per well for MLR

[00392] - Antibodies are added at desired concentration and culture is incubated for 5 days

[00393] - Supernatant is saved for ELISA screening (IL2 and IFNy)

[00394] **aCTLA4 Antibodies MLR 1 & 2:**

[00395] MLR1:

[00396] - 2 T cell Donors, 2 DC Donors

[00397] - DC cultured for 7 days- Secondary cytokines added on day 5

[00398] - Cells combined and cultured for 4 days

[00399] - Positive control: aPD-1 Antibody

[00400] - Negative control: aSARS2 Antibody

[00401] MLR 2:

[00402] - Testing 2 aCTLA4 antibodies (D7, C10) in combination with aPD-1 antibody.

[00403] – 4 plates: 2 T cell donors, 2 concentrations of aPD1

[00404] - Used aPD-1 media to make antibody dilutions (starting at 100nM, 5 4-fold dilutions): 5nM aPD-1 media and 100nM aPD-1 media

[00405] - 100000 T cells + 10000 MoDC per well

[00406] - 50ul of antibody combined with 50ul T cells first

[00407] - Ab/T cells then added to DC

[00408] - Controls: aPD-1 + cells, aPD-1 high + cells, DC + T cell

[00409] - Incubate for 5 days

[00410] **FACS to confirm that our CTLA4 phages can bind to CTLA-4 expressing 1G5 Jurkat cells** (Fig. 31)

[00411] - To ensure we were able to find a suitable candidate, we went back and screened a 2nd plate of CTLA4 PMPL phage colonies and combined them with data from plate E1. All unique colonies were cloned into scFv-Fc expression vectors and transfected into Expi293F cells for high throughput screening via Octet.

[00412] - SA sensors were loaded with biotinyated CTLA4. scFv-Fc conc in expi293 supernatant was measured via IgG quantification ELISA (Bethyl) and used to normalize samples. Binding of scFv-Fc in sup was measured using an OctetRed96.

[00413] **Non-Limiting Examples of Categories Considered analyzing data here:**

[00414] Very Important

[00415] 1. CD80 blockade

[00416] 2. CD86 blockade

[00417] 3. Dissociation constant (Kd)

[00418] Moderately Important

[00419] 1. Mouse Cross Reactivity

[00420] Of low Importance

[00421] 1. Response

[00422] Exemplary Selected Candidate:

[00423] **E1-A8**

[00424] Non-Limiting Reasons for Candidate Selection:

[00425] Shows highest CD80 blockade amongst the shortlisted candidates

[00426] CD86 blockade is comparable to Ipilimumab

[00427] Shows Significant Cross-Reactivity with Mouse CTLA4

[00428] Has higher Response than both Ipilimumab and E1-D7

[00429] Shortcomings:

[00430] Shows a relatively higher dissociation rate when compared to most other antibodies tested

[00431] Notes:

[00432] E1-A8 has an identical heavy chain to E2-A4 which shows amongst the highest response rates and a low dissociation constant.

[00433] E1-A8 is derived from the same V gene (IGHV3) but a different allele as Ipilimumab

EXAMPLE 5 – Engineering and Characterization of an antiPD1/anti-CTLA4 bispecific antibody

[00434] **Dual Checkpoint Blockade by Bispecific Antibodies (Fig. 53):**

[00435] Without wishing to be bound by theory, advantages can comprise: lower therapeutic dosage, cooperative binding, targeted therapy, and reduced manufacturing cost.

[00436] **Non-limiting Overview of goals described herein:**

[00437] 1. Discovery and characterization of new anti-CTLA4 antibody:

[00438] 1A: Kinetic Screening and Characterization

[00439] 1B: Epitope binning

[00440] 1C: Cell binding assay

[00441] 1D: Biological assay

[00442] 2. Engineering and Characterization of antiPD1/anti-CTLA4 bispecific antibody

[00443] 3. Characterization of antiPD1/anti-CTLA4 bispecific antibody as a CAR T payload

[00444] **hCTLA2 ELISA binding curve data and results** (Fig.56 panel A):

[00445] -ELISA binding curve to demonstrate binding affinity of anti-CTLA4 candidates to hCTLA4.

[00446] - All candidates have comparable binding affinity to hCTLA4 at the highest concentration.

[00447] - Most candidates show comparable binding affinity to ipilimumab

[00448] -Top 3: I, J, H

[00449] -A, E, I have the best saturating concentrations

[00450] **mCTLA4 ELISA binding curve data and results** (Fig. 56 Panel B)

[00451] - Candidates that show high cross-reactivity: E, F, A

[00452] - Candidates that show moderate cross-reactivity: J, H

[00453] - Ipilimumab and Biolegend anti-CTLA4 do not show cross-reactivity true to the literature

[00454] **BSA Negative Curve** (Fig. 56 Panel C)

[00455] -indicates binding affinity of anti-CTLA4 candidates to BSA (negative control)

[00456] Binding affinity of anti-CTLA4 candidates to CTLA4+ Jurkat Cells (Fig. 64)

[00457] - Apparent inconsistency in the binding affinities of the antibodies to cells vs. to soluble protein.

[00458] - J and H have a much higher binding affinity and a lower saturating concentration to Ipilimumab

[00459] - E and F have comparable binding characteristics to ipilimumab

[00460] **Non-Limiting, Exemplary Conclusions from Data Described Herein:**

[00461] - 5 anti-CTLA4 antibodies screened from a library of different candidates show:

[00462] a. significant binding affinity to CTLA4

[00463] b. ability to block CTLA4 interaction with CD80/86

[00464] c. biological functional relevance by facilitating CD80/CD28 signaling in effector cells.

[00465] Without wishing to be bound by theory, the following experiments can supplement the data described herein:

[00466] - Further experiments with the bispecific format to determine the most suited anti-CTLA4 antibody for the antiPD1/anti-CTLA4 bispecific

[00467] - In-vitro assays to characterize the Bispecific antibody

[00468] - Characterization and efficacy studies of the Bispecific as a payload in CAR T cell therapy.

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EQUIVALENTS

[00469] Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific substances and procedures described herein. Such equivalents are considered to be within the scope of this invention and are covered by the following claims.

What is claimed:

1. An isolated antibody or fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising:

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 61, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 62, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 63; or

(b) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 29, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 30, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 65, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 66; or

(c) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 32, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 33, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 67, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 68, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 69; or

(d) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 35, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 36, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 70, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 71, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 72; or

(e) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 39, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 73, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 74, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or

(f) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 42, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 76, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 77, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 78; or

(g) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 45, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 79, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 80, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 81; or

(h) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 47, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 48, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 82, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 83, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 84; or

(i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 50, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 51, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 85, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 86, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or

(j) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 53, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 54, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 88, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 90; or

(k) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 91, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 92, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 93; or

(l) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 59, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 60, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 95, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 96; or

(m) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 413, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 414, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 415, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 455, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 456, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 457; or

(n) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 416, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 417, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 418, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 458, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 459, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 460; or

(o) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 419, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 420, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 421, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 461, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 462, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 463; or

(p) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 422, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 423, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 424, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 464, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 465, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 466; or

(q) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 425, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 426, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 427, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 467, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 468, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 469; or

(r) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 428, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 429, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 430, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 470, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 471, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 472; or

(s) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 431, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 432, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 433, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 473, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 474, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 475; or

(t) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 434, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 435, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 436, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 476, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 477, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 478; or

(u) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 437, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 439, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 479, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 480, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 481; or

(v) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 440, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 441, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 442, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 482, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 483, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 484; or

(w) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 443, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 444, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 445, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 485, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 486, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 487; or

(x) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 446, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 447, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 448, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 488, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 489, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 490; or

(y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 449, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 450, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 451, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 491, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 492, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 493; or

(z) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 452, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 453, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 454, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 494, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 495, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 496; or

(aa) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 857, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 858, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 859, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 892, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 893, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 894; or

(bb) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 860, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 861, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 862, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 895, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 896, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 897; or

(cc) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 863, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 864, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 865, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 898, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 899, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 900; or

(dd) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 866, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 867, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 868, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 901, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 902, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 903; or

(ee) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 869, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 870, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 871, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 904, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 905, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 906; or

(ff) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 872, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 873, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 874, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 907, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 908, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 909; or

(gg) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 875, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 876, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 877, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 910, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 911, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 912; or

(hh) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 1000, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 879, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 913, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 914, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 915; or

(ii) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 880, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 881, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 882, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 916, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 917, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 918; or

(jj) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 883, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 884, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 885, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 920, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 921; or

(kk) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 886, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 887, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 888, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 922, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 923, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 924; or

(ll) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 889, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 890, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 891, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 925, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 926, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 927.

2. An isolated scFv antibody, that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising:

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 61, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 62, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 63; or

(b) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 29, a VH CDR3

comprising the amino acid sequence of SEQ ID NO: 30, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 65, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 66; or

(c) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 32, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 33, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 67, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 68, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 69; or

(d) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 35, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 36, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 70, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 71, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 72; or

(e) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 39, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 73, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 74, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or

(f) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 42, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 76, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 77, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 78; or

(g) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 45, a VL CDR1 comprising the

amino acid sequence of SEQ ID NO: 79, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 80, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 81; or

(h) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 47, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 48, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 82, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 83, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 84; or

(i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 50, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 51, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 85, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 86, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or

(j) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 53, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 54, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 90; or

(k) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 91, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 92, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 93; or

(l) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 59, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 60, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 95, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 96; or

(m) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 413, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 414, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 415, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 455, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 456, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 457; or

(n) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 416, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 417, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 418, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 458, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 459, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 460; or

(o) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 419, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 420, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 421, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 461, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 462, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 463; or

(p) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 422, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 423, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 424, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 464, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 465, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 466; or

(q) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 425, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 426, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 427, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 467, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 468, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 469; or

(r) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 428, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 429, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 430, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 470, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 471, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 472; or

(s) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 431, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 432, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 433, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 473, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 474, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 475; or

(t) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 434, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 435, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 436, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 476, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 477, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 478; or

(u) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 437, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 439, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 479, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 480, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 481; or

(v) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 440, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 441, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 442, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 482, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 483, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 484; or

(w) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 443, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 444, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 445, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 485, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 486, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 487; or

(x) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 446, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 447, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 448, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 488, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 489, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 490; or

(y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 449, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 450, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 451, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 491, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 492, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 493; or

(z) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 452, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 453, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 454, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 494, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 495, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 496; or

(aa) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 857, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 858, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 859, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 892, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 893, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 894; or

(bb) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 860, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 861, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 862, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 895, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 896, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 897; or

(cc) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 863, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 864, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 865, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 898, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 899, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 900; or

(dd) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 866, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 867, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 868, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 901, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 902, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 903; or

(ee) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 869, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 870, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 871, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 904, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 905, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 906; or

(ff) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 872, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 873, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 874, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 907, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 908, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 909; or

(gg) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 875, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 876, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 877, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 910, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 911, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 912; or

(hh) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 1000, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 879, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 913, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 914, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 915; or

(ii) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 880, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 881, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 882, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 916, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 917, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 918; or

(jj) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 883, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 884, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 885, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 920, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 921; or

(kk) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 886, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 887, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 888, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 922, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 923, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 924; or

(ll) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 889, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 890, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 891, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 925, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 926, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 927.

3. An isolated antibody or fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 1001, 1003, 1005, 1007, 1009, 1011, 1013, 1015, 1017, 1019, 1021, and 1023 and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 368, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 1002, 1004, 1006, 1008, 1010, 1012, 1014, 1016, 1018, 1020, 1022, and 1024.

4. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 385, 387, 389, 391, 393, 395, 397, 399, 401, 403, 405, 407, 409, 411, 1001, 1003, 1005, 1007, 1009, 1011, 1013, 1015, 1017, 1019, 1021, and 1023 and a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 368, 388, 390, 392, 394, 396, 398, 400, 402, 404, 406, 408, 410, 412, 1002, 1004, 1006, 1008, 1010, 1012, 1014, 1016, 1018, 1020, 1022, and 1024.

5. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 1, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 2.

6. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 2.

7. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 3, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 4.

8. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 3, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 4.

9. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 5, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 6.

10. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 5, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 6.

11. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 7, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 8.

12. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 7, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 8.

13. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 9, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 10.

14. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 9, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 10.

15. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 11, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 12.

16. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 11, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 12.

17. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 13, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 14.

18. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 13, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 14.

19. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 15, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 16.

20. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 15, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 16.

21. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 17, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 18.

22. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 17, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 18.

23. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 19, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 20.

24. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 19, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 20.

25. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 21, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 22.

26. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 21, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 22.

27. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 23, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 24.

28. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 23, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 24.

29. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 385, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 386.

30. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 385, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 386.

31. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 387, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 388.

32. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 387, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 388.

33. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 389, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 390.

34. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 389, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 390.

35. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 391, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 392.

36. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 391, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 392.

37. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 393, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 394.

38. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 393, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 394.

39. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 395, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 396.

40. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 395, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 396.

41. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 397, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 398.

42. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 397, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 398.

43. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 399, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 400.

44. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 399, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 400.

45. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 401, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 402.

46. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 401, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 402.

47. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 403, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 404.

48. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 403, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 404.

49. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 405, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 406.

50. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 405, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 406.

51. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 407, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 408.

52. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 407, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 408.

53. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 409, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 410.

54. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 409, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 410.

55. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 411, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 412.

56. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 411, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 412.

57. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1001, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1002.

58. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1001, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1002.

59. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 1003, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1004.

60. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1003, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1004.

61. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1005, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1006.

62. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1005, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1006.

63. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1007, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1008.

64. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1007, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1008.

65. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 1009, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1010.

66. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1009, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1010.

67. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1011, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1012.

68. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1011, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1012.

69. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1013, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1014.

70. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1013, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1014.

71. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 1015, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1016.

72. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1015, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1016.

73. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1017, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1018.

74. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1017, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1018.

75. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1019, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1020.

76. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1019, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1020.

77. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an

amino acid sequence about 95% identical to SEQ ID NO: 1021, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1022.

78. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1021, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1022.

79. An isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1023, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1024.

80. An isolated scFv antibody that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) comprising a heavy chain, a light chain, or a combination thereof, wherein the heavy chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1023, and the light chain comprises an amino acid sequence about 95% identical to SEQ ID NO: 1024.

81. An isolated monoclonal antibody or antigen-binding fragment of claims 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, or 79, wherein the isolated monoclonal antibody or antigen-binding fragment comprises a wildtype Fc or a modified Fc.

82. An isolated bispecific antibody comprising an antibody or fragment of any one of claims 1-81, and a second antigen-binding fragment having specificity to a molecule on an immune cell.

83. The bispecific antibody of claim 82, wherein the molecule is selected from the group consisting of CCR4, B7H3, B7H4, CD27, CD28, CD40, CD40L, CD47, CD122, CTLA-4, GITR, GITRL, ICOS, ICOSL, LAG-3, LIGHT, OX-40, OX40L, PD-1, TIM3, 4-1BB, TIGIT, VISTA, HEVM, BTLA, CD47, PDL1, MICA, MICB, and KIR.

84. The bispecific antibody of claim 82, wherein the fragment and the second fragment each is independently selected from a Fab fragment, a single-chain variable fragment (scFv), or a single-domain antibody.

85. The bispecific antibody of claim 82, further comprising a Fc fragment.

86. The bispecific antibody of claim 85, wherein the Fc fragment comprises a wildtype Fc fragment or a modified Fc fragment.

87. A nucleic acid encoding the antibody according to any one of claims 1-81.

88. A nucleic acid encoding the bispecific antibody according to any one of claims 82-86.

89. A pharmaceutical composition comprising the antibody or fragment thereof according to any one of claims 1-81, and a pharmaceutically acceptable carrier or excipient.

90. The pharmaceutical composition of claim 89, further comprising at least one additional therapeutic agent.

91. The pharmaceutical composition of claim 90, wherein the therapeutic agent is a toxin, a radiolabel, a siRNA, a small molecule, or a cytokine.

92. A pharmaceutical composition comprising the bispecific antibody according to any one of claims 82-86, and a pharmaceutically acceptable carrier or excipient.

93. The pharmaceutical composition of claim 92, further comprising at least one additional therapeutic agent.

94. The pharmaceutical composition of claim 93, wherein the therapeutic agent is a toxin, a radiolabel, a siRNA, a small molecule, or a cytokine.

95. An isolated cell comprising one or more polynucleotide(s) encoding the antibody or fragment thereof of any one of claims 1-81.

96. An isolated cell comprising one or more polynucleotide(s) encoding the bispecific antibody or fragment thereof of any one of claims 82-86.

97. The isolated cell of claim 95 or claim 96, wherein the isolate cell is an immune cell.

98. The isolated cell of claim 97, wherein the immune cell is a T cell, an NK cell, or a B cell.

99. A vector comprising the nucleic acid of claims 87 or 88.

100. A cell comprising the vector of claim 99.

101. The cell of claim 100, wherein the cell is an immune cell.

102. The cell of claim 101, wherein the immune cell is a T cell, an NK cell, or a B cell.

103. A method of treating a cancer in a subject in need thereof, the method comprising administering to a subject a therapeutically effective amount of the CTLA-4 antibody or fragment thereof of any one of claims 1-81.

104. A method of treating a cancer in a subject in need thereof, the method comprising administering to a subject a therapeutically effective amount of the CTLA-4 bispecific antibody of any one of claims 82-86.

105. A chimeric antigen receptor (CAR) comprising an intracellular signaling domain, a transmembrane domain and an extracellular domain, wherein the extracellular domain is an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4), wherein the monoclonal antibody or fragment thereof comprises a heavy chain, light chain, or combination thereof, wherein the heavy chain comprises

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 61, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 62, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 63; or

(b) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 29, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 30, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 65, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 66; or

(c) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 32, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 33, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 67, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 68, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 69; or

(d) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 35, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 36, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 70, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 71, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 72; or

(e) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 39, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 73, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 74, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or

(f) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 42, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 76, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 77, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 78; or

(g) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 45, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 79, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 80, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 81; or

(h) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 47, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 48, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 82, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 83, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 84; or

(i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 50, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 51, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 85, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 86, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or

(j) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 53, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 54, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 90; or

(k) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 91, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 92, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 93; or

(l) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 59, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 60, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 95, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 96; or

(m) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 413, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 414, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 415, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 455, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 456, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 457; or

(n) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 416, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 417, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 418, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 458, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 459, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 460; or

(o) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 419, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 420, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 421, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 461, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 462, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 463; or

(p) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 422, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 423, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 424, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 464, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 465, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 466; or

(q) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 425, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 426, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 427, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 467, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 468, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 469; or

(r) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 428, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 429, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 430, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 470, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 471, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 472; or

(s) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 431, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 432, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 433, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 473, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 474, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 475; or

(t) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 434, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 435, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 436, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 476, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 477, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 478; or

(u) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 437, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 439, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 479, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 480, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 481; or

(v) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 440, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 441, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 442, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 482, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 483, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 484; or

(w) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 443, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 444, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 445, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 485, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 486, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 487; or

(x) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 446, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 447, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 448, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 488, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 489, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 490; or

(y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 449, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 450, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 451, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 491, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 492, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 493; or

(z) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 452, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 453, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 454, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 494, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 495, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 496; or

(aa) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 857, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 858, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 859, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 892, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 893, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 894; or

(bb) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 860, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 861, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 862, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 895, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 896, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 897; or

(cc) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 863, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 864, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 865, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 898, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 899, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 900; or

(dd) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 866, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 867, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 868, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 901, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 902, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 903; or

(ee) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 869, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 870, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 871, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 904, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 905, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 906; or

(ff) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 872, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 873, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 874, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 907, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 908, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 909; or

(gg) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 875, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 876, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 877, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 910, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 911, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 912; or

(hh) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 1000, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 879, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 913, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 914, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 915; or

(ii) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 880, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 881, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 882, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 916, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 917, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 918; or

(jj) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 883, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 884, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 885, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 920, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 921; or

(kk) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 886, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 887, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 888, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 922, a VL CDR2 comprising the amino acid

sequence of SEQ ID NO: 923, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 924; or

(ll) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 889, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 890, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 891, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 925, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 926, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 927.

106. The CAR of claim 105, wherein the transmembrane domain further comprises a stalk region positioned between the extracellular domain and the transmembrane domain.

107. The CAR or claim 105, wherein the transmembrane domain comprises CD28.

108. The CAR of claim 105, further comprising one or more additional costimulatory molecules positioned between the transmembrane domain and the intracellular signaling domain

109. The CAR of claim 105, wherein the costimulatory molecules is CD28, 4-1BB, ICOS, or OX40.

110. The CAR of claim 105, wherein the intracellular signaling domain comprises a CD3 zeta chain.

111. The CAR of claim 105, wherein the antibody is a Fab or a scFV.

112. A nucleic acid encoding the CAR of any one of claims 105-111.

113. The nucleic acid of claim 112, further comprising a nucleic acid encoding a polypeptide positioned after the intracellular signaling domain.

114. The nucleic acid of claim 113, wherein the polypeptide is an antibody or a cytokine.

115. The nucleic acid of claim 114, wherein the antibody is a scFV.

116. A nucleic acid encoding a CAR, wherein the CAR comprises an intracellular signaling domain, a transmembrane domain and an extracellular domain, further comprising a nucleic acid encoding a polypeptide positioned after the intracellular signaling domain,

wherein the polypeptide comprises an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4), wherein the monoclonal antibody or fragment thereof comprises a heavy chain, light chain, or combination thereof,

wherein the heavy chain comprises

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 61, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 62, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 63; or

(b) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 29, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 30, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 65, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 66; or

(c) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 32, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 33, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 67, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 68, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 69; or

(d) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 35, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 36, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 70, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 71, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 72; or

(e) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 39, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 73, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 74, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or

(f) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 42, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 76, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 77, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 78; or

(g) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 45, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 79, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 80, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 81; or

(h) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 47, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 48, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 82, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 83, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 84; or

(i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 50, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 51, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 85, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 86, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or

(j) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 53, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 54, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 90; or

(k) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 91, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 92, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 93; or

(l) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 59, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 60, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 95, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 96; or

(m) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 413, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 414, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 415, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 455, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 456, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 457; or

(n) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 416, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 417, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 418, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 458, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 459, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 460; or

(o) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 419, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 420, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 421, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 461, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 462, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 463; or

(p) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 422, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 423, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 424, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 464, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 465, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 466; or

(q) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 425, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 426, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 427, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 467, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 468, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 469; or

(r) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 428, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 429, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 430, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 470, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 471, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 472; or

(s) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 431, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 432, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 433, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 473, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 474, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 475; or

(t) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 434, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 435, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 436, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 476, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 477, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 478; or

(u) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 437, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 439, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 479, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 480, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 481; or

(v) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 440, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 441, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 442, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 482, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 483, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 484; or

(w) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 443, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 444, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 445, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 485, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 486, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 487; or

(x) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 446, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 447, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 448, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 488, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 489, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 490; or

(y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 449, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 450, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 451, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 491, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 492, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 493; or

(z) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 452, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 453, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 454, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 494, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 495, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 496; or

(aa) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 857, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 858, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 859, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 892, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 893, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 894; or

(bb) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 860, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 861, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 862, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 895, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 896, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 897; or

(cc) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 863, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 864, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 865, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 898, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 899, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 900; or

(dd) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 866, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 867, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 868, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 901, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 902, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 903; or

(ee) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 869, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 870, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 871, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 904, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 905, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 906; or

(ff) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 872, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 873, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 874, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 907, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 908, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 909; or

(gg) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 875, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 876, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 877, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 910, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 911, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 912; or

(hh) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 1000, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 879, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 913, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 914, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 915; or

(ii) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 880, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 881, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 882, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 916, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 917, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 918; or

(jj) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 883, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 884, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 885, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 920, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 921; or

(kk) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 886, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 887, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 888, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 922, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 923, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 924; or

(ll) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 889, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 890, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 891, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 925, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 926, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 927.

117. A vector comprising the nucleic acid of any one of claims 112-116.

118. A cell comprising the vector of claim 117.

119. The cell of claim 118, wherein the cell is an immune cell.

120. A genetically engineered cell which expresses and bears on the cell surface membrane the chimeric antigen receptor of any one of claims 105-111.

121. The cell of claim 120, wherein the immune cell is a T-cell, an NK cell or a B cell.

122. The cell of claim 121, wherein the T cell is CD4+ or CD8+.

123. The genetically engineered cell of claim 122, which comprises a mixed population of CD4+ and CD8 cells+.

124. A genetically engineered cell which express and bear on the cell surface membrane a chimeric antigen receptor, and which is further engineered to express and secrete a polypeptide, wherein polypeptide is an isolated monoclonal antibody or antigen-binding fragment thereof that binds to human Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4), wherein the monoclonal antibody or fragment thereof comprises a heavy chain, light chain, or combination thereof,

wherein the heavy chain comprises

(a) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 25, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 26, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 27, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 61, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 62, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 63; or

(b) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 28, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 29, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 30, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 64, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 65, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 66; or

(c) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 32, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 33, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 67, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 68, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 69; or

(d) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 34, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 35, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 36, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 70, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 71, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 72; or

(e) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 37, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 38, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 39, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 73, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 74, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 75; or

(f) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 40, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 41, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 42, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 76, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 77, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 78; or

(g) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 43, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 45, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 79, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 80, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 81; or

(h) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 46, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 47, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 48, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 82, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 83, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 84; or

(i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 49, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 50, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 51, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 85, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 86, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 87; or

(j) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 52, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 53, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 54, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 88, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 89, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 90; or

(k) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 55, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 56, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 57, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 91, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 92, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 93; or

(l) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 58, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 59, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 60, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 94, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 95, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 96; or

(m) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 413, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 414, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 415, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 455, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 456, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 457; or

(n) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 416, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 417, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 418, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 458, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 459, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 460; or

(o) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 419, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 420, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 421, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 461, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 462, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 463; or

(p) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 422, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 423, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 424, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 464, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 465, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 466; or

(q) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 425, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 426, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 427, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 467, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 468, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 469; or

(r) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 428, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 429, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 430, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 470, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 471, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 472; or

(s) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 431, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 432, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 433, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 473, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 474, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 475; or

(t) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 434, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 435, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 436, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 476, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 477, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 478; or

(u) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 437, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 438, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 439, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 479, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 480, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 481; or

(v) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 440, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 441, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 442, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 482, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 483, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 484; or

(w) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 443, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 444, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 445, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 485, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 486, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 487; or

(x) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 446, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 447, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 448, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 488, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 489, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 490; or

(y) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 449, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 450, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 451, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 491, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 492, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 493; or

(z) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 452, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 453, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 454, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 494, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 495, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 496; or

(aa) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 857, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 858, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 859, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 892, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 893, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 894; or

(bb) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 860, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 861, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 862, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 895, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 896, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 897; or

(cc) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 863, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 864, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 865, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 898, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 899, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 900; or

(dd) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 866, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 867, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 868, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 901, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 902, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 903; or

(ee) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 869, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 870, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 871, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 904, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 905, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 906; or

(ff) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 872, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 873, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 874, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 907, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 908, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 909; or

(gg) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 875, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 876, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 877, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 910, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 911, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 912; or

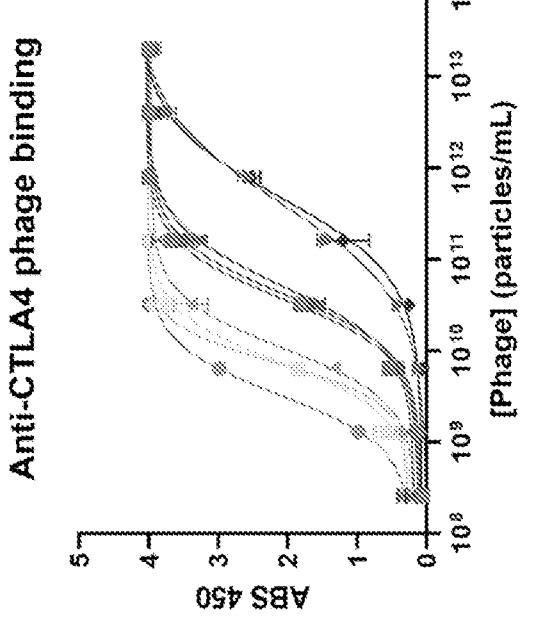
(hh) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 878, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 1000, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 879, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 913, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 914, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 915; or

(ii) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 880, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 881, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 882, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 916, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 917, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 918; or

(jj) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 883, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 884, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 885, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 919, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 920, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 921; or

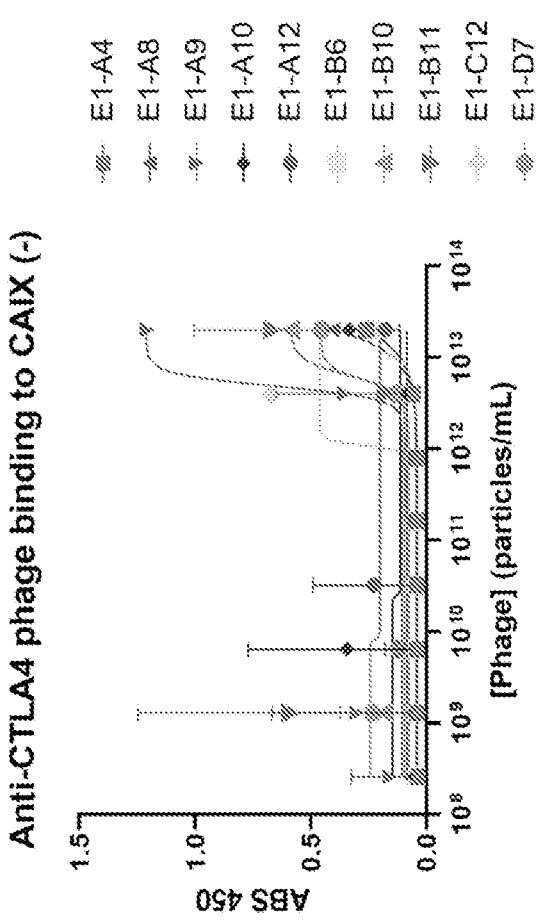
(kk) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 886, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 887, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 888, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 922, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 923, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 924; or

(ll) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 889, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 890, a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 891, a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 925, a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 926, and a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 927.



E1-D7 is positive control phage identified in first set of soluble protein panning

FIG. 1



E1-D7 is positive control phage identified in first set of soluble protein panning

FIG. 1 CON'T

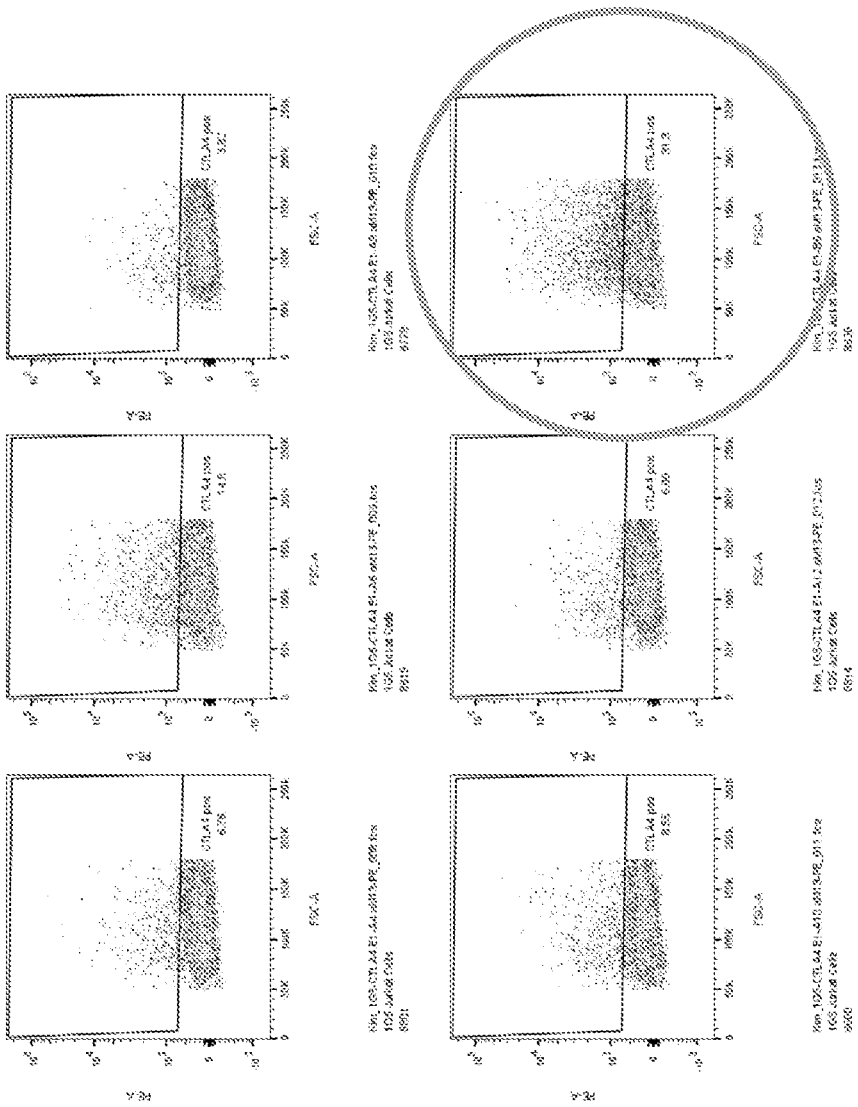


FIG. 2

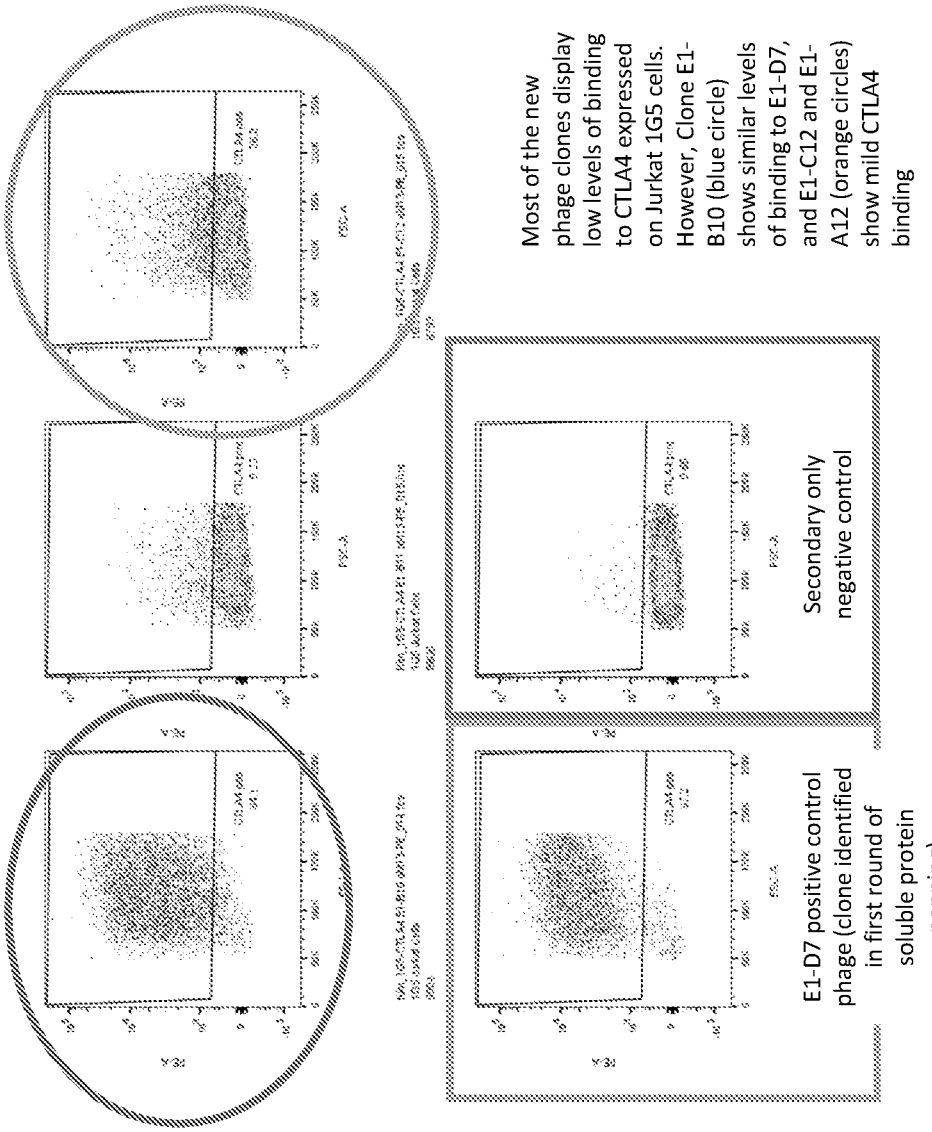

Most of the new phage clones display low levels of binding to CTLA4 expressed on Jurkat 1G5 cells. However, Clone E1-B10 (blue circle) shows similar levels of binding to E1-D7, and E1-C12 and E1-A12 (orange circles) show mild CTLA4 binding
Secondary only negative control
E1-D7 positive control phage (clone identified in first round of soluble protein panning)

FIG. 2 CON'T

HC (NUC)	aCTLA4_E1-D7	aCTLA4_T2-C10
FR1-IMGT	caggtgcagctgcaggagtcgggggga...ggcgtggt ccagcctgggaggtctctgagactcctcctgtgcagcctct	gaggtgcagctggtgcagtctgggggga...ggcgtgg tccagcctgggaggtccctgagactcctcctgtgcagc ctct
CDR1-IMGT	ggattcaccttc.....agcagctatggc	ggattcaccttc.....agtagctatgct
FR2-IMGT	atgcactgggtccgccagccccccagggggagggcctgg agtggattgggcac	atgcactgggtccgccaggctccaggcaaggggct ggagtgggtggcagtt
CDR2-IMGT	atcttacagt.....ggcaacact	atatcatatgat.....ggaagcaataaa
FR3-IMGT	tactacaaccgtcgctcaga...agtcgatttagtatttca aaagacacgtccaagaatcagtttctccctgcacctgag gtctgtgactgccgcagacacggccgttttattactgt	tactacgcagactccgtgaag...ggccgatttcaccat ctccagagacaattccaagaacacgctgtatctgca aatgaacagcctgagagctgaggacacggctgtgt attactgt
CDR3-IMGT	gccagactgccatattgtagtggtggtaactgctcacgata tggacgtc	gcgagagatttcagcagccgttcctccctttggtggcta c
FR4-IMGT	tgggggccaaggcaccctggtcaccgtctcctca	tggggccagggaaccctggtcaccgtctcctcag

FIG. 3

LC (NUC)	aCTLA4_E1-D7	aCTLA4_T2-C10
FR1-IMGT	aatttatgctgactcagccccactct...atgtcggagtctc cggggaagacggtgaccatctcctgcacccgcagc	ctgcctgtgctgactcaatcatcctct...gcctctgcttc cctgggatccctcggtcaagctcacctgcactctgagc
CDR1-IMGT	agtggcagcatt.....gccagcaactat	agtgggcacagt.....agctacatc
FR2-IMGT	gtgcagtggttccagcagcgcccgggcagtgccccca ccactgtgatctat	atcgcatggcatcagcagccagggaaggccc ctcggtacttgatgaag
CDR2-IMGT	gaggat.....aac	cttgaaggtagt.....ggaagctac
FR3-IMGT	caacgaccctctgggggtccct...gatcggttctctggctc catcgacaggtcctccaactctgcctccctcatcatctctg gactgaagactgaggacgaggctgactactactgt	aacaagggggagcggagttccct...gatcgcttctcag gctccagc.....tctgggggctgaccgctacctcaccat ctccaacctccagtctgaggatgaggctgattattact gt
CDR3-IMGT	cagtcttatgatagcaccaatgtggta	gagacctgggacagtaacctcccttctttgggtg
FR4-IMGT	ttcggcggagggaccaagctgaccgtcctg	ttcggcggagggaccaagctgaccgtccta

FIG. 3 CON'T

HC (AA)	aCTLA4_E1-D7	aCTLA4_T2-C10
FR1-IMGT	QVQLQESGG.GVVQPGRSLRLSCAAS	EVQLVQSGG.GVVQPGRSLRLSCAAS
CDR1-IMGT	GFTF....SSYG	GFTF....SSYA
FR2-IMGT	MHWVRQPPGEGLEWIGH	MHWVRQAPGKGLEWVAV
CDR2-IMGT	ISYS...GNT	ISYD..GSNK
FR3-IMGT	YYNPSLR.SRFSISKDTSKNQFSLHLRSVTAADTAVYYC	YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC
CDR3-IMGT	ARLPYCSGGNCYDMDV	ARDFSSSFILGGY
FR4-IMGT	WGQGTLVTVSS	WGQGTLVTVSS

FIG. 3 CON'T

LC (AA)	aCTLA4_E1-D7	aCTLA4_T2-C10
FR1-IMGT	NFMLTQPHS.MSESPGKTVTISCTRS	LPVLTQSSS.ASASLGSSVKLTCTLS
CDR1-IMGT	SGSI....ASNY	SGHS.....SYI
FR2-IMGT	VQWFQQRPGSAPTTVIY	IAWHQQQPGKAPRYLMK
CDR2-IMGT	ED.......N	LEGS...GSY
FR3-IMGT	QRPSGVP.DRFSGSIDRSSNSASLIISGLKTEDEADYYC	NKGSGVP.DRFSGSS..SGADRYLTISNLQSEDEADYYC
CDR3-IMGT	QSYDSTNVV	ETWDSNLPSWV
FR4-IMGT	FGGGTKLTVL	FGGGTKLTVL

FIG. 3 CON'T

Sequence ID	V-GENE and allele	J-GENE and allele	D-GENE and allele
CTLA4-PMPL-Rd2-A4	Homsap IGHV1-69*01 F	Homsap IGHJ3*02 F	Homsap IGHD1-1*01 F
CTLA4-PMPL-Rd2-B11	Homsap IGHV3-72*01 F	Homsap IGHJ6*03 F	Homsap IGHD3-3*01 F
aCTLA4_T2-C10	Homsap IGHV3-30-3*01 F	Homsap IGHJ4*02 F	Homsap IGHD6-6*01 F
CTLA4-PMPL-Rd2-B10	Homsap IGHV3-23*04 F	Homsap IGHJ4*02 F	Homsap IGHD1-7*01 F
CTLA4-PMPL-Rd2-A9	Homsap IGHV1-46*01 F	Homsap IGHJ6*02 F	Homsap IGHD1-1*01 F
CTLA4-PMPL-Rd2-A8	Homsap IGHV3-23*04 F	Homsap IGHJ3*02 F	Homsap IGHD6-19*01 F
CTLA4-PMPL-Rd2-A12	Homsap IGHV1-18*01 F	Homsap IGHJ6*04 F	Homsap IGHD2-15*01 F
CTLA4-PMPL-Rd2-B12	Homsap IGHV1-18*01 F	Homsap IGHJ6*04 F	Homsap IGHD2-15*01 F
CTLA4-PMPL-Rd2-B6	Homsap IGHV1-18*01 F	Homsap IGHJ6*02 F	Homsap IGHD1-14*01 ORF
CTLA4-PMPL-Rd2-C12	Homsap IGHV1-18*01 F	Homsap IGHJ6*02 F	Homsap IGHD1-14*01 ORF
aCTLA4_E1-D7	Homsap IGHV4-30-4*08 (F)	Homsap IGHJ6*02 F	Homsap IGHD2-15*01 F
CTLA4-PMPL-Rd2-A10	Homsap IGHV3-13*01 F	Homsap IGHJ6*04 F	Homsap IGHD6-6*01 F

conclusion - A12 and B12 are the same

FIG. 4

FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT
QVQLVQSGA.EVKKPGSSVKVSCKAS	GGTF...STYP	ISWVRQAPGQGLEWMGG	IIPI..LGTP
EVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF...SDHY	MDWVRQAPGKGLEWVGR	SRNKANSYTT
EVQLVQSGG.GVVQPGRSLRLSCAAS	GFTF...SSYA	MHWVRQAPGKGLEWVAV	ISYD..GSNK
QVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF...SSYA	MSWVRQAPGKGLEWVSA	ISGS..GGST
EVQLVQSGA.EVKKPGASVKVSCKAS	GYTF...TSYY	MHWVRQAPGQGLEWMGI	INPS..GGST
QVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF...SSYV	MSWVRQAPGKGLEWVSS	ISGS..GGST
QVQLVQSGG.EVKKPGASVKVSCKAS	GDTF...SRYG	ITWVRQAPGQGLEWMGW	MSTV..TGNT
QVQLVQSGG.EVKKPGASVKVSCKAS	GDTF...SRYG	ITWVRQAPGQGLEWMGW	MSTV..TGNT
QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF...TSYG	FTWVRQAPGQGLEWMGW	ISSY..NGNT
QVQLVQSGA.EVKKPGASVKVSCKAS	GYIF...TSYG	FTWVRQAPGQGLEWMGW	ISSY..NGNT
QVQLQESGG.GVVQPGRSLRLSCAAS	GFTF...SSYG	MHWVRQPPGEGLEWIGH	ISYS..GNT
QVQLVQSGG.GLVQSGGSLRLSCAAS	GFTF...SGYD	MHWVRQAAGKGLEWVSN	IGIR..GDT

FIG. 4 CON'T

FR3-IMGT	CDR3-IMGT	FR4-IMGT
KYAQKFQ.DRVTITADESTSTAYMELSSLRSDDTAAYYC	AQDNGAFDT	WGQGTMVTVSS
EYAASVK.GRFTISRDESENSLYLQMNSLRAEDTAVYYC	ARARGYMDV	WGKGTTVTVSS
YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC	ARDFSSSFLLGGY	WGQGTLVTVSS
YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC	AREEGITGTGFDY	WGQGTLVTVSS
SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC	ARELKRGDYYYYYGMDV	WGQGTTVTVSS
DYADSVK.GRFPISRDNSKNTLYLEMNSLRAEDTAVYYC	ARGGSAWSLDI	WGQGTTVTVSS
NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC	ARGLORDSSCLTPYYYYGMDV	WGKGTLVTVSS
NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC	ARGLORDSSCLTPYYYYGMDV	WGKGTLVTVSS
DYAQKFE.GRVTMTTDTSTTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
DYAQKFE.GRVTMTTDTSTTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
YYNPSLR.SRFSISKDTSKNQFSLHLRSVTAADTAVYYC	ARLPYCSGGNCYDMDV	WGQGTLVTVSS
YYSDSVK.GRFIISRENAKSSLYLQMNSLRAGDTAVYYC	VRDPSGHGMDV	WGKGTTVTVSS

FIG. 4 CON'T

Sequence ID	V-GENE and allele	J-GENE and allele	FR1-IMGT
CTLA4-PMPL-Rd2-A4	Homsap IGLV2-11*01 F	Homsap IGLJ1*01 F	QSALTQPRSVSGSPGQSVTISCTGT
CTLA4-PMPL-Rd2-B11	Homsap IGLV6-57*01 F	Homsap IGLJ1*01 F	NFMLTHPHSVSESPGKTVTISCTRS
aCTLA4_T2-C10	Homsap IGLV4-60*03 F	Homsap IGLJ3*02 F	LPVLTQSSSASASLGSSVKLTCTLS
CTLA4-PMPL-Rd2-B10	Homsap IGLV8-61*01 F	Homsap IGLJ3*02 F	QTVVTQEPSFSVSPGGTVTLTCGLS
CTLA4-PMPL-Rd2-A9	Homsap IGLV6-57*04 (F)	Homsap IGLJ2*01 F	QPVLTQPHSVSESPGKTVTISCTRS
CTLA4-PMPL-Rd2-A8	Homsap IGKV1D-12*01 F	Homsap IGKJ5*01 F	DIQMTQSPSSVSASIGDRVTITCRAS
CTLA4-PMPL-Rd2-A12	Homsap IGLV7-46*01 F	Homsap IGLJ3*02 F	QTVVTQEPSLTVSPGGTVTLTCGSS
CTLA4-PMPL-Rd2-B12	Homsap IGLV7-46*01 F	Homsap IGLJ3*02 F	QTVVTQEPSLTVSPGGTVTLTCGSS
CTLA4-PMPL-Rd2-B6	Homsap IGLV1-40*01 F	Homsap IGLJ1*01 F	QSVLTQPPSVSGAPGQRVTISCTGS
CTLA4-PMPL-Rd2-C12	Homsap IGLV1-40*01 F	Homsap IGLJ1*01 F	QSVLTQPPSVSGAPGQRVTISCTGS
aCTLA4_E1-D7	Homsap IGLV6-57*03 F	Homsap IGLJ2*01 F	NFMLTQPHSMSESPGKTVTISCTRS
CTLA4-PMPL-Rd2-A10	Homsap IGLV3-21*02 F	Homsap IGLJ2*01 F	QPVLTQPPSVSVAPGQTARITCGGN

FIG. 4 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT
SSDVG...GSDY	VSWYQQHPGKAPKLIIY	EV.....S
SGSI...ASYF	VQWYQQRPGSSPTTVIY	DD.....N
SGHS...SYI	IAWHQQQPGKAPRYLMK	LEGS...GSY
SGSVS...TSYY	PSWYQQTPGQAPRTLIY	TT.....N
GGSF...ADNY	VQWYQQRPGSAPTLMIY	EH.....H
QDI...SNS	LAWYQQKPGKAPKLLIY	GA.....S
TGAVT...TGHY	PYWFQQKPGQAPTTLIY	DA.....T
TGAVT...TGHY	PYWFQQKPGQAPTTLIY	DA.....T
SSNIG...AGYD	VHWYQQLPGTAPKLLIY	GN.....S
SSNIG...AGYD	VHWYQQLPGTAPKLLIY	GN.....S
SGSI...ASNY	VQWFQQRPGSAPTTVIY	ED.....N
NIG.....SKS	VHWYQQKPGQAPVLVVY	DD.....S

FIG. 4 CON'T

FR3-IMGT	CDR3-IMGT	FR4-IMGT
KRPSGVS.DRFSGSK..SGNTASLRISGLQAQDEADYYC	CSYAGSSTFV	FGSGTEVTVL
QRPSGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYHSSTFYV	FGTGTKVTVL
NKGSGVP.DRFSGSS..SGADRYLTISNLQSEDEADYYC	ETWDSNLPSWV	FGGGTKLTVL
TRSSGVP.DRFSGSI..LGNKAALTITGAQADDESDYYC	VLYMGSGIWV	FGGGTKLTVL
QRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYDSSTPVV	FGGGTKLTVL
NLRSGVP.SRFSGGG..SGTYFTLTISSLQPEDFATYYC	QQGNSFPIT	FGQGTRLEIK
HKHSWTP.ARFSGSV..LGGKAALTLSGAQPEDEADYYC	LLSYSGARV	FGGGTKLTVL
HKHSWTP.ARFSGSV..LGGKAALTLSGAQPEDEADYYC	LLSYSGARV	FGGGTKLTVL
SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
SRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
QRPSGVP.DRFSGSIDRSSNSASLIISGLKTEDEADYYC	QSYDSTNVV	FGGGTKLTVL
DRPSGIP.ERFSGSN..SGNTATLTISRVEAGDEADYYC	QVWANSTVV	FGGGTKVTVL

FIG. 4 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
aCTLA4_E1-D7	productive	Homsap IGHV4-30-4*08 (F)	Homsap IGHJ6*02 F	Homsap IGHD2-15*01 F	caggtgcagctgcaggagtcgggcccaggactggtgaagcctcggagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtagttactactggagctggatccggcagcccccagggaaggacctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagaga

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
ggattcacctic .....agta gctatggc	atgcactgggt ccgccaggctc caggcaaggg gctggagtgggt tggcagtt	atatcatatgat .....ggaagca ataaa	tactacgcaga ctccgtgaag.. .ggccgattca ccatctccaga gacaattccaa gaacacgcctgt atatgcaaatg aacagcctga gagctgaggca cacggctatgt attactgt	gcgagagatttt cagcagctcgt. tcctacttgctg gctac	tgtgcgagaga tttcagcagctc gttcctacttggt ggctactgg	tggctactggg gccaggggaac cctggtcaccg tctcctcag	tggggccagg gaaccctggtc accgtctcctca g

FIG. 5 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-A8_PelB-F_2021-07-12_A08	productive	Homsap IGHV3-23*04 F	Homsap IGHJ3*02 F	Homsap IGHD6-19*01 F	caggtgcagctggtgcagtctgggggaggcttggtacagcctggggggtccctgagactctcctgtgcagcctctggattcacgtttt.....agcatgaactgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcacatactacgcagactccgtgaagggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgaaagatcgtgggatagcagctggtacgacgcctttgatatctggggccaagggacaatggtcaccgtctcttcag	caggtgcagctggtgcagtctgggggaggcttggtacagcctggggggtccctgagactctcctgtgcagcctctggattcacgtttt.....agcatgaactgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcacatactacgcagactccgtgaagggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgaaagatcgtgggatagcagctggtacgacgcctttgatatctggggccaagggacaatggtcaccgtctcttcag	caggtgcagctggtgcagtctgggggaggcttggtacagcctggggggtccctgagactctcctgtgcagcctctggattcacgtttt.....agcatgaactgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcacatactacgcagactccgtgaagggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgaaagatcgtgggatagcagctggtacgacgcctttgatatctggggccaagggacaatggtcaccgtctcttcag	caggtgcagctggtgcagtctgggggaggcttggtacagcctggggggtccctgagactctcctgtgcagcctctggattcacgtttt.....agcatgaactgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcacatactacgcagactccgtgaagggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgaaagatcgtgggatagcagctggtacgacgcctttgatatctggggccaagggacaatggtcaccgtctcttcag	caggtgcagct ggtgcagtctg gggga...ggct tggtacagcct gggtccgccag gctccagggaa ggggctggag tgggtctcag ctattagtgg tagtggtggt agcacatact acgcagactcc gtgaagggcc gattcaccat ctccagagac aattccaaga acacgctgta tctgcaaatg aacagcctga gagccgagga cacggccgta tattactgtg cgaaagatcg tgggatagca gctggtacga cgcctttgat atctggggcc aagggacaat ggtcaccgtc tcttcag
CTLA4-PMPL-Rd2-B10_PelB-F_2021-07-12_F08	productive	Homsap IGHV3-23*04 F	Homsap IGHJ4*02 F	Homsap IGHD1-7*01 F	caggtgcagctggtgcagtctgggggaggcttggtacagcctggggggtccctgagactctcctgtgcagcctctggattcacctttt.....agcagctatgccatgcgctgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcacatactacgcagactccgtgaagggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgaaagatcgtgggatagcagctggtacgacgcctttgatatctggggccaagggacaatggtcaccgtctcttcag	caggtgcagctggtgcagtctgggggaggcttggtacagcctggggggtccctgagactctcctgtgcagcctctggattcacctttt.....agcagctatgccatgcgctgggtccgccaggctccagggaaggggctggagtgggtctcagctattagtggtagtggtggtagcacatactacgcagactccgtgaagggccgattcaccatctccagagacaattccaagaacacgctgtatctgcaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgaaagatcgtgggatagcagctggtacgacgcctttgatatctggggccaagggacaatggtcaccgtctcttcag	caggtgcagct ggtgcagtctg gggga...ggct tggtacagcct gggtccgccag gctccagggaa ggggctggag tgggtctcag ctattagtgg tagtggtggt agcacatact acgcagactcc gtgaagggcc gattcaccat ctccagagac aattccaaga acacgctgta tctgcaaatg aacagcctga gagccgagga cacggccgta tattactgtg cgaaagatcg tgggatagca gctggtacga cgcctttgat atctggggcc aagggacaat ggtcaccgtc tcttcag

FIG. 5 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
ggattcacgttt.. .....agca gctatgtc	atgagtgggtc cgccaggctcc agggaagggg ctggagtgggt ctcaagt	attagtggtagt.. .....ggtggtag caca	gactacgcag actccgtgaag ...ggccggttc cccatctccag agacaattcca agaacacattg tatctgcaaatg aacagcctga gagctgagga cacggctgtat attactgt	gcgagagggag gcagtgcctgg tcgcttgatatc	tgtgcgagagg aggcagtgcct ggttccttgata tctgg	ttgatatctggg gccaaggac cacggtcaacc gtctcctcag	tgggggccaag ggaccacggt caccgtctcctc ag
ggattcacttt.. .....agca gctatgcc	atgagctgggt ccgccaggctc cagggaaggg gctggagtgggg tctcagct	attagtggtagt.. .....ggtggtag caca	tactacgcaga ctccgtgaag.. .ggccggttca ccatctccaga gacaattccaa gaacacgctgt atctgcaaatg aacagcctga gagctgagga cacggctgtgt attactgt	gcgagagaagg aggatataact ggaactggcttt gactac	tgtgcgagaga atagggtataa ctggaactggc ttttgatatctgg	cttttgactactg gggccagggc accctggtcac cgtctcctcag	tgggggccaagg gcaccctggtc accgtctcctca g

FIG. 5 CONT

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PIMPLRd2-A10_PeIB-F_2021-07-12_C08	productive	Homsap IGHV3-13*01 F	Homsap IGHJ6*04 F	Homsap IGHD6-6*01 F	caggtgcagctggtgcagtctgggga...ggc ttggtacagtcgggggtccctgagactctcct gtgcagcctctggattcaccttc.....agtg gctacgcatgcactgggtccgccaagcagc aggaaaggtctagagtgggtctcaaatattg gtataacgt.....ggtgacacatactattcaga ctccgtgaag...ggccgattcatcatccaga gaaaatgccaagagcttcctgtatcttcaaatg aacagcctgagagccgaggacacggctgtgt attattgtgtaagagatcgtcctggccaagtgtat ggaagtctgggccaaagggtcaccgtctcac		caggtgcagctggtgcagtctgggga...ggcttgg tacagtcgggggtccctgagactctcctgtgcagc ctctggattcaccttc.....agtggctacgcatcat gcactgggtccgccaggcagccaaggaaagggtcta gagtgggtctcaaatattggtatacgt.....ggtga cacatactattcagactccgtgaag...ggccgattca tcatctccagagacaattccaagagcttcctgtatctt caaatgaacagcctgagagccgaggacacggct gtgtattattgtgtaagaga	cagatgcagct ggtgcagtct gggga...ggct gtacgcatgtg gcactgggtc cgccaggcag ccaaggaaag ggtctagagt gggtctcaaa tattggtata cgtggtaccg gcagaagcct ggaaagtctc ctgaagctct
CTLA4-PIMPLRd2-B11_PeIB-F_2021-07-12_G08	productive	Homsap IGHV3-72*01 F	Homsap IGHJ6*03 F	Homsap IGHD3-3*01 F	gaggtgcagctggtgcagtctgggga...ggc ttggtccagcctggaggttccctgagactctcct gtgcagcctctggattcaccttt.....agtg accactacatggactgggtccgccaggctcca gggaaggggctggagtgggttggccgtatagta gaaacaaagctacagttacaaccacagaata cgccgcgtctgtgaaa...ggcagattcaccatc tcaagagatgaatcagagaacactcactgtatctg caaatgaacagcctgagagccgaggacacgg gctctgtattactctgtgagagccgaggggctac atggacgtctgggccaaagggaccacggtca ccgtctcctca		gaggtgcagctggtgcagtctgggga...ggcttgg tccagcctggaggttccctgagactctcctgtgcag cctctggattcaccttt.....agtgaccactacat ggactgggtccgccaggctccagggaaagggctg gagtgggttggccgtattagaaacaaagctaacagt tacaccacagaatacgccgcgtctgtgaaa...ggc agattcaccatctcaagagatgaatcagaactc ctgtatctgcaaatgaacagcctgagagccgag gacacggctgtattactctgtgagagcg	gaggtgcagct ggtgcagtct gggga...ggct tggtccagcc tggaggttcc ctgagactct cctgtgcagc ctctggattc accttt.....agt gaccactacat ggactgggtc cgccaggctc cagggaaagg gctggagtgg gttggccgta ttagaaacaa agctaacagt tacaccacag aatacgccgc gtctgtgaaa...ggc agattcacca tctcaagaga tgaatcagaa ctcactgtat ctgcaaatga acagcctgag agccgaggac acggctgtat tactctgtga gagcg

FIG. 5 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
ggattcacctttc .....agtg gctacgac	atgcactgggt ccgccaggca gcaggaaaag gtctagagtgg gtctcaaat	attggtatacgt. .....ggtgac aca	tactattcagac tccgtgaag... ggccgattcat catctccagg aaaatgccaa gagctcgttgta tcttcaatgaa cagcctgaga gccgggaca cggctgtgtatt attgt	gtaagagatcc gtccggccac ggtatggacgt c	tgtgtaagagat ccgtccggcca cggtatggacg tctgg	acggtatggac gtctgggcaa agggaccacg gtcaccgtctcc tcag	tggggcaaag ggaccacgt caccgtctcctc ag
ggattcacttt. .....atgca ccatcac	atggactgggt ccgccaggctc caggcaaggg gctggagtgggt ttggccgt	agtagaaaca aagctaacagt tacaccaca	gaatacgccg cgtctgtgaaa. ..ggcagattca ccatctcaaga gatgaatcaga gaactcactgt atctgcaaatg aacagcctga gagccgagga cacggctgtgt attactgt	gcgagagcga ggcgctacatg gacgtc	tgtgcgagagc gaggggtac atggacgtctg g	ctacatggacg tctgggcaaa ggaaccacgg tcaccgtctcct ca	tggggcaaag ggaccacgt caccgtctcctc a

FIG. 5 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PIMPL-Rd2-A9_PelB-F_2021-07-12_B08	productive	Homsap IGHV1-46*01 F, or Homsap IGHV1-46*03 F	Homsap IGHJ6*02 F	Homsap IGHD1-1*01 F	gaggtgcagctggtgcagtctgggggct...gag gtgaagaagcctgggggcctcagtgaaggtttcc ctgcaaggcatctggatacaccttc.....a ccagctactatgcactgggtgcgacaggcc cctggacaagggcttgagtggatgggaataat caacctagt.....ggtggtagcacaagctac gcacagaagttccag...ggcagagtcaccat gaccaggacacgtccacgagcacagtctac atggagctgagcagcctgagatctgaggaca cggccgtgtattactgtgcgagaactaaaa cgcgggggattactactactacggtatggac gtctgggggccaagggaccacggtcaccgtctc	gaggtgcagctggtgcagtctgggggct...gaggtga agaagcctgggggcctcagtgaagtttcctgcaag gcatctggatacaccttc.....accagctactat atgcactgggtgcgacaggcccctggacaagggct tgaatggatgggaataatcaaccctagt.....ggtggg tagcacaagtacgcacagaagttccag...ggca gagtcaccatgaccaggacacgtccacgagcac agtctacatggagctgagcagcctgagatctgag acaaggccgtgtattactgtgcgagaga	cagctacagctgcagcagtcaggaact...gaggtg aagaagcctgggggcctcagtgaaagtctcctgcaa ggcttctggttacatcttt.....acgagttatggttt cactgggtgcgacaggcccctggacaagggcttg atggatgggatggatcagttcttac.....aatggta acacagactatgcacaaaagttccag...ggcaga gtcaccatgaccagagacacatccagcacagcctac ctatatggagttgagggctctgaaatctgacgacc cggccatgtattattgtgcgagag	gaggtgcagct ggtgcagtctg gggctcagg tgaaggtct...gagg gtatccatg ggtccgccaa gctccagggaa ggggctagagt gggtctcagt tattactatgc tacgccgact ctgtgaagg ccgattcacc atctccagag acaattccaag aacacgctgtat ctgcaaatga acagcctgag agccgaggac acggccgtat attactgtgcg aaa
CTLA4-PIMPL-Rd2-B6_PelB-F_2021-07-12_E08	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*02 F, or Homsap IGHJ6*03 F	Homsap IGHD1-14*01 ORF	cagctacagctgcagcagtcaggaact...ga ggtgaagaagcctgggggcctcagtgaaagtct cctgcaaggcttctggttacatctt.....ac gagttatggtttcactgggtgcgacaggcccc cggacaagggcttgagtggatgggatgatca gttcttac.....aatggtaacacagactatgcac agaaagttccag...ggcagagtcaccatgacc acagacacatccagcacagcctatatgg agttgagggctctgaaatctgacgacacggcc atgtattattgtgcgagagtccgcgaaatggac gtctgggccaagggaccacggtcaccgtctc	cagctacagctgcagcagtcaggaact...gaggtg aagaagcctgggggcctcagtgaaagtctcctgcaa ggcttctggttacatctt.....acgagttatggttt cactgggtgcgacaggcccctggacaagggcttg atggatgggatggatcagttcttac.....aatggta acacagactatgcacaaaagttccag...ggcaga gtcaccatgaccagagacacatccagcacagcctac ctatatggagttgagggctctgaaatctgacgacc cggccatgtattattgtgcgagag	cagctacagct gcagcagtca ggaggaact...gag gtgaaggagc ctgggaggtc ctgaaagtct cctgcaagtc tgtgaaaggc tacgccttca ccacctacgt tatgcactgg gtgcgacagg cccctggaca agggcttgag tggatgggat ggatcaaccc tgacaatggt aacacaaact atgcacagaa gtttcagggc agagtcacca tgaccaggga cacgtccatc agcacagcct acatggagct gagcaggctg acatctgacg acacggccgt gtattactgt gcgagaga

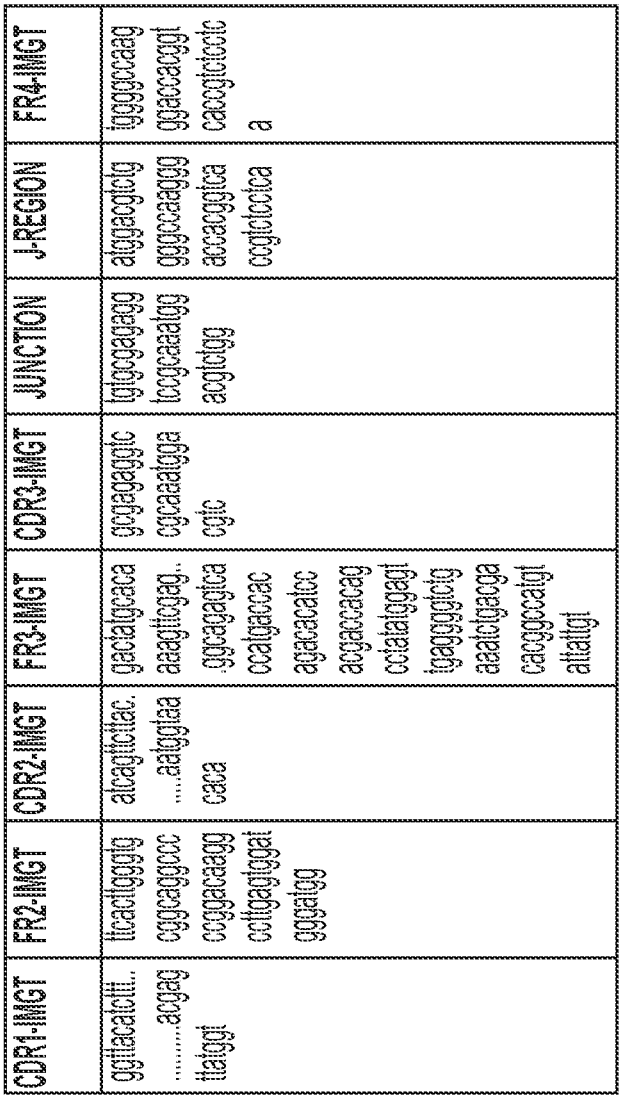
FIG. 5 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
ggatacacctt c.....acc agctactat	atgcactgggt gcgacaggcc cctggacaag ggcttgagtgg atgggaata	atcaaccctag t.....ggtggta gcaca	agctacgcac agaagttccag ...ggcagagtc accatgacca ggacacagtc cacagcaca gtctacatgga gctgagcagc ctgagatctga ggacacggcc gtgtattactgt	gcgagagaac taaaacggg ggattactacta ctactacggtat ggacgtc	tgtgcgagaga actaaaacgc gggattacta ctactactacg gtatggacgtct gg	attactactact actacggtatg gacgtctgggg ccaagggacc acggtcaccgt ctcctca	tgggccaag ggaccacggt caccgtctcctc a
ggttacatcttt.. .....acgag ttatggt	ttcactggtgg cggcaggccc cggacaagg cctgagtggat ggagtgg	atcagttctac. .....aatggtaa caca	gactatgcaca aaagttcgag.. .ggcagagtca ccatgaccac agacacatcc acgaccacag cctatatggagct tgagggctctg aaatctgacga caccgccatgt attattgt	gcgagagtc cgcaaatgga cgtc	tgtgcgagagg tcccgcaaatgg acgtctgg	atggacgtctg gggccaaggg accacggtca ccgtctcctca	tgggccaag ggaccacggt caccgtctcctc a

FIG. 5 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-C12_PelB-F_2021-07-12_A09	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*02 F, or Homsap IGHJ6*03 F	Homsap IGHD1-14*01 ORF	caggtgcagctggtgcagtctgggggct...gaggtgaagaagcctgggggcctcagtgaagatctcctgcaaggcttctggttacaccttt.....acgagttatgttatcagtgggtgcgacaggcccctggacaagggcttgagtggatgggatggatcagcgctacaatggtaacacaaactatgcacagaagctccagggcagagtcaccatgaccacagacacatccacgagcacagcctacatggagctgaggagcctgagatctgacgacacggccgtctattactgtgcgagag		caggtgcagctggtgcagtctgggggct...gaggtgaagaagcctgggggcctcagtgaagatctcctgcaaggcttctggttacaccttt.....acgagttatgttatcagtgggtgcgacaggcccctggacaagggcttgagtggatgggatggatcagcgctacaatggtaacacaaactatgcacagaagctccagggcagagtcaccatgaccacagacacatccacgagcacagcctacatggagctgaggagcctgagatctgacgacacggccgtctattactgtgcgagag	caggtgcagct ggtgcagtctg gggct...gagg tgaagaagcct gggggcctcagt gaagatctcct gcaaggcttct

FIG. 5 CON'T



CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
ggttcacatctt.....acgag ttatggt	ttcactgggtg cggcaggccc cggacaagg ccttgagtggat gggatgg	attagttctac.....aatggtaa caca	gactatgcaca aaagttcgag..ggcagagtca ccattaccac agacacatcc acgaccacag cctatatggagt tgagggtctg aaatctgacga cacggccatgt attattgt	gcgagagatc cgcaaatgga cgtc	tgtgcgagagg tcgcaaatgg aggtctgg	atgaacgtctg ggccaaggg accacggtca ccgtctcctca	tggggccaag ggaccacggt caccgtctcctc a

FIG. 5 CONT

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-A4_PelB-F_2021-07-12_H07	productive	Homsap IGHV1-69*01 F, or Homsap IGHV1-69D*01 F	Homsap IGHJ3*02 F	Homsap IGHD1-1*01 F	caggtgcagctggtgcagtctggagct...gag gtgaagaagcctgggtcctcggtgaaggctcc ctgcaagcttctggaggcacttttc.....ag cacctatcctatcagctggtgcgacaggcccc ctgcaacaagggcttgagtgggtgggatgatt atcctatt.....cttggaacacaaagtacgc acagaagttccag...gacagagtcaccatt accgaggacacatctacagcacagcctac cgcggacgaatccacgagccgcctacatg gagctgagcagcctgagatctgaggacacg gccgtctattattgtgctcaagggacaatcgttacc tgatacctgggggccaagggaacaatggtcacc	caggtgcagctggtgcagtctggagct...gaggtga agaagcctgggtcctcggtgaaggctcctgcaag gcttctggaggcacttttc.....agcactatcata tcagctggtgcgacaggcccctggacaagggctt gagtgggtgggatgatcctatt.....cttggaa caccaaagtacgcacagaagttccag...gacaga gtcaccattaccgcggacgaatccacgagcgcc cctacatggagctgagcagcctgagatctgagac acggccgtctattattgtgc	caggtgcagctggtgcagtctggagct...gaggtga agaagcctgggtcctcagtgaaggtctccaag gcttctggtacaccttt.....agcagttatggc atcacctgggtgcgacaggcccctggacaagggctt gagtggatgggatggatcagcgctac...actgg aaacacaaactccgccagaagttccag...ggca gagtcttcttgaccgagacacatccacgagcacg gcctacttggagctgaggagcctgagacctgacga cacggccgtctatttctgtgcgaag	caggtgcagct ggtgcagtctg gaggt...gagg tgaagaagcct gggggcctcagt gaaggtctcct gcaaggcttct
CTLA4-PMPL-Rd2-A12_PelB-F_2021-07-12_D08	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*04 F	Homsap IGHD2-15*01 F	caggtgcagctggtgcagtctggagct...gag gtgaagaagcctgggcctcagtgaaggtctc ctgcaaggcttctggttacacctt.....ag caggtatggatcacctgggtgcgacaggccc ctggacaagggcttgagtggatgggatgg agcacggtc.....actggaaacacaaactccg cgcagaagttccag...ggcagagtcaccatg accgcggacacatccacgagcacagcctacttg gagctgaggagcctgagatctgacgacacg gccgtctattactgtgcgagagactatgtcgtg atatggagtcgtcaaccccctactactttgac cagggcaccctggtcaccgtctcctcag	caggtgcagctggtgcagtctggagct...gaggtga agaagcctgggcctcagtgaaggtctccaag gcttctggtacaccttt.....agcaggtatggg atcacctgggtgcgacaggcccctggacaagggctt gatggatgggatggatcagcgctac...actgg aaacacaaactccgccagaagttccag...ggca gagtcttcttgaccgagacacatccacgagcacg gcctacttggagctgaggagcctgagacctgacga cacggccgtctatttctgtgcgaag	caggtgcagct ggtgcagtctg gaggt...gagg tgaagaagcct gggggcctcagt gaaggtctcct gcaaggcttct

FIG. 5 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
ggaggcacttttt .....agca cctatcct	atcagctgggt gcgacaggcc ctgtgacaag ggctgagtgg atgggaggg	attatcctatt... ....ctggaaca cca	aagtacgcac agaagttccag ...gacagagtc acgattacggc ggacgaatcc acgagcaagg cctacatggag ctgagcagcct gagatcgagc gacacggccg cctattattgt	gctcaagaca atggtgctttttga tacc	tgtgctcaaga caatggtgctttt gatacctgg	tggtgctttgat acctgggcc aagggacaat ggtcacgtct cttcag	tgggccaag ggacaatggtc accgtcttca g
ggtgacacttttt .....agca ggtatggg	atcacctggat gcgtcaggcc cctggacaag ggctgagtgg atgggatgg	atgagcaccgt c.....actgga aacaca	aactccggcc agaagttccag ...ggcagagtc ttcttgaccgga gacacatcca cgagcacagc ctactttggagct gaggagcctg agacctgacg acacggccgt ctattactgt	gcggagaggac tatgtcgtgata gcagtggcta accgctactca ctattacggtat ggacgtc	tgtgcgagagg actatttcgtga tagcagctgcc taaccccctact actattacggta tggacgtctgg	ctactactatta cggtatggacg tctgggcaaa ggcacctgct cacgtctctc ag	tgggccaaag gcacccttggtc accgtctcctca g

FIG. 5 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-B12_PeIB-F_2021-07-12_H08	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*04 F	Homsap IGHD2-15*01 F	caggtgcagctggtgcagtctggagct...gag gtgaagaagcctggggcctcagtgaaggtctcc ctgcaaggcttctgtgtgacacctttt.....ag caggtatgggatcacctgggtgcgtcaggccc ctggacaagggcttgagtggatgggatggatg agcaccgtc.....actggaaacacaaactcag cgcagaagttccag...ggcagagtcttcttgac ccggacacatccacagcgcacagcctacttg gagctgaggagcctgacctgacggacacg gccgtctattactgtgcgagagactatctctg atagcagtggctaacccctactactattacg gtatggacgtctgggcaaagccaccctgatc accgtctcctcag		caggtgcagctggtgcagtctggagct...gaggtga agaagcctgggcctcagtgaaggtctctgcaag ggttctggtgacacctttt.....agcagtatggg atcacctgggtgcgtcaggcccctggacaagggctt gagtggatgggatggatgagcaccgtc.....actgg aacacaaactccagcgcagaggcttcag...ggca gagtctttgaccgagacacatccacgagcaca gcctacttgcagctgagcagcctgagatctgacga cacggccgtctattactgtgcgagag	caggtgcagct ggtgcagtctg gaggt...gagg tgaagaagcct ggggcctcagt gaaggtctcct gcaaggcttct

FIG. 5 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
ggtgacacttt .....agca ..... ggtatggg	atcactggat ggatcaggcc cctggacaag ggcttgagtgg atgggatgg	atgagcaccgt c.....actgga aacaca	aactccgcgc agaagttccag ....ggcagagtc ttcttgaccgga gacacactcca cgagcacagc ctacttggagct gaggagcctg agacctgacg acacggccgt ctatttactgt	gggagaggac tatgtctgtgata gcagctgccta accccctacta ctatttacggtat ggacgtc	tgtgcgagagg atatgtcgtga tagcagctgcc taaccccctact actatttacggta tggagtctgg	ctactactatta cggtatgtgacg tctgggcaaa ggcaccctggt caccgtctcctc ag	tggggccaag gcaccctggtc accgtctcctca g

FIG. 5 CONT

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
aCTLA4_E1-D7	productive	Homsap IGHV4-30-4*08 (F)	Homsap IGHJ6*02 F	Homsap IGHD2-15*01 F	QVQLQESGG.GVVQPGRSLRLSCAA SGFTF....SSYGMHWVRQPPGEGLE WIGHISYS...GNTYYNPSLR.SRFSIS KDTSKNQFSLHLRSVTAADTAVYYC ARLPYCSGGNCYDMDVWGQGTLV TVSS		QVQLQESGG.GVVQPGRSLRLSCAAS GFTF....SSYGMHWVRQPPGEGLEWIG HISYS...GNTYYNPSLR.SRFSISKDTSK NQFSLHLRSVTAADTAVYYCAR	QVQLQESG G.GVVQPG RSLRLSCA AS
aCTLA4_T2-C10	productive	Homsap IGHV3-30-3*01 F	Homsap IGHJ4*02 F	Homsap IGHD6-6*01 F	EVQLVQSGG.GVVQPGRSLRLSCAA SGFTF....SSYAMHWVRQAPGKGLE WVAVISYD..GSNKYYADSVK.GRFTI SRDNSKNTLYLQMNSLRAEDTAVYY CARDFSSSFLGGYWGQGTLVTVS S		EVQLVQSGG.GVVQPGRSLRLSCAAS GFTF....SSYAMHWVRQAPGKGLEWV AVISYD..GSNKYYADSVK.GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAR	EVQLVQSG G.GVVQPG RSLRLSCA AS
CTLA4-PMPL-Rd2-A8 PelB-F_2021-07-12_A08	productive	Homsap IGHV3-23*04 F	Homsap IGHJ3*02 F	Homsap IGHD6-19*01 F	QVQLVQSGG.GLVQPGGSLRLSCAA SGFTF....SSYWMSWVRQAPGKGLE WVSSISGS..GGSTDYADSVK.GRFPI SRDNSKNTLYLEMNSLRAEDTAVYY CARGGSAWSLDIWGQGTTVTVSS		QVQLVQSGG.GLVQPGGSLRLSCAAS GFTF....SSYWMSWVRQAPGKGLEWV SSISGS..GGSTDYADSVK.GRFPISRD NSKNTLYLEMNSLRAEDTAVYYCAR	QVQLVQSG G.GLVQPG GSLRLSCA AS
CTLA4-PMPL-Rd2-B10 PelB-F_2021-07-12_F08	productive	Homsap IGHV3-23*04 F	Homsap IGHJ4*02 F	Homsap IGHD1-7*01 F	QVQLVQSGG.GLVQPGGSLRLSCAA SGFTF....SSYAMSWVRQAPGKGLE WVSAISGS..GGSTYYADSVK.GRFTI SRDNSKNTLYLQMNSLRAEDTAVYY CAREEGITGTGFDYWGQGTLVTVS S		QVQLVQSGG.GLVQPGGSLRLSCAAS GFTF....SSYAMSWVRQAPGKGLEWV SAISGS..GGSTYYADSVK.GRFTISRDN SKNTLYLQMNSLRAEDTAVYYCAR	QVQLVQSG G.GLVQPG GSLRLSCA AS

FIG. 6

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
GFTF....SSY G	MHWVRQP PGEGLEW GH	ISYS...GNT	YYNPSLR.S RFSISKDTS KNQFSLHL RSVTAADT AVYYC	ARLPYCSG GNCYDMD V	CARLPYCS GGNCYDM DVW	CYDMDVW GQGTLVTV SS	WGQGTLVT VSS
GFTF....SSY A	MHWVRQA PGKGLEWV AV	ISYD..GSNK	YYADSVK.G RFTISRDNS KNTLYLQM NSLRAEDT AVYYC	ARDFSSSF LLGGY	CARDFSSS FLLGGYW	GYWGQGT LVTVSS	WGQGTLVT VSS
GFTF....SSY V	MSWVRQA PGKGLEWV SS	ISGS..GGS T	DYADSVK. GRFPISRD NSKNTLYL EMNSLRAE DTAVYYC	ARGGSAW SLDI	CARGGSA WSLDIW	DIWGQGTT VTVSS	WGQGTTV TVSS
GFTF....SSY A	MSWVRQA PGKGLEWV SA	ISGS..GGS T	YYADSVK.G RFTISRDNS KNTLYLQM NSLRAEDT AVYYC	AREEGITG TGFDY	CAREEGIT GTGFDYW	FDYWGQG TLVTVSS	WGQGTLVT VSS

FIG. 6 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PIMPL-Rd2-A10_PelB-F_2021-07-12_C08	productive	Homsap IGHV3-13*01 F	Homsap IGHJ6*04 F	Homsap IGHD6-6*01 F	QVQLVQSGG.GLVQSGGSLRLSCAA SGFTF....SGYDMHWVRQAAGKGLE WVSNIGIR...GDTYYSDSVK.GRFIIS RENAKSSLYLQMNSLRAGDTAVYY CVRDPSGHGMDVWGKGTTVTVSS		QVQLVQSG G.GLVQSG GSLRLSCA AS	QVQLVQSG G.GLVQSG GSLRLSCA AS
CTLA4-PIMPL-Rd2-B11_PelB-F_2021-07-12_G08	productive	Homsap IGHV3-72*01 F	Homsap IGHJ6*03 F	Homsap IGHD3-3*01 F	EVQLVQSGG.GLVQPGGSLRLSCAA SGFTF....SDHYMDWVRQAPGKGLE WVGRSRNKANSYTTEYAASVK.GR FTISRDESENSLYLQMNSLRAEDTA VYYCARARGYMDVWGKGTTVTVSS		EVQLVQSG G.GLVQPG GSLRLSCA AS	EVQLVQSG G.GLVQPG GSLRLSCA AS
CTLA4-PIMPL-Rd2-A9_PelB-F_2021-07-12_B08	productive	Homsap IGHV1-46*01 F, or Homsap IGHV1-46*03 F	Homsap IGHJ6*02 F	Homsap IGHD1-1*01 F	EVQLVQSGA.EVKKPGASVKVSCKA SGYTF....TSYYMHWVRQAPGQGLE WMGIINPS..GGSTSYAQKFQ.GRVT MTRDTSTSTVYMELSSLRSEDTAVY YCARELKRGDYYYYGMDVWGQG TTVTVSS		EVQLVQSGA.EVKKPGASVKVSCKAS GYTF....TSYYMHWVRQAPGQGLEWM GIINPS..GGSTSYAQKFQ.GRVTMTRD TSTSTVYMELSSLRSEDTAVYYCAR	EVQLVQSG A.EVKKPG ASVKVSCK AS
CTLA4-PIMPL-Rd2-B6_PelB-F_2021-07-12_E08	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*02 F, or Homsap IGHJ6*03 F	Homsap IGHD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKA SGYIF....TSYGFTWVRQAPGQGLE WMGWISSY..NGNTDYAQKFE.GRV TMTTDTSTTTAYMELRGLKSDDTAM YYCARGPQMDVWGQGTTVTVSS		QVQLQQSGT.EVKKPGASVKVSCKAS GYIF....TSYGFTWVRQAPGQGLEWMG WISSY..NGNTDYAQKFE.GRVTMTTDT STTTAYMELRGLKSDDTAMYYCAR	QVQLQQSG T.EVKKPGA SVKVSCKA S

FIG. 6 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
GFTF...SG YD	MHWVRQA AGKGLEWV SN	IGIR...GDT	YYSDSVK.G RFTISRENA KSSLYLQM NSLRAGDT AVYYC	VRDPSGHG MDV	CVRDPSGH GMDVW	GMDVWGK GTTVTVSS	WGKGTTVT VSS
GFTF...SD HY	MDWVRQA PGKGLEWV GR	SRNKANSY TT	EYAASVK.G RFTISRDES ENSLYLQM NSLRAEDT AVYYC	ARARGYM DV	CARARGYM DVW	YMDVWGK GTTVTVSS	WGKGTTVT VSS
GYTF...TSY Y	MHWVRQA PGQGLEW MGI	INPS..GGST	SYAQKFQ. GRVTMTRD TSTSTVYM ELSSLRSE DTAVYYC	ARELKRGD YYYYYGMD V	CARELKRG DYYYYYGM DVW	YYYYYGMD VWGQGTT VTVSS	WGQGTTV TVSS
GYIF...TSY G	FTWVRQAP GQGLEWM GW	ISSY..NGNT	DYAQKFE. GRVTMTTD TSTTAYM ELRGLKSD DTAMYYC	ARGPQMD V	CARGPQM DVW	MDVWGQG TTVTVSS	WGQGTTV TVSS

FIG. 6 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PIMPL-Rd2-C12_PelB-F_2021-07-12_A09	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*02 F, or Homsap IGHJ6*03 F	Homsap IGHD1-14*01 ORF	QVQLVQSGA.EVKKPGASVKVSCKA SGYIF....TSYGFTWVRQAPGQGLE WMGWISSY..NGNTDYAQKFE.GRV TMTTDTSTTAYMELRGLKSDDTAM YYCARGPQMDVWGQGTTVTVSS		QVQLVQSG A.EVKKPG ASVKVSCK AS	QVQLVQSG A.EVKKPG ASVKVSCK AS
CTLA4-PIMPL-Rd2-A4_PelB-F_2021-07-12_H07	productive	Homsap IGHV1-69*01 F, or Homsap IGHV1-69D*01 F	Homsap IGHJ3*02 F	Homsap IGHD1-1*01 F	QVQLVQSGA.EVKKPGSSVKVSCKA SGGTF....STYPISWVRQAPGQGLE WMGGIIPI..LGTPKYAQKFQ.DRVTIT ADESTSTAYMELSSLRSDDTAAYYC AQDNCAFDTWGQGTMVTVSS		QVQLVQSGA.EVKKPGSSVKVSCKAS GGTF....STYPISWVRQAPGQGLEWMG GIIPI..LGTPKYAQKFQ.DRVTITADEST STAYMELSSLRSDDTAAYYC	QVQLVQSG A.EVKKPG SSVKVSCK AS
CTLA4-PIMPL-Rd2-A12_PelB-F_2021-07-12_D08	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*04 F	Homsap IGHD2-15*01 F	QVQLVQSGG.EVKKPGASVKVSCKA SGDTF....SRYGITWVRQAPGQGLE WMGWMSTV..TGNTNSAQKFQ.GRV FLTRDTSTSTAYLELRSLRPDDTAV YYCARGLCRDSSCLTPYYYYGMDV WGKGTLVTVSS		QVQLVQSGG.EVKKPGASVKVSCKAS GDTF....SRYGITWVRQAPGQGLEWMG WMSTV..TGNTNSAQKFQ.GRVFLTRD TSTSTAYLELRSLRPDDTAVYYCAR	QVQLVQSG G.EVKKPG ASVKVSCK AS
CTLA4-PIMPL-Rd2-B12_PelB-F_2021-07-12_H08	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*04 F	Homsap IGHD2-15*01 F	QVQLVQSGG.EVKKPGASVKVSCKA SGDTF....SRYGITWVRQAPGQGLE WMGWMSTV..TGNTNSAQKFQ.GRV FLTRDTSTSTAYLELRSLRPDDTAV YYCARGLCRDSSCLTPYYYYGMDV WGKGTLVTVSS		QVQLVQSGG.EVKKPGASVKVSCKAS GDTF....SRYGITWVRQAPGQGLEWMG WMSTV..TGNTNSAQKFQ.GRVFLTRD TSTSTAYLELRSLRPDDTAVYYCAR	QVQLVQSG G.EVKKPG ASVKVSCK AS

FIG. 6 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
GYIF....TSY G	FTWVRQAP GQGLEWM GW	ISSY..NGNT	DYAQKFE. GRVTMTTD TSTTTAYM ELRGLKSD DTAMYYC	ARGPQMD V	CARGPQM DVW	MDVWGQG TTVTVSS	WGQGTTV TVSS
GGTF....ST YP	ISWVRQAP GQGLEWM GG	IIPI..LGTP	KYAQKFQ. DRVTITADE STSTAYME LSSLRSDD TAVYYC	AQDNGAFD T	CAQDNGAF DTW	GAFDTWG QGTMVTVS S	WGQGTMV TVSS
GDTF....SR YG	ITWVRQAP GQGLEWM GW	MSTV..TGN T	NSAQKFQ. GRVFLTRD TSTSTAYLE LRSLRPDD TAVYYC	ARGLORDS SCLTPYYY YGMDV	CARGLORD SSCLTPYY YYGMDVWW	YYYYGMDV WGKGTLVT VSS	WGKGTLVT VSS
GDTF....SR YG	ITWVRQAP GQGLEWM GW	MSTV..TGN T	NSAQKFQ. GRVFLTRD TSTSTAYLE LRSLRPDD TAVYYC	ARGLORDS SCLTPYYY YGMDV	CARGLORD SSCLTPYY YYGMDVWW	YYYYGMDV WGKGTLVT VSS	WGKGTLVT VSS

FIG. 6 CONT

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
aCTLA4_E1-D7	productive	Homsap IGLV6-57*03 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F			aatttttatgctgactcagccccactct...atgtcggagtct ccgggggaagacggtgaccatcacctgcacccgcagc agtggcagcaatt.....gccagcaactatgtgcagt ggttccagcagcgccccgggcagtgccccacactgt gatctatgaggat.....aaccaacgaccct ctgggtcccct...gatcgttctctggctccatcgacag gtcctccaactcgtcctccttcaccatctctggactgaag actgaggacgaggctgactactgtcagtcttatgat agcaccaatctgtattcggcggagggaccaagctga ccgtcctg	ctgcctgctgactcaatcatcttct...gcctctgttcc ctggatcctcggtcaagctcaccctgcactctgagcagt gggcacagt.....agctcatcatcgcatggca tcagcagccaggcagggaagccctcgtactttgatg aagttgaaggtagt.....ggaagctacaacaagg ggagcggagttcct...gatcgttctcagcctccagc... ...tctgggctgaccgatttaccttgtgagactctgg agtctgaggatgaggctgattactgtgaagcctcggg acaatatccttcttggtgttcggcggagggaccc aagctgaccgtccta	aatttttatgctgactcagccccactct...atgtcggagtct ccgggggaagacggtgaccatcacctgcacccgcagc agtggcagcaatt.....gccagcaactatgtgcagt ggttccagcagcgccccgggcagtgccccacactgt gatctatgaggat.....aaccaacgaccct ctgggtcccct...gatcgttctctggctccatcgacag gtcctccaactcgtcctccttcaccatctctggactgaag tcctccaactctgcctccttcaccatctctggactgaaga ctgaggacgaggctgactactgtcagtcttatgata gcaccaat	aatttttatgctga ct...atgtcgga gtctccgggcaa ctcgacgtgaccat gaccgtgaccat ctgctgcaccag cagc
aCTLA4_T2-C10	productive	Homsap IGLV4-60*03 F	Homsap IGLJ3*02 F			ctgcctgctgactcaatcatcttct...gcctctgttcc ctggatcctcggtcaagctcaccctgcactctgagcagt gggcacagt.....agctcatcatcgcatggca tcagcagccaggcagggaagccctcgtactttgatg aagttgaaggtagt.....ggaagctacaacaagg ggagcggagttcct...gatcgttctcagcctccagc... ...tctgggctgaccgatttaccttgtgagactctgg agtctgaggatgaggctgattactgtgaagcctcggg acaatatccttcttggtgttcggcggagggaccc aagctgaccgtccta	ctgcctgctgactcaatcatcttct...gcctctgttcc ctggatcctcggtcaagctcaccctgcactctgagcagt gggcacagt.....agctcatcatcgcatggca tcagcagccaggcagggaagccctcgtactttgatg aagttgaaggtagt.....ggaagctacaacaagg ggagcggagttcct...gatcgttctcagcctccagc..... tctgggctgaccgatttaccttgtgagactctgg agtctgaggatgaggctgattactgtgaagcctcggg acaatatccttcttggtgttcggcggagggaccc agtaac	ctgcctgctgctga ctcaatcatcctc l...gcctctgttcc cctggatcctc ggtcaagctcac ctgcactctgag c

FIG. 7

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
agtggcagcatt .....gcca gcaactat	gtgcagtggttcc agcagccgccag ggcagtgcccc caccactgcat ctat	gaggat..... .....aac	caagcagcccict gggctcoct...g atcggttctctgg ctccatcgacag gtcctccaacict gcctcctcatc atctctggactga agactgaggac gaggctgactac tactgt	cagtctatgata gcaccaatctgg ta	tgtcagtctatg atagcaccaatg tggtattc	gtggtattcggc ggagggacca agctgaccgtcc tg	ttcggcggaggg gaccaagctgga ccgtcctg
agtggccaccag t.....ag ctaccatc	atcgcatggcat cagcagcagccc agggaagccccc ctcggtacttgat gaag	cttgaaggtagt. .....ggaagcct ac	gaccctcggga ctgggctgacc gctacctcacca tctccaacctcc agtctgaggatg aggctgattatta ctgt	gagcactctggga cagtaacctccc ttcttcggctg	tgtgagcctgg gacagtaacctc cattcttggtgtt c	ttggtgttcggc ggagggacca agctgaccgtcc tta	ttcggcggaggg gaccaagctgga ccgtccta

FIG. 7 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-A8_PelB-F_2021-07-12_A08	productive	Homsap IGKV1D-12*01 F	Homsap IGKJ5*01 F			gacatccagatgaccagtctccatctttcctgtctgtctgcat ctatagggagacagagtcaccatcacttgtcgggcgagt.. cagyatatt.....agcaactcgttagcctggt atcagcagaaaccagggaaagcccctaaactcctga tctatgctgca.....tccaattlgcgaagtg ggtcccat...tcaagttcagcggcagtgga.....ictg ggacgatttcactctcaccatcagcagtctg aagattttgcgacttatattgtcaacagggtaacagttttc cggatcacctttggccaagggacacgactggagattta aac	gacatccagatgaccagtctccatctttcctgtctgtctgcat ctatagggagacagagtcaccatcacttgtcgggcgagt.. cagyatatt.....agcaactcgttagcctggt atcagcagaaaccagggaaagcccctaaactcctga tctatgctgca.....tccaattlgcgaagtg ggtcccat...tcaagttcagcggcagtgga.....ictgg aagattttgcgacttatattgtcaacagggtaacagttttc cggatcacctttggccaagggacacgactggagattta aac	gacatccagatgaccagtctccatctttcctgtctgtctgcat ctatagggagacagagtcaccatcacttgtcgggcgagt.. cagyatatt.....agcaactcgttagcctggt atcagcagaaaccagggaaagcccctaaactcctga tcaycagaaaccagggaaagcccctaaactcctgatc tatgctgca.....tccaattlgcgaagtg gtcccat...tcaagttcagcggcagtgga.....ictggg aagattttgcgacttatattgtcaacagggtaacagttttc cggatcacctttggccaagggacacgactggagattta aac	gacatccagatgaccagtctccatctttcctgtctgtctgcat ctatagggagacagagtcaccatcacttgtcgggcgagt.. cagyatatt.....agcaactcgttagcctggt atcagcagaaaccagggaaagcccctaaactcctgatc tatgctgca.....tccaattlgcgaagtg gtcccat...tcaagttcagcggcagtgga.....ictggg aagattttgcgacttatattgtcaacagggtaacagttttc cggatcacctttggccaagggacacgactggagattta aac	gacatccagatg accagtctcca ttttctgtctgtc gcc tatagggagaga tcaccatcacttg tcgggcgagt.. cagyatatt.....agcaactcgttagcctggt atcagcagaaaccagggaaagcccctaaactcctgatc tatgctgca.....tccaattlgcgaagtg gtcccat...tcaagttcagcggcagtgga.....ictggg aagattttgcgacttatattgtcaacagggtaacagttttc cggatcacctttggccaagggacacgactggagattta aac
CTLA4-PMPL-Rd2-B10_PelB-F_2021-07-12_F08	productive	Homsap IGLV8-61*01 F	Homsap IGLJ3*02 F			cagactgtgtggcatcagggagccatgg...ttctcagtgt ccctgagggacagtcacactactgtgggttgagc tctggctcagtctct.....actagttatatcccctagctg gtaccagcagacccccaggccacggtctcacgcacact catctacaccaca.....aaractcgctctt ctgggtccct...gatcgcttctctggctccatc.....cttg ggaacaaagctgcctcaccatcacgggggcccaagg cagatcgatgaatctgattattatgtgtctctatatatcgct agtggcattlggggttcggcggagggaccaagctgac cgtcctag	cagactgtgtggcatcagggagccatgg...ttctcagtgt ccctgagggacagtcacactactgtgggttgagc ctggctcagtctct.....actagttatatcccctagctg gtaccagcagacccccaggccacggtctcacgcacact catctacaccaca.....aaractcgctctt ctgggtccct...gatcgcttctctggctccatc.....cttg ggaacaaagctgcctcaccatcacgggggcccaagg cagatcgatgaatctgattattatgtgtctctatatatcgct agtggcattlggggttcggcggagggaccaagctgac gtgcctag	cagactgtgtggcatcagggagccatgg...ttctcagtgt ccctgagggacagtcacactactgtgggttgagc ctggctcagtctct.....actagttatatcccctagctg gtaccagcagacccccaggccacggtctcacgcacact catctacaccaca.....aaractcgctctt ctgggtccct...gatcgcttctctggctccatc.....cttgg ggaacaaagctgcctcaccatcacgggggcccaagg cagatcgatgaatctgattattatgtgtctctatatatcgct agtggcattlggggttcggcggagggaccaagctgac gtgcctag	cagactgtgtg actcagtctcca actcagggagcc atgg...ttctcagct gtcccctgggagcg tcacatcacttgc cgggcaagtcag tacattagtgcttg tatcagcagaaacc agatggaactgtt aaactcctgatc tactctgcatcc actttgcaaagtg gagtcccatcaa ggttcagtggca gtggatctggga cagaattcactc accatcagcagc ctgcagcctgaa gattttgcaacttac tactgtcaacag agttacagtacc cctcggacgttc ggccaagggacc aaggtggaaatc aaacgtacggtg gctgcaccatct gtcttcatcttc ccgccatctgat gagcagttgaaa tctggaactgcc tctgttgtgtgc ctgctgaataac ttctatcccaga gaggccaaagta cagtggaaggtg gataacgccctc caatcgggtaac tcccaggagagt gtcacagagcag gacagcaaggac agcacctacagc ctcagcagcacc ctgacgctgagc aaagcagactac gagaaacacaaa gtctacgcctgc gaagtcacccat cagggcctgagc tcgcccgtcaca aagagcttcaac aggggagagtgt tag	cagactgtgtg actcaggagcc actcaggagcc atgg...ttctcagct gtcccctgggagcg tcacatcacttgc cgggcaagtcag tacattagtgcttg tatcagcagaaacc agatggaactgtt aaactcctgatc tactctgcatcc actttgcaaagtg gagtcccatcaa ggttcagtggca gtggatctggga cagaattcactc accatcagcagc ctgcagcctgaa gattttgcaacttac tactgtcaacag agttacagtacc cctcggacgttc ggccaagggacc aaggtggaaatc aaacgtacggtg gctgcaccatct gtcttcatcttc ccgccatctgat gagcagttgaaa tctggaactgcc tctgttgtgtgc ctgctgaataac ttctatcccaga gaggccaaagta cagtggaaggtg gataacgccctc caatcgggtaac tcccaggagagt gtcacagagcag gacagcaaggac agcacctacagc ctcagcagcacc ctgacgctgagc aaagcagactac gagaaacacaaa gtctacgcctgc gaagtcacccat cagggcctgagc tcgcccgtcaca aagagcttcaac aggggagagtgt tag

FIG. 7 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
caggatatt..... .....agca actcg	ttagcctggtatc agcagaaacca gggaaagcccc taaactctgatc tat	ggtgca..... .....tcc	aatttggaagt agggtcct...tc aaggttcagcg gcggtgga..... tctgggagtatt tcactctactat caglagcctaca gcctgaagattt gcgactactatt gt	caacaggtaa cagtttccgatc aac	ttgtcaacaggct taacgttccctg atcacctte	gatcacctlcgg ccaaggyagcgc gatctggagatta aac	ttcggccaaggg acgcgactcga gattaaac
tctgyctcagtct ct.....actag ttactac	cccagctgctac cagcagaccccc aggccagggtc cacgcacactc atctac	accaca..... .....aac	actcgctcttctg ccatc.....cttg ggaacaaagct gcctctaccatc acggcgccca ggcagtgatg aatctgatatta ctgt	gtcctatatatgg gtatgtgcattttg ggtg	ttgtgtctatatat gggtagtggcat ttggctgttc	gggtgttcggcg gaggaccaa gctgaccgtcct ag	ttcggcggagg gaccaagctga ccgtcctag

FIG. 7 CON'T

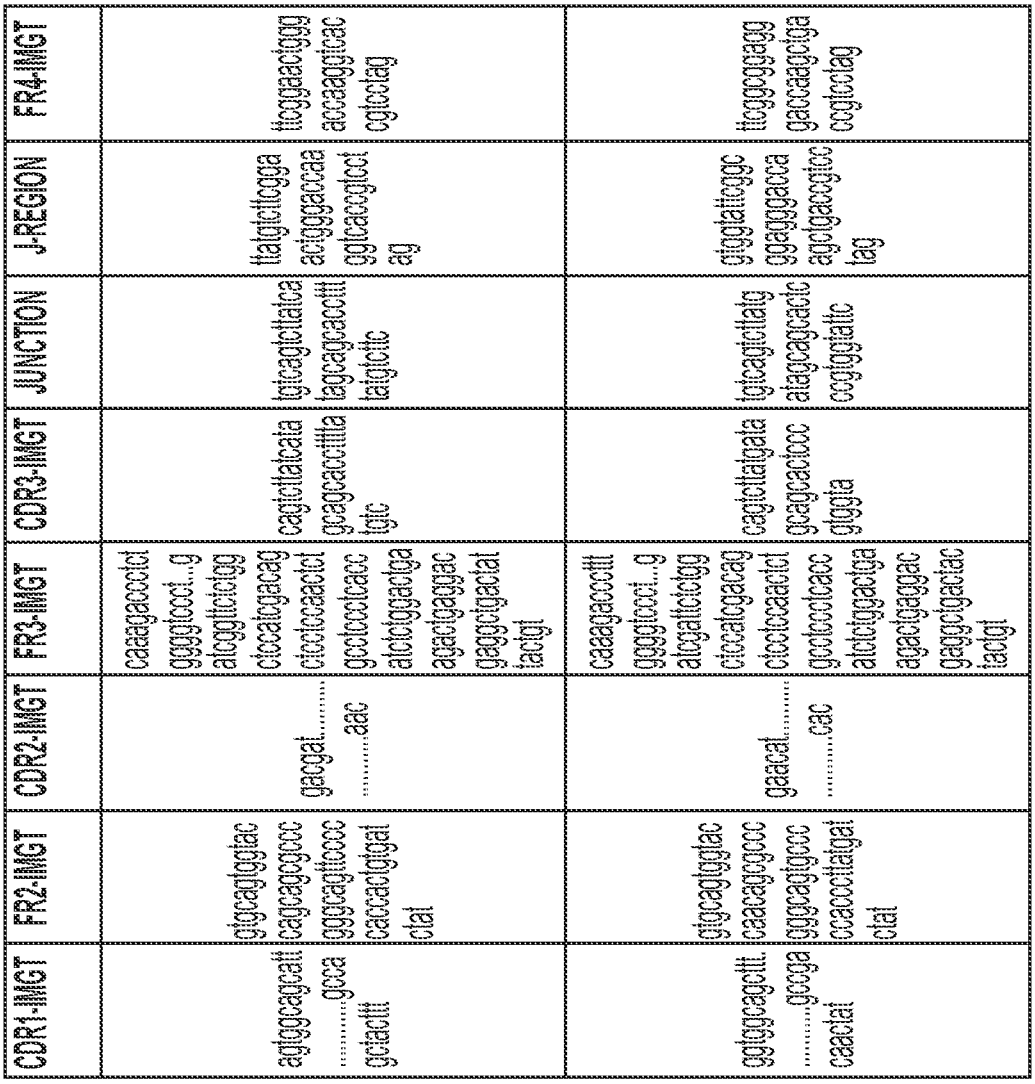
Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-A10_PelB-F_2021-07-12_C08	productive	Homsap IGLV3-21*02 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F			cagcctgtgctgactcagccaccctca...gtgtcagtgg ccccaggacagaaggccagattacctgtgggggaa acaacattgga.....agtaaagtgtgcagt ggtaccagcagaagccaggccaggcccctgtgttgtt cgtctatgatgac.....agcgaccggccct cagggatccct...gagcgattctctggctccaac.....tc ctgggaacacggccaacctgaccatcagcgggctcg aagccgaggatgaggccgactattactgtcaggtgtgg gccaacagcactgtggttcggcggagggaccaag gtgaccgtcctcgg	cagcctgtgctgactcagccaccctca...gtgtcagtgg ccccaggacagaaggccagattacctgtgggggaa acaacattgga.....agtaaagtgtgcact ggtaccagcagaagccaggccaggcccctgttgtt cgtctatgatgac.....agcgaccggccct cagggatccct...gagcgattctctggctccaac.....tc tgggaacacggccaacctgaccatcagcgggctcga agccgaggatgaggccgactattactgtcaggtgtgg agccgggatgaggccgactattactgtcagggtgggg ccaacagcactg	cagcctgtgctg aatcagccacc ctca...gtgtcag tggcccagga cagaggccaag gattacctgtgg gggaaac

FIG. 7 CONT

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
aacattgga.....agta aagct	gtgcactgtac cagcagaagcc aggcaggccc ctgtgttggtctgctc tat	gatgac.....agc	gaccggccctc aggatcct... gagcgattctctg gctccaac.....t ctggaacacg gccacctgac catcaggaggt cgaggccggg atgaggccgact attactgt	caggtgtggccc aacagcactctg gtc	tgtcaggtgtgg gccaacagcac tgtggtcttc	tggtattggcgg aggaccag gtgaccgtcctg g	ttcggcggagg gaccaagctga ccgtcctgg

FIG. 7 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-B11_PelB-F_2021-07-12_G08	productive	Homsap IGLV6-57*01 F	Homsap IGLJ1*01 F			aatttatgctgactcaccccactct...gtgtcggagtct ccgggaagacggtaacatcctctgaccccgcagc agtggcagcatt.....gccagctacttttgtcagtg gtaccagcagccgccccgggcagttcccccaccactgtg atctatgacgat.....aaccaaagaccctc tgggtccct...gatcggttctctggctccatcgacagct cctccaactctgcctcccaccatctctggactgaaga ctgaggacgaggctgactattactgtcagtcttatcatag cagca



CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
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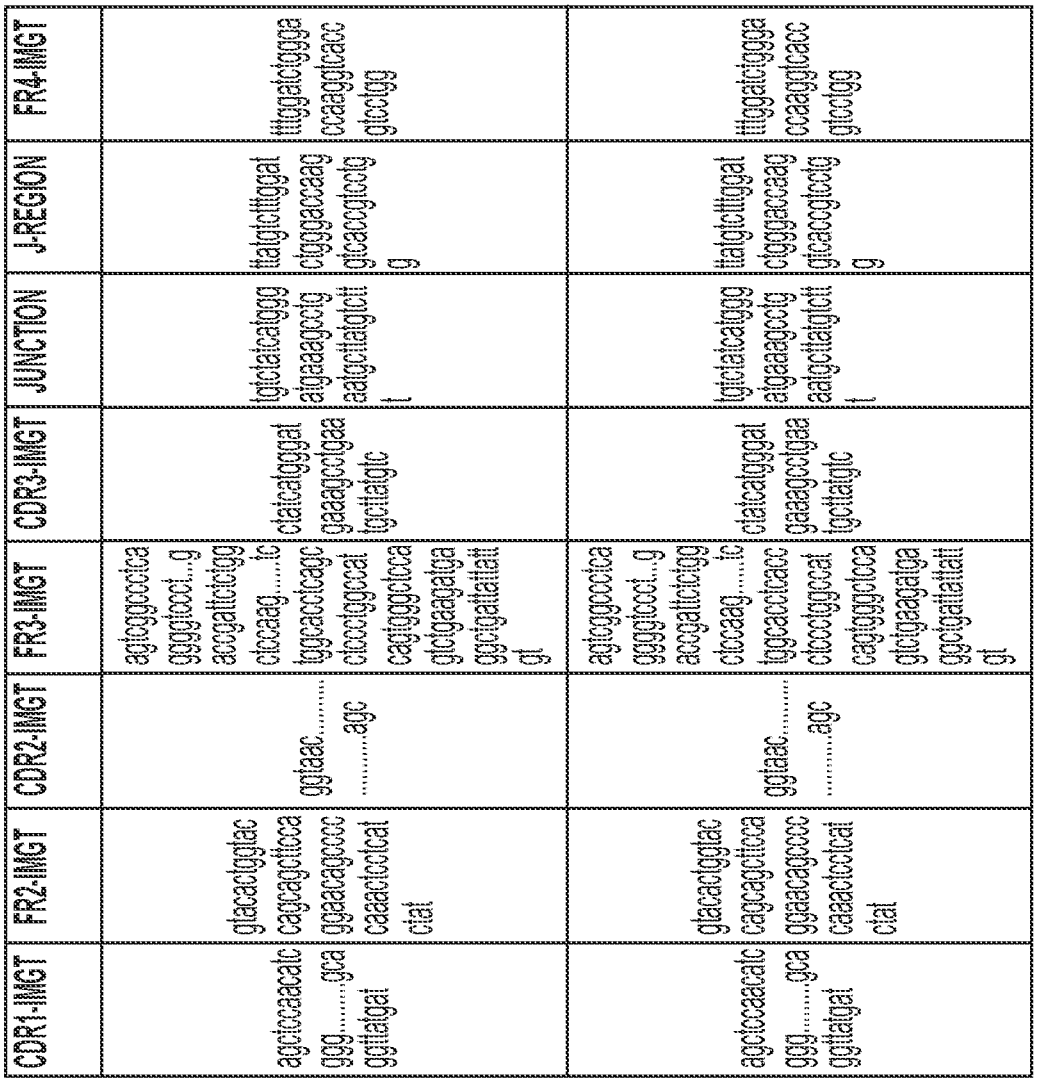
agtggcagcgtttt. .....gccga caactat	gtgcagtggtac caacagcgccc gggcagtgccc ccacccttatgat ctat	gaacat..... .....cac	caaagtacgctttt gggatccct...g atcgattctctgg ctccatgacacg ctcctccaactct gcctcctcacc atctctgcactga agactgaggac gaggctgactac tactgt	cagtcttatgata gcagcactccc gtggta	tgtcagtcttatg atagcagcactc ccgtggtattc	gtggtattcggc ggagggaccca agcgtgaccgtcc tag	ttcggcggtagg gaccaagctgga ccgtcctag

FIG. 7 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-B6_PelB-F_2021-07-12_E08	productive	Homsap IGLV1-40*01 F	Homsap IGLJ1*01 F			cagtctgtgctgactcagccaccctca...gtgtctgggg ccccagggcagaggtcaccatctcctgcactgggag cagctccaacatcgggg.....gcaggttatgatgtaca ctggtaccagcagcttccaggaacagcccccaaactc ctcatctatggtaac.....agcagtcggcc ctcaggggtccct...gaccgattctctggctccaag..... tctggcaactcagcctcctgccatcagtgggctccaa gtctgaagatgaggctgattattactgtcagtcatgggato aaagcctgaatgctatgtcttcggatctgggaccaagggt caccgtcctgg	cagtctgtgctgactcagccaccctca...gtgtctgggg ccccagggcagaggtcaccatctcctgcactgggag cagctccaacatcgggg.....gcaggttatgatgtaca ctggtaccagcagcttccaggaacagcccccaaactc ctcatctatggtaac.....agcagtcggcc ctcaggggtccct...gaccgattctctggctccaag..... tctggcaactcagcctcctgccatcagtgggctccaa gtctgaagatgaggctgattattactgtcagtcatgggato aaagcctgaatgctatgtcttcggatctgggaccaagggt caccgtcctgg	cagtctgtgctgactcagccaccctca...gtgtctgggg ccccagggcagaggtcaccatctcctgcactgggag cagctccaacatcgggg.....gcaggttatgatgtaca ctggtaccagcagcttccaggaacagcccccaaactc ctcatctatggtaac.....agcagtcggcc ctcaggggtccct...gaccgattctctggctccaag..... tctggcaactcagcctcctgccatcagtgggctccaa gtctgaagatgaggctgattattactgtcagtcatgggato aaagcctgaatgctatgtcttcggatctgggaccaagggt caccgtcctgg	cagtctgtgctgactcagccaccctca...gtgtctgggg ccccagggcagaggtcaccatctcctgcactgggag cagctccaacatcgggg.....gcaggttatgatgtaca ctggtaccagcagcttccaggaacagcccccaaactc ctcatctatggtaac.....agcagtcggcc ctcaggggtccct...gaccgattctctggctccaag..... tctggcaactcagcctcctgccatcagtgggctccaa gtctgaagatgaggctgattattactgtcagtcatgggato aaagcctgaatgctatgtcttcggatctgggaccaagggt caccgtcctgg	cagtctgtgctgactcagccaccctca...gtgtctgggg ccccagggcagaggtcaccatctcctgcactgggag cagctccaacatcgggg.....gcaggttatgatgtaca ctggtaccagcagcttccaggaacagcccccaaactc ctcatctatggtaac.....agcagtcggcc ctcaggggtccct...gaccgattctctggctccaag..... tctggcaactcagcctcctgccatcagtgggctccaa gtctgaagatgaggctgattattactgtcagtcatgggato aaagcctgaatgctatgtcttcggatctgggaccaagggt caccgtcctgg	cagtctgtgctgactcagccaccctca...gtgtctgggg ccccagggcagaggtcaccatctcctgcactgggag cagctccaacatcgggg.....gcaggttatgatgtaca ctggtaccagcagcttccaggaacagcccccaaactc ctcatctatggtaac.....agcagtcggcc ctcaggggtccct...gaccgattctctggctccaag..... tctggcaactcagcctcctgccatcagtgggctccaa gtctgaagatgaggctgattattactgtcagtcatgggato aaagcctgaatgctatgtcttcggatctgggaccaagggt caccgtcctgg	cagtctgtgctga ctcagccaccct ca...gtgtctgg ggcccaggcgc agagggtcacc atctctgcagtg gagc
CTLA4-PMPL-Rd2-C12_PelB-F_2021-07-12_A09	productive	Homsap IGLV1-40*01 F	Homsap IGLJ1*01 F			cagtctgtgctgactcagccaccctca...gtgtctgggg ccccagggcagaggtcaccatctcctgcactgggag cagctccaacatcgggg.....gcaggttatgatgtaca ctggtaccagcagcttccaggaacagcccccaaactc ctcatctatggtaac.....agcagtcggcc ctcaggggtccct...gaccgattctctggctccaag..... tctggcaactcagcctcctgccatcagtgggctccaa gtctgaagatgaggctgattattactgtcagtcatgggato aaagcctgaatgctatgtcttcggatctgggaccaagggt caccgtcctgg	cagtctgtgctgactcagccaccctca...gtgtctgggg ccccagggcagaggtcaccatctcctgcactgggag cagctccaacatcgggg.....gcaggttatgatgtaca ctggtaccagcagcttccaggaacagcccccaaactc ctcatctatggtaac.....agcagtcggcc ctcaggggtccct...gaccgattctctggctccaag..... tctggcaactcagcctcctgccatcagtgggctccaa gtctgaagatgaggctgattattactgtcagtcatgggato aaagcctgaatgctatgtcttcggatctgggaccaagggt caccgtcctgg	cagtctgtgctgactcagccaccctca...gtgtctgggg ccccagggcagaggtcaccatctcctgcactgggag cagctccaacatcgggg.....gcaggttatgatgtaca ctggtaccagcagcttccaggaacagcccccaaactc ctcatctatggtaac.....agcagtcggcc ctcaggggtccct...gaccgattctctggctccaag..... tctggcaactcagcctcctgccatcagtgggctccaa gtctgaagatgaggctgattattactgtcagtcatgggato aaagcctgaatgctatgtcttcggatctgggaccaagggt caccgtcctgg	cagtctgtgctgactcagccaccctca...gtgtctgggg ccccagggcagaggtcaccatctcctgcactgggag cagctccaacatcgggg.....gcaggttatgatgtaca ctggtaccagcagcttccaggaacagcccccaaactc ctcatctatggtaac.....agcagtcggcc ctcaggggtccct...gaccgattctctggctccaag..... tctggcaactcagcctcctgccatcagtgggctccaa gtctgaagatgaggctgattattactgtcagtcatgggato aaagcctgaatgctatgtcttcggatctgggaccaagggt caccgtcctgg	cagtctgtgctga ctcagccaccct ca...gtgtctgg ggcccaggcgc agagggtcacc atctctgcagtg gagc

FIG. 7 CONT



CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
agtctccaacatc ggg.....gca ggttatgat	gtacactggtac cagcagcttcca ggaacagcccc caaactcctcat ctat	ggtaac..... .....agc	agtcggcctca gggtcoct...g acccgattcctggg ctccaag.....tc tggcacctcagc ctcctggcgcat cactgggctcca gtctgaagatga ggctgatattatatt gt	ctatcatgggat gaaagcctgaa tgcttatgtc t	tgtctatcatggg atgaaagcctg aatgcttatgtctt t	ttatgtcttttggat ctgggaccaag gtcaccgtcctg g	ttttggatctgggа ccaagtcacc gtcctgg
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FIG. 7 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PIMPL-Rd2-A4_PelB-F_2021-07-12_H07	productive	Homsap IGLV2-11*01 F	Homsap IGLJ1*01 F			cagtctgcctgactcagccctgcctca...gtgtccgggt ctcctggacagtcagtcaccatctcctgcactggaacc agcagtgatgttggt.....ggttctgactatgtctcctg gtaccaacagcaccccaggcaaagcccccaaactcat aatttatgaggtc.....agtaagcggccct cagggttttct...gatcgctttctggctccaag.....tct ggcaacacggcctcactgaggctccgggctccagg ctcaggaccagggctgattattactgcgtttcataatgtgg aagtatgatttttgtcttctggtagtgggaccgagggtcacc gtcctgg	cagtctgcctgactcagccctgcctca...gtgtccgggt ctcctggaagtcagtcaccatctcctgcactggaacc agcagtgatgttggt.....ggttctgactatgtctcctgg gtaccaacagcaccccaggcaaagcccccaaactcat aatttatgaggtc.....agtaagcggccct cagggttttct...gatcgctttctggctccaag.....tctgg ggcaacacggcctcactgaggctccgggctccagg ctcaggaccagggctgattattactgcgtttcataatgtgg aagtatgatttttgtcttctggtagtgggaccgagggtcacc gtcctgg	cagtctgcctgactcagccctgcctca...gtgtccgggt ctcctggaagtcagtcaccatctcctgcactggaacc agcagtgatgttggt.....ggttctgactatgtctcctgg taccaacagcaccccaggcaaagcccccaaactcata aatttatgaggtc.....agtaagcggccctca cagggttttct...gatcgctttctggctccaag.....tctgg ggcaacacggcctcactgaggctccgggctccagg ctcaggaccagggctgattattactgcgtttcataatgtggaa gtattcttttgtcttctggtagtgggaccgagggtcacc gtcctgg	cagtctgcctgactcagccctgcctca...gtgtccgggt ctcctggaagtcagtcaccatctcctgcactggaacc agcagtgatgttggt.....ggttctgactatgtctcctgg taccaacagcaccccaggcaaagcccccaaactcata aatttatgaggtc.....agtaagcggccctca cagggttttct...gatcgctttctggctccaag.....tctgg ggcaacacggcctcactgaggctccgggctccagg ctcaggaccagggctgattattactgcgtttcataatgtggaa gtattcttttgtcttctggtagtgggaccgagggtcacc gtcctgg	cagtctgcctgactcagccctgcctca...gtgtccgggt ctcctggaagtcagtcaccatctcctgcactggaacc agcagtgatgttggt.....ggttctgactatgtctcctgg taccaacagcaccccaggcaaagcccccaaactcata aatttatgaggtc.....agtaagcggccctca cagggttttct...gatcgctttctggctccaag.....tctgg ggcaacacggcctcactgaggctccgggctccagg ctcaggaccagggctgattattactgcgtttcataatgtgg aagtatgat

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
agcagtgatgtt ggt.....ggtt ctgactat	gtctcctggtacc aacagcaccca ggccaagccccc caaactcataatt tat	gaggtc..... .....agt	aagcggcctc aggggttttct..g atcgctctctgg ctccaag.....tc tggcaacaggg cctccctgagaa tctcgggcctcc aggctcaggac gaggctgattatt attgc	tgttcatatgctg gaagtgtactttt tgtc	tgctgttcatatgc tggaagtgtac ttttqtctttc	tgtcttcgtagt ggcaccgaggct caccgtcctgg	ttcggtagtggg accgaggtcac cgtcctgg

FIG. 7 CONT

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-A12_PeIB-F_2021-07-12_D08	productive	Homsap IGLV7-46*01 F	Homsap IGLJ3*02 F			cagactgtggtgactcaggagccctca...ctgactgtgt cccccaggagggacagtcactctcacctgtggctccag cactggagctgtcacc.....actggtcattatcccctact tggttccagcagaagcctggccaggcccccacgtaca ctgattatgatgca.....actcacaaacac tcctggaccctt...gcccggttctcaggctccctc....ct ttgggggcaaagctgccctgaccctttcgggtggcgcag cctgaagatgaggctgactattactgctgtctcctata gtggtgctcgggggtttcggcggagggaccaagctgac cgtcctca	cagactgtggtgactcaggagccctca...ctgactgtgt cccccaggagggacagtcactctcacctgtggctccag cactggagctgtcacc.....actggtcattatcccctact ggttccagcagaagcctggccaggcccccacgcac tgattttatgatgca.....actcacaaacact ccctggaccctt...gcccggttctcaggctccctc....ct tgggggcaaagctgccctgaccctttcgggtggcagc ctgaagatgaggctgactattactgctgtctcctatag tggtgctcgg	caggtgtggtg actcaggagcc ctca...ctgactg tgtcccaggag ggacagtcactc tcaccgtggctc cagc
CTLA4-PMPL-Rd2-B12_PeIB-F_2021-07-12_H08	productive	Homsap IGLV7-46*01 F	Homsap IGLJ3*02 F			cagactgtggtgactcaggagccctca...ctgactgtgt cccccaggagggacagtcactctcacctgtggctccag cactggagctgtcacc.....actggtcattatcccctact tggttccagcagaagcctggccaggcccccacgaca ctgattttatgatgca.....actcacaaacac tcctggaccctt...gcccggttctcaggctccctc....ct ttgggggcaaagctgccctgaccctttcgggtggcgag cctgaagatgaggctgactattactgctgtctcctata gtggtgctcgggggtttcggcggagggaccaagctgac cgtcctca	cagactgtggtgactcaggagccctca...ctgactgtgt cccccaggagggacagtcactctcacctgtggctccag cactggagctgtcacc.....actggtcattatcccctact ggttccagcagaagcctggccaggcccccacgaaac tgattttatgatgca.....actcacaaaact ccctggaccctt...gcccggttctcaggctccctc....ct tgggggcaaagctgccctgaccctttcgggtggcagc ctgaagatgaggctgactattactgctgtctcctatag tggtgctcgg	cagactgtggtg actcaggagcc ctca...ctgactg tgtcccaggag ggacagtcactc tcaccgtggctc cagc

FIG. 7 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
atggagctgtc acc.....atg gtcattat	cctactggttcc agcagaagcct ggccaggcccc cacgacactgat ttat	gatgca..... .....act	cacaaacactc atggacctcct... gcccggttctca ggctccgtc..... cttgggggcaa agctgccctgac cattcgggtgcg cagcctgaagat gaggctgactat tactgc	ctgctcctata gtggtgcctggg tg	tgctgctcttct atagtggtgctc ggatgttc	gtgttcggcgga gggaccaagct gaccgtcctca	ttcggcgaggg gaccaagctga ccgtcctca
atggagctgtc acc.....atg gtcattat	cctactggttcc agcagaagcct ggccaggcccc cacgacactgat ttat	gatgca..... .....act	cacaaacactc atggacctcct... gcccggttctca ggctccgtc..... cttgggggcaa agctgccctgac cattcgggtgcg cagcctgaagat gaggctgactat tactgc	ctgctcctata gtggtgcctggg tg	tgctgctcttct atagtggtgctc ggatgttc	gtgttcggcgga gggaccaagct gaccgtcctca	ttcggcgaggg gaccaagctga ccgtcctca

FIG. 7 CONT

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
aCTLA4_E1-D7	productive	Homsap IGLV6-57*03 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F			NFMLTQPHS.MSESPGK TVTISCTRSSGSI...ASNY VQWFQQRPGSAPTTVIY ED.....NQRPSGVP.DRF SGSIDRSSNSASLIISGLK TEDEADYYCQSYDSTNV VFGGGTKLTVL	NFMLTQPHS.MSESPGK TVTISCTRSSGSI...ASN YVQWFQQRPGSAPTTVI ED.....NQRPSGVP.DR SGSIDRSSNSASLIISGL TEDEADYYCQSYDSTN VFGGGTKLTVL	NFMLTQPH S.MSESPG KTVTISCTR S
aCTLA4_T2-C10	productive	Homsap IGLV4-60*03 F	Homsap IGLJ3*02 F			LPVLTQSSS.ASASLGSS VKLTCTLSSGHS....SYII AWHQQQPGKAPRYLMK LEGS...GSYNKGSGVP.D RFSGSS..SGADRYLTIS LQSEDEADYYCETWDSN LPSWVFGGGTKLTVL	LPVLTQSSS.ASASLGSS VKLTCTLSSGHS....SYII AWHQQQPGKAPRYLMK LEGS...GSYNKGSGVP.D RFSGSS..SGADRYLTIS NLQSEDEADYYCETWD SN	LPVLTQSS S.ASASLGS SVKLTCTL S
CTLA4-PIMPL-Rd2-A8_PelB-F_2021-07-12_A08	productive	Homsap IGKV1D-12*01 F	Homsap IGKJ5*01 F			DIQMTQSPSSVSASIGDR VTITCRASQDI.....SNSLA WYQQKPGKAPKLLIYGA. .....SNLRSGVP.SRFSGS G.SGTYFTLTISSLQPED FATYYCQQGNSFPITFG QGTRLEIK	DIQMTQSPSSVSASIGD RVTITCRASQDI.....SNS LAWYQQKPGKAPKLLIY GA.....SNLRSGVP.SRF SGSG.SGTYFTLTISSLQ PEDFATYYCQQGNSF	DIQMTQSP SSVSASIG DRVTITCR AS

FIG. 8

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
SGSL...ASN Y	VQWFQQR PGSAPTTVI Y	ED.....N	QRPSGVP. DRFSGSID RSSNSASLI ISGLKTEDE ADYYC	QSYDSTNV V	CQSYDSTN VVF	WVFGGGTK LTVL	FGGGTKLT VL
SGHS...SY I	IAWHQQQP GKAPRYLM K	LEGS...GSY	NKGSGVP. DRFSGSS. SGADRYLTI SNLQSEDE ADYYC	ETWDSNLP SWV	CETWDSNL PSWVF	WVFGGGT KLTVL	FGGGTKLT VL
QDI.....SNS	LAWYQQKP GKAPKLLIY	GA.....S	NLRSGVP. SRFSGGG.. SGTYFTLTI SSLQPEDF ATYYC	QQGNSFPI T	CQQGNSF PITF	ITFGQGTR LEIK	FGQGTRLE IK

FIG. 8 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-B10_PelB-F_2021-07-12_F08	productive	Homsap IGLV8-61*01 F	Homsap IGLJ3*02 F			QTVVTQEPS.FSVSPGGT VTLTCGLSSGSVS...TSY YPSWYQQTPGQAPRTLI YTT.....NTRSSGVP.DRF SGSI..LGNKAALTITGAQ ADDESDYYCVLYMGSGI WVFGGGTKLTVL	QTVVTQEPS.FSVSPGG TVTLTCGLSSGSVS...TS YYPSWYQQTPGQAPRT LIYTT.....NTRSSGVP.D RFSGSI..LGNKAALTITG AQADDESDYYCVLYMG SGI	QTVVTQEP S.FSVSPG GTVTLTCG LS
CTLA4-PMPL-Rd2-A10_PelB-F_2021-07-12_C08	productive	Homsap IGLV3-21*02 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F			QPVLTQPPS.VSVAPGQT ARITCGGNNIG.....SKSV HWYQQKPGQAPVLVVY DD.....SDRPSGIP.ERFS GSN..SGNTATLTISRVEA GDEADYYCQVWANSTV VFGGGTKVTVL	QPVLTQPPS.VSVAPGQ TARITCGGNNIG.....SKS VHWYQQKPGQAPVLVV YDD.....SDRPSGIP.ER FSGSN..SGNTATLTISRV EAGDEADYYCQVWANS T	QPVLTQPP S.VSVAPG QTARITCG GN
CTLA4-PMPL-Rd2-B11_PelB-F_2021-07-12_G08	productive	Homsap IGLV6-57*01 F	Homsap IGLJ1*01 F			NFMLTHPHS.VSESPGKT VTISCTRSSGSI...ASYFV QWYQQRPGSSPTTVIYD D.....NQRPSGVP.DRFS GSIDSSSNSASLTISGLKT EDEADYYCQSYHSSTFY VFGTGTKVTVL	NFMLTHPHS.VSESPGK TVTISCTRSSGSI...ASY FVQWYQQRPGSSPTTVI YDD.....NQRPSGVP.DR FSGSIDSSSNSASLTISG LKTEDEADYYCQSYHSS	NFMLTHPH S.VSESPGK TVTISCTRS

FIG. 8 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
SGSVS...TS YY	PSWYQQT PGQAPRTL IY	TT.....N	TRSSGVP. DRFSGSI..L GNKAALTIT GAQADDES DYYC	VLYMGSGI WV	CVLYMGSG IWVF	VFGGGTKL TVL	FGGGTKLT VL
NIG.....SKS	VHWYQQK PGQAPVLV VY	DD.....S	DRPSGIP.E RFSGSN..S GNTATLTIS RVEAGDEA DYYC	QVWANST VV	CQVWANS TVVF	VFGGGTKV TVL	FGGGTKVT VL
SGSI...ASY F	VQWYQQR PGSSPTTVI Y	DD.....N	QRPSGVP. DRFSGSID SSSNSASL TISGLKTED EADYYC	QSYHSSTF YV	CQSYHSST FYVF	YVFGTGTK VTVL	FGTGTKVT VL

FIG. 8 CON'T

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PIMPL-Rd2-A9_PelB-F_2021-07-12_B08	productive	Homsap IGLV6-57*04 (F)	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F			QPVLTQPHSVSESPGKTVTISCTRSGGSF...ADNYVQWYQQRPGSAPTLMIYEH.....HQRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSTPWFGGGTKLTVL	QPVLTQPHSVSESPGKTVTISCTRSGGSF...ADNYVQWYQQRPGSAPTLMIYEH.....HQRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSTPWFGGGTKLTVL	QPVLTQPHSVSESPCKTVTISCTRS
CTLA4-PIMPL-Rd2-B6_PelB-F_2021-07-12_E08	productive	Homsap IGLV1-40*01 F	Homsap IGLJ1*01 F			QSVLTQPPSVSGAPGQRVTISCTGSSSNIG..AGYDVHWYQQLPGTAPKLLIYGN.....SSRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYCLSWDESLNAYVFGSGTKVTVL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIG..AGYDVHWYQQLPGTAPKLLIYGN.....SSRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYCLSW	QSVLTQPPSVSGAPCQRVTISCTGS
CTLA4-PIMPL-Rd2-C12_PelB-F_2021-07-12_A09	productive	Homsap IGLV1-40*01 F	Homsap IGLJ1*01 F			QSVLTQPPSVSGAPGQRVTISCTGSSSNIG..AGYDVHWYQQLPGTAPKLLIYGN.....SSRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYCLSWDESLNAYVFGSGTKVTVL	QSVLTQPPSVSGAPGQRVTISCTGSSSNIG..AGYDVHWYQQLPGTAPKLLIYGN.....SSRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYCLSW	QSVLTQPPSVSGAPCQRVTISCTGS

FIG. 8
CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
GGSF...AD NY	VQWYQQR PGSAPTLM IY	EH.....H	QRPFGVP. DRFSGSID SSSNSASL TISGLKTED EADYYC	QSYDSSTP VV	CQSYDSST PWF	WVFGGGTK LTVL	FGGGTKLT VL
SSNIG..AG YD	VHWYQQL PGTAPKLLI Y	GN.....S	SRPSGVP. DRFSGSK.. SGTSASLAI SGLQSEDE ADYYC	LSWDESLN AYV	CLSWDESL NAYVF	YVFGSGTK VTVL	FGSGTKVT VL
SSNIG..AG YD	VHWYQQL PGTAPKLLI Y	GN.....S	SRPSGVP. DRFSGSK.. SGTSPSLAI SGLQSEDE ADYYC	LSWDESLN AYV	CLSWDESL NAYVF	YVFGSGTK VTVL	FGSGTKVT VL

FIG. 8 CONT

Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION	FR1-IMGT
CTLA4-PMPL-Rd2-A4_PeIB-F_2021-07-12_H07	productive	Homsap IGLV2-11*01 F	Homsap IGLJ1*01 F			QSALTQPRS.VSGSPGQ SVTISCTGTSSDVG..GS DYVSWYQQHPGKAPKLII YEV.....SKRPSGVS.DRF SGSK..SGNTASLRISGLQ AQDEADYYCCSYAGSST FVFGSGTEVTVL	QSALTQPRS.VSGSPGQ SVTISCTGTSSDVG..GS DYVSWYQQHPGKAPKLII IYEV.....SKRPSGVS.DR FSGSK..SGNTASLRISGL QAQDEADYYCCSYAGS ST	QSALTQPR S.VSGSPG QSVTISCT GT
CTLA4-PMPL-Rd2-A12_PeIB-F_2021-07-12_D08	productive	Homsap IGLV7-46*01 F	Homsap IGLJ3*02 F			QTWVTQEPS.LTVSPGGT VTLTCGSSTGAVT...TGH YPYWFQQKPGQAPTTLI YDA.....THKHSWTP.AR FSGSV..LGGKAALTLSGA QPEDEADYYCLLSYSGA RVFGGGTKLTVL	QTWVTQEPS.LTVSPGG TVTLTCGSSTGAVT...TG HYPYWFQQKPGQAPTT LIYDA.....THKHSWTP.A RFSGSV..LGGKAALTLS GAQPEDEADYYCLLSYS GAR	QTWVTQEP S.LTVSPGG TVTLTCGS S
CTLA4-PMPL-Rd2-B12_PeIB-F_2021-07-12_H08	productive	Homsap IGLV7-46*01 F	Homsap IGLJ3*02 F			QTWVTQEPS.LTVSPGGT VTLTCGSSTGAVT...TGH YPYWFQQKPGQAPTTLI YDA.....THKHSWTP.AR FSGSV..LGGKAALTLSGA QPEDEADYYCLLSYSGA RVFGGGTKLTVL	QTWVTQEPS.LTVSPGG TVTLTCGSSTGAVT...TG HYPYWFQQKPGQAPTT LIYDA.....THKHSWTP.A RFSGSV..LGGKAALTLS GAQPEDEADYYCLLSYS GAR	QTWVTQEP S.LTVSPGG TVTLTCGS S

FIG. 8 CON'T

CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
SSDVG..G SDY	VSWYQQH PGKAPKLII Y	EV.....S	KRPSGVS. DRFSGSK.. SGNTASLRI SGLQAQDE ADYYC	CSYAGSST FV	CCSYAGSS TFVF	VFGSGTEV TVL	FGSGTEVT VL
TGAVT...TG HY	PYWFQQK PGQAPTLLI Y	DA.....T	HKHSWTP. ARFSGSV.. LGGKAALT LSGAQPED EADYYC	LLSYSGAR V	CLLSYSGA RVF	VFGGGTKL TVL	FGGGTKLT VL
TGAVT...TG HY	PYWFQQK PGQAPTLLI Y	DA.....T	HKHSWTP. ARFSGSV.. LGGKAALT LSGAQPED EADYYC	LLSYSGAR V	CLLSYSGA RVF	VFGGGTKL TVL	FGGGTKLT VL

FIG. 8 CONT

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

Sequence ID	V-GENE and allele	J-GENE and allele	D-GENE and allele	FR1-IMGT	CDR1-IMGT
CTLA4pmpl-Rd2-E2-A7	HV3-30-3*01 F	HJ3*02 F	HD4-17*01 F	QVQLVQSGG.SVVRPGRSLRLACAAS	GFTF....RSYA
CTLA4pmpl-Rd2-E2-D4	HV1-46*01 F	HJ4*02 F	HD2-21*01 F	QVQLVQSGA.EVKKPGASVKLSCKGS	GYTF....ITDY
CTLA4pmpl-Rd2-E2-G9	HV1-46*01 F	HJ4*02 F	HD2-21*01 F	QVQLVQSGA.EVKKPGASVKLSCKGS	GYTF....ITDY
CTLA4pmpl-Rd2-E2-A10	HV1-69*04 F	HJ4*02 F		QVQLQQSGA.EVKKPGSSVKVSCKAS	GGTF....SSYA
CTLA4pmpl-Rd2-E2-A12	HV3-23*04 F	HJ4*02 F	HD1-7*01 F	QVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF....SSYA
CTLA4pmpl-Rd2-E2-E5	HV3-23*04 F	HJ4*02 F	HD1-7*01 F	QVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF....SSYA
CTLA4pmpl-Rd2-E2-H5	HV1-46*01 F	HJ6*02 F	HD5-24*01 ORF	EVQLVESGA.EVKKPGASVKVSCKAS	GYTF....TSYY
CTLA4pmpl-Rd2-E2-C4	HV1-46*01 F	HJ6*02 F	HD1-1*01 F	EVQLVQSGA.EVKKPGASVKVSCKAS	GYTF....TSYY
CTLA4pmpl-Rd2-E2-A4	HV3-23*04 F	HJ3*02 F	HD6-19*01 F	QVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF....SSYV
CTLA4pmpl-Rd2-E2-H10	HV1-18*01 F	HJ6*04 F	HD2-15*01 F	QVQLVQSGG.EVKKPGASVKVSCKAS	GDTF....SRYG
CTLA4pmpl-Rd2-E2-F1	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLVQSGA.EVKKPGASVKVSCKAS	GYIF....TSYG
CTLA4pmpl-Rd2-E2-H8	HV3-53*08	HJ1*01 F	HD5-24*01 ORF	EVQLVQSGG.GLIQPGGSLRLSCAAS	GFTV....SSEY
CTLA4pmpl-Rd2-E2-G5	HV1-18*01 F	HJ6*02 F	HD2-15*01 F	EVQLVESGA.EVRKPGESLTISCKAS	GYTF....TSYG
CTLA4pmpl-Rd2-E2-H9	HV3-23*04 F	HJ1*01 F	HD4-23*01 ORF	EVQLVESGG.GLVQPGGSLRLPCAAS	GFTF....SSYA

FIG. 9

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	FR4-IMGT
MHWVRQTPGKGLEWVAV	ISYD..GDNT	FYADAVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC	AKLGVTTYAFDI	WGQGTLVTVSS
IHWVRQAPGQGLEWMGR	LIPS..DGST	IYAQKFR.GRVTMTRDTSTRTVYMELSSLRSEDTALYYC	ARDGSHYDFDN	WGQGTLVTVSS
IHWVRQAPGQGLEWMGR	LIPS..DGST	IYAQKFR.GRVTMTRDTSTRTVYMELSSLRSEDTALYYC	ARDGSHYDFDN	WGQGTLVTVSS
ISWVRQAPGQGLEWMGR	IIPI..LGIA	NYAQKFQ.GRVTITADESTSTAYMELSSLRSEDTAVYYC	ARDWDY	WGQGTLVTVSS
MSWVRQAPGKGLEWVSA	ISGS..GGST	YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC	AREEGITGTGFDY	WGQGTLVTVSS
MSWVRQAPGKGLEWVSS	ITGN..GGST	YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC	AREEGITGTGFDY	WGQGTLVTVSS
MHWVRQAPGQGLEWMGI	ITGN..GGST	SYAQKFQ.GRVTMTRDMSTSTVYMELSSLRSEDTAVYYC	AREEMAPFLSNYGMDV	WGQGTMVTVSS
MHWVRQAPGQGLEWMGI	INPS..GGST	SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC	ARELKRGDVYYYYGMDV	WGQGTTVTVSS
MSWVRQAPGKGLEWVSS	ISGS..GGST	DYADSVK.GRFPISRDNSKNTLYLEMNSLRAEDTAVYYC	ARGGSAWSLDI	WGQGTTVTVSS
ITWVRQAPGQGLEWMGW	MSTV..TGNT	NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC	ARGLCRDSSCLTPYYYGMDV	WGKGTLVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
MTWVRQAPGKGLEWVSN	IYTS..GPT	YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC	ARVGNGGGYNL	WGQGTLVTVSS
ISWVRQAPGQGLEWMGW	ISAY..NGNT	NYAQKLQ.GRVTMTTDTSTSTAYMELRSLRSDDTAVYYC	ATDLIWPIYCSGGSCYETSYYGMDV	WGQGTLVTVSS
MSWVRQAPGKGLEWVSV	ISGS..GTNT	HYADSVK.GRFTISRDNFKNTVYLQVNSPRAEDTAVYYC	VREFGGPSNY	WGQGTLVTVSS

FIG. 9 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

Sequence ID	V-GENE and allele	J-GENE and allele	D-GENE and allele	FR1-IMGT	CDR1-IMGT
CTLA4pmpl-Rd2-E2-A7	LV2-11*01 F	LJ1*01 F		QSALTQPRS.VSGSPGQSVTISCTGT	SSDVG...GYKY
CTLA4pmpl-Rd2-E2-D4	LV2-11*01 F	LJ2*01 F		QPVLTQPRS.VSGSPGQSVTISCTGT	SSDVG...GYNY
CTLA4pmpl-Rd2-E2-G9	LV2-11*01 F	LJ2*01 F		QPVLTQPRS.VSGSPGQSVTISCTGT	SSDVG...GYNY
CTLA4pmpl-Rd2-E2-A10	LV8-61*01 F	LJ2*01 F		QTVVTQEPS.FSVAPGGTVTLTCALS	SGSVS...SNYH
CTLA4pmpl-Rd2-E2-A12	LV8-61*01 F	LJ3*02 F		QTVVTQEPS.FSVSPGGTVTLTCGLS	SGSVS...TSYY
CTLA4pmpl-Rd2-E2-E5	LV8-61*01 F	LJ3*02 F		HTVVTQEPS.FSVTPGGTVTLTCGLS	SGSIS...TSYY
CTLA4pmpl-Rd2-E2-H5	LV6-57*02 F	LJ3*02 F		NFMLTHPHS.VSESPGKTVTISCTGS	SDSL....ASNY
CTLA4pmpl-Rd2-E2-C4	LV6-57*04 (F)	LJ2*01 F		QPVLTQPHS.VSESPGKTVTISCTRS	GGSF....ADNY
CTLA4pmpl-Rd2-E2-A4	KV1D-12*01 F	KJ5*01 F		DIQMTQSPSSVSASIGDRVTITCRAS	QDI.....SNS
CTLA4pmpl-Rd2-E2-H10	LV7-46*01 F	LJ3*02 F		QTVVTQEPS.LTVSPGGTVTLTCGSS	TGAVT...TGHY
CTLA4pmpl-Rd2-E2-F1	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-H8	LV2-14*01 F	LJ1*01 F		QSALTQPAS.VSGSPGQSITISCTGT	SGDVG...AHDY
CTLA4pmpl-Rd2-E2-G5	LV1-47*02 F	LJ3*02 F		QPGLTQPPS.ASGTPGQRVTLSCSGS	SSNI....GSNY
CTLA4pmpl-Rd2-E2-H9	LV1-40*01 F	LJ1*01 F		QSVLTHPPS.VSGAPGQRVTISCTGN	SSNIG...APYD

FIG. 9 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	FR4-IMGT
VSWYQHHPGKAPKLMIY	DV.....S	ERPSGVP.DRFSGSK..SGNTASLTISGLQAEDEADYYC	SSYAGSNSHFV	FGTGTKVTVL
VSWYQQHPGKAPKLIIY	EV.....N	KRPSGVP.DRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSYSSSSTLV	FGGGTKLTVL
VSWYQQHPGKAPKLIIY	EV.....N	KRPSGVP.DRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSYSSSSTLV	FGGGTKLTVL
PSWFQQTPGQAPRTLIY	NT.....D	IRSHGVP.DRFSGSL..LGNKAALTITGAQPNDESEYYC	ALYMGSGISI	FGGGTKVTVL
PSWYQQTPGQAPRTLIY	TT.....N	TRSSGVP.DRFSGSI..LGNKAALTITGAQADDESDYYC	VLYMGSGIWV	FGGGTKLTVL
PIWYQHTPGQAPRTLIY	TT.....N	TPSSGVP.DRFSGSI..LGNKAALTITGAQEDDESDYYC	VLYMGSGIWV	FGGRTKLTVL
VQWYQQRPGSAPTTVIY	EN.....N	QRPSGVP.DRFSGSIDGSSNSASLTISALETEDEADYYC	QSYDGTPV	FGTGTKLTVL
VQWYQQRPGSAPTLMIY	EH.....H	QRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYDSSTPVV	FGGGTKLTVL
LAWYQQKPGKAPKLLIY	GA.....S	NLRSGVP.SRFSGGG..SGTYFTLTISSLQPEDFATYYC	QQGNSFPIT	FGQGTRLEIK
PYWFQQKPGQAPTTLIY	DA.....T	HKHSWTP.ARFSGSV..LGGKAALTLSGAQPEDEADYYC	LLSYSGARV	FGGGTKLTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VSWYQQHPGKAPKLMIY	EG.....S	KRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSFAGTNNYV	FGTGTKVAVL
VFWYQQLPGTAPKLLIY	SN.....N	QRPSGVP.DRFSASK..SGTSASLAISGLRSEDEADYYC	AAWDDSLSGWV	FGGGTKLTVL
VHWYQQLPGTAPKLLIY	AN.....K	YRPSGVP.DRFSGSK..SGTSASLAISGLRSKDEADYYC	AAWDDSLGGLYV	FGTGTKVTVL

FIG. 9 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

Sequence ID	V-GENE and allele	J-GENE and allele	D-GENE and allele	FR1-IMGT	CDR1-IMGT
CTLA4pmpl-Rd2-E2-A7	HV3-30-3*01 F	HJ3*02 F	HD4-17*01 F	QVQLVQSGG.SVVRPGRSLRLACAAS	GFTF..RSYA
CTLA4pmpl-Rd2-E2-D4	HV1-46*01 F	HJ4*02 F	HD2-21*01 F	QVQLVQSGA.EVKKPGASVKLSCKGS	GYTF..ITDY
CTLA4pmpl-Rd2-E2-G9	HV1-46*01 F	HJ4*02 F	HD2-21*01 F	QVQLVQSGA.EVKKPGASVKLSCKGS	GYTF..ITDY
CTLA4pmpl-Rd2-E2-A10	HV1-69*04 F	HJ4*02 F		QVQLQQSGA.EVKKPGSSVKVSCKAS	GGTF..SSYA
CTLA4pmpl-Rd2-E2-A12	HV3-23*04 F	HJ4*02 F	HD1-7*01 F	QVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF..SSYA
CTLA4pmpl-Rd2-E2-E5	HV3-23*04 F	HJ4*02 F	HD1-7*01 F	QVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF..SSYA
CTLA4pmpl-Rd2-E2-H5	HV1-46*01 F	HJ6*02 F	HD5-24*01 ORF	EVQLVESGA.EVKKPGASVKVSCKAS	GYTF..TSYY
CTLA4pmpl-Rd2-E2-C4	HV1-46*01 F	HJ6*02 F	HD1-1*01 F	EVQLVQSGA.EVKKPGASVKVSCKAS	GYTF..TSYY
CTLA4pmpl-Rd2-E2-D11	HV1-46*01 F	HJ6*02 F	HD1-1*01 F	EVQLVQSGA.EVKKPGASVKVSCKAS	GYTF..TSYY
CTLA4pmpl-Rd2-E2-H1	HV1-46*01 F	HJ6*02 F	HD1-1*01 F	EVQLVQSGA.EVKKPGASVKVSCKAS	GYTF..TSYY
CTLA4pmpl-Rd2-E2-E11	HV1-46*01 F	HJ6*02 F	HD1-1*01 F	EVQLVQSGA.EVKKPGASVKVSCKAS	GYTF..TSYY
CTLA4pmpl-Rd2-E2-A4	HV3-23*04 F	HJ3*02 F	HD6-19*01 F	QVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF..SSYV
CTLA4pmpl-Rd2-E2-H10	HV1-18*01 F	HJ6*04 F	HD2-15*01 F	QVQLVQSGG.EVKKPGASVKVSCKAS	GDTF..SRYG
CTLA4pmpl-Rd2-E2-F3	HV1-18*01 F	HJ6*04 F	HD2-15*01 F	QVQLVQSGG.EVKKPGASVKVSCKAS	GDTF..SRYG
CTLA4pmpl-Rd2-E2-F6	HV1-18*01 F	HJ6*04 F	HD2-15*01 F	QVQLVQSGG.EVKKPGASVKVSCKAS	GDTF..SRYG

FIG. 10

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	FR4-IMGT
MHWVRQTPGKGLEWVAV	ISYD..GDNT	FYADAVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC	AKLGVTTYAFDI	WGQGTLVTVSS
IHWVRQAPGQGLEWMGR	LIPS..DGST	IYAQKFR.GRVTMTRDTSTRTVYMELSSLRSEDTALYYC	ARDGSHYDFDN	WGQGTLVTVSS
IHWVRQAPGQGLEWMGR	LIPS..DGST	IYAQKFR.GRVTMTRDTSTRTVYMELSSLRSEDTALYYC	ARDGSHYDFDN	WGQGTLVTVSS
ISWVRQAPGQGLEWMGR	IIPI..LGIA	NYAQKFQ.GRVTITADESTSTAYMELSSLRSEDTAVYYC	ARDWDY	WGQGTLVTVSS
MSWVRQAPGKGLEWVSA	ISGS..GGST	YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC	AREEGITGTGFDY	WGQGTLVTVSS
MSWVRQAPGKGLEWVSS	ITGN..GGST	YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC	AREEGITGTGFDY	WGQGTLVTVSS
MHWVRQAPGQGLEWMGI	INPS..GGST	SYAQKFQ.GRVTMTRDMSTSTVYMELSSLRSEDTAVYYC	AREEMAPFLSNYGMDV	WGQGTMVTVSS
MHWVRQAPGQGLEWMGI	INPS..GGST	SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC	ARELKRGDYYYYGMDV	WGQGTTVTVSS
MHWVRQAPGQGLEWMGI	INPS..GGST	SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC	ARELKRGDYYYYGMDV	WGQGTTVTVSS
MHWVRQAPGQGLEWMGI	INPS..GGST	SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC	ARELKRGDYYYYGMDV	WGQGTTVTVSS
MHWVRQAPGQGLEWMGI	INPS..GGST	SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC	ARELKRGDYYYYGMDV	WGQGTTVTVSS
MSWVRQAPGKGLEWVSS	ISGS..GGST	DYADSVK.GRFPISRDNSKNTLYLEMNSLRAEDTAVYYC	ARGGSAWSLDI	WGQGTTVTVSS
ITWVRQAPGQGLEWMGW	MSTV..TGNT	NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC	ARGLCRDSSCLTPYYYYGMDV	WGKGTLVTVSS
ITWVRQAPGQGLEWMGW	MSTV..TGNT	NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC	ARGLCRDSSCLTPYYYYGMDV	WGKGTLVTVSS
ITWVRQAPGQGLEWMGW	MSTV..TGNT	NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC	ARGLCRDSSCLTPYYYYGMDV	WGKGTLVTVSS

FIG. 10 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

Sequence ID	V-GENE and allele	J-GENE and allele	D-GENE and allele	FR1-IMGT	CDR1-IMGT
CTLA4pmpl-Rd2-E2-D8	HV1-18*01 F	HJ6*04 F	HD2-15*01 F	QVQLVQSGG.EVKKPGASVKVSCKAS	GDTF..SRYG
CTLA4pmpl-Rd2-E2-D10	HV1-18*01 F	HJ6*04 F	HD2-15*01 F	QVQLVQSGG.EVKKPGASVKVSCKAS	GDTF..SRYG
CTLA4pmpl-Rd2-E2-H6	HV1-18*01 F	HJ6*04 F	HD2-15*01 F	QVQLVQSGG.EVKKPGASVKVSCKAS	GDTF..SRYG
CTLA4pmpl-Rd2-E2-F12	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-H2	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-E1	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-F10	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-E9	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-G2	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-H11	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-E7	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-D5	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-G3	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-A8	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-D6	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF..TSYG

FIG. 10 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	FR4-IMGT
ITWVRQAPGQGLEWMGW	MSTV..TGNT	NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC	ARGLCRDSSCLTPYYYYGMDV	WGKGTLVTVSS
ITWVRQAPGQGLEWMGW	MSTV..TGNT	NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC	ARGLCRDSSCLTPYYYYGMDV	WGKGTLVTVSS
ITWVRQAPGQGLEWMGW	MSTV..TGNT	NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC	ARGLCRDSSCLTPYYYYGMDV	WGKGTLVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS

FIG. 10 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

Sequence ID	V-GENE and allele	J-GENE and allele	D-GENE and allele	FR1-IMGT	CDR1-IMGT
CTLA4pmpl-Rd2-E2-G10	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLVQSGA.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-F1	HV1-18*01 F	HJ6*02 F	HD1-14*01 ORF	QVQLVQSGA.EVKKPGASVKVSCKAS	GYIF..TSYG
CTLA4pmpl-Rd2-E2-C10	HV3-53*01	HJ1*01 F	HD5-24*01 ORF	EVQLVQSGG.GLIQPGGSLRLSCAAS	GFTV..SSEY
CTLA4pmpl-Rd2-E2-F2	HV3-53*02	HJ1*01 F	HD5-24*01 ORF	EVQLVQSGG.GLIQPGGSLRLSCAAS	GFTV..SSEY
CTLA4pmpl-Rd2-E2-E2	HV3-53*03	HJ1*01 F	HD5-24*01 ORF	EVQLVQSGG.GLIQPGGSLRLSCAAS	GFTV..SSEY
CTLA4pmpl-Rd2-E2-G6	HV3-53*04	HJ1*01 F	HD5-24*01 ORF	EVQLVQSGG.GLIQPGGSLRLSCAAS	GFTV..SSEY
CTLA4pmpl-Rd2-E2-D3	HV3-53*05	HJ1*01 F	HD5-24*01 ORF	EVQLVQSGG.GLIQPGGSLRLSCAAS	GFTV..SSEY
CTLA4pmpl-Rd2-E2-H3	HV3-53*06	HJ1*01 F	HD5-24*01 ORF	EVQLVQSGG.GLIQPGGSLRLSCAAS	GFTV..SSEY
CTLA4pmpl-Rd2-E2-H12	HV3-53*07	HJ1*01 F	HD5-24*01 ORF	EVQLVQSGG.GLIQPGGSLRLSCAAS	GFTV..SSEY
CTLA4pmpl-Rd2-E2-H8	HV3-53*08	HJ1*01 F	HD5-24*01 ORF	EVQLVQSGG.GLIQPGGSLRLSCAAS	GFTV..SSEY
CTLA4pmpl-Rd2-E2-G5	HV1-18*01 F	HJ6*02 F	HD2-15*01 F	EVQLVESGA.EVRKPGESLTISCKAS	GYTF..TSYG
CTLA4pmpl-Rd2-E2-H9	HV3-23*04 F	HJ1*01 F	HD4-23*01 ORF	EVQLVESGG.GLVQPGGSLRLPCAAS	GFTF..SSYA

FIG. 10 CON'T

Alignment of CTLA4 PMP1 Rd 2 plate E2 phage sequencing

FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	FR4-IMGT
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTAYMELRGLKSDDTAMYYC	ARGPQMDV	WGQGTTVTVSS
MTWVRQAPGKGLEWVSN	IYTS..GPT	YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC	ARVGNGGGYNL	WGQGTLVTVSS
MTWVRQAPGKGLEWVSN	IYTS..GPT	YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC	ARVGNGGGYNL	WGQGTLVTVSS
MTWVRQAPGKGLEWVSN	IYTS..GPT	YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC	ARVGNGGGYNL	WGQGTLVTVSS
MTWVRQAPGKGLEWVSN	IYTS..GPT	YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC	ARVGNGGGYNL	WGQGTLVTVSS
MTWVRQAPGKGLEWVSN	IYTS..GPT	YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC	ARVGNGGGYNL	WGQGTLVTVSS
MTWVRQAPGKGLEWVSN	IYTS..GPT	YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC	ARVGNGGGYNL	WGQGTLVTVSS
MTWVRQAPGKGLEWVSN	IYTS..GPT	YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC	ARVGNGGGYNL	WGQGTLVTVSS
MTWVRQAPGKGLEWVSN	IYTS..GPT	YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC	ARVGNGGGYNL	WGQGTLVTVSS
ISWVRQAPGQGLEWMGW	ISAY..NGNT	NYAQKLQ.GRVTMTTDTSTSTAYMELRSLRSDDTAVYYC	ATDLWPIYCSGGSCYETSYYGMDV	WGQGTLVTVSS
MSWVRQAPGKGLEWVSV	ISGS..GTNT	HYADSVK.GRFTISRDNFKNTVYLQVNSPRAEDTAVYYC	VREFGGPSNY	WGQGTLVTVSS

FIG. 10 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

Sequence ID	V-GENE and allele	J-GENE and allele		FR1-IMGT	CDR1-IMGT
CTLA4pmpl-Rd2-E2-A7	LV2-11*01 F	LJ1*01 F		QSALTQPRS.VSGSPGQSVTISCTGT	SSDVG...GYKY
CTLA4pmpl-Rd2-E2-D4	LV2-11*01 F	LJ2*01 F		QPVLTQPRS.VSGSPGQSVTISCTGT	SSDVG...GYNY
CTLA4pmpl-Rd2-E2-G9	LV2-11*01 F	LJ2*01 F		QPVLTQPRS.VSGSPGQSVTISCTGT	SSDVG...GYNY
CTLA4pmpl-Rd2-E2-A10	LV8-61*01 F	LJ2*01 F		QTVVTQEPS.FSVAPGGTVTLTCALS	SGSVS...SNYH
CTLA4pmpl-Rd2-E2-A12	LV8-61*01 F	LJ3*02 F		QTVVTQEPS.FSVSPGGTVTLTCGLS	SGSVS...TSYY
CTLA4pmpl-Rd2-E2-E5	LV8-61*01 F	LJ3*02 F		HTVVTQEPS.FSVTPGGTVTLTCGLS	SGSIS...TSYY
CTLA4pmpl-Rd2-E2-H5	LV6-57*02 F	LJ3*02 F		NFMLTHPHS.VSESPGKTVTISCTGS	SDSL...ASNY
CTLA4pmpl-Rd2-E2-C4	LV6-57*04 (F)	LJ2*01 F		QPVLTQPHS.VSESPGKTVTISCTRS	GGSF...ADNY
CTLA4pmpl-Rd2-E2-D11	LV6-57*04 (F)	LJ2*01 F		QPVLTQPHS.VSESPGKTVTISCTRS	GGSF...ADNY
CTLA4pmpl-Rd2-E2-H1	LV6-57*04 (F)	LJ2*01 F		QPVLTQPHS.VSESPGKTVTISCTRS	GGSF...ADNY
CTLA4pmpl-Rd2-E2-E11	LV6-57*04 (F)	LJ2*01 F		QPVLTQPHS.VSESPGKTVTISCTRS	GGSF...ADNY
CTLA4pmpl-Rd2-E2-A4	KV1D-12*01 F	KJ5*01 F		DIQMTQSPSSVSASIGDRVTITCRAS	QDI...SNS
CTLA4pmpl-Rd2-E2-H10	LV7-46*01 F	LJ3*02 F		QTVVTQEPS.LTVSPGGTVTLTCGSS	TGAVT...TGHY
CTLA4pmpl-Rd2-E2-F3	LV7-46*01 F	LJ2*01 F		QTVVTQEPS.LTVSPGGTVTLTCGSS	TGAVT...SGHY
CTLA4pmpl-Rd2-E2-F6	LV7-46*01 F	LJ2*01 F		QTVVTQEPS.LTVSPGGTVTLTCGSS	TGAVT...SGHY

FIG. 10 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	FR4-IMGT
VSWYQHHPGKAPKLMIY	DV.....S	ERPSGVP.DRFSGSK..SGNTASLTISGLQAEDEADYYC	SSYAGSNSHFV	FGTGTKVTVL
VSWYQQHPGKAPKLIIY	EV.....N	KRPSGVP.DRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSYSSSSTLV	FGGGTKLTVL
VSWYQQHPGKAPKLIIY	EV.....N	KRPSGVP.DRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSYSSSSTLV	FGGGTKLTVL
PSWFQQTPGQAPRTLIY	NT.....D	IRSHGVP.DRFSGSL..LGNKAALTITGAQPNDESEYYC	ALYMGSGISI	FGGGTKVTVL
PSWYQQTPGQAPRTLIY	TT.....N	TRSSGVP.DRFSGSI..LGNKAALTITGAQADDESDYYC	VLYMGSGIWV	FGGGTKLTVL
PIWYQHTPGQAPRTLIY	TT.....N	TPSSGVP.DRFSGSI..LGNKAALTITGAQEDDESDYYC	VLYMGSGIWV	FGGRTKLTVL
VQWYQQRPGSAPTTVIY	EN.....N	QRPSGVP.DRFSGSIDGSSNSASLTISALETEDEADYYC	QSYDGTPV	FGTGTKLTVL
VQWYQQRPGSAPTLMIY	EH.....H	QRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYDSSTPVV	FGGGTKLTVL
VQWYQQRPGSAPTLMIY	EH.....H	QRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYDSSTPVV	FGGGTKLTVL
VQWYQQRPGSAPTLMIY	EH.....H	QRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYDSSTPVV	FGGGTKLTVL
VQWYQQRPGSAPTLMIY	EH.....H	QRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYDSSTPVV	FGGGTKLTVL
LAWYQQKPGKAPKLLIY	GA.....S	NLRSGVP.SRFSGGG..SGTYFTLTISSLQPEDFATYYC	QQGNSFPIT	FGQGTRLEIK
PYWFQQKPGQAPTTLIY	DA.....T	HKHSWTP.ARFSGSV..LGGKAALTLSGAQPEDEADYYC	LLSYSGARV	FGGGTKLTVL
PYWFQQKPGQAPRTLIY	DT.....T	NRHSWTP.ARFSGSL..LGAKAALTLSGVQPEDEADYYC	LLSYSGDRV	FGGGTKLTVL
PYWFQQKPGQAPRTLIY	DT.....T	NRHSWTP.ARFSGSL..LGAKAALTLSGVQPEDEADYYC	LLSYSGDRV	FGGGTKLTVL

FIG. 10 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

Sequence ID	V-GENE and allele	J-GENE and allele		FR1-IMGT	CDR1-IMGT
CTLA4pmpl-Rd2-E2-D8	LV7-46*01 F	LJ2*01 F		QTVVTQEPS.LTVSPGGTVTLTCGSS	TGAVT...SGHY
CTLA4pmpl-Rd2-E2-D10	LV7-46*01 F	LJ2*01 F		QTVVTQEPS.LTVSPGGTVTLTCGSS	TGAVT...SGHY
CTLA4pmpl-Rd2-E2-H6	LV7-46*01 F	LJ2*01 F		QTVVTQEPS.LTVSPGGTVTLTCGSS	TGAVT...SGHY
CTLA4pmpl-Rd2-E2-F12	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-H2	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-E1	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-F10	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-E9	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-G2	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-H11	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-E7	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-D5	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-G3	LV1-40*01 F	LJ1*01 F		QSVLTHPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-A8	LV1-40*01 F	LJ1*01 F		QSVLTHPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-D6	LV1-40*01 F	LJ1*01 F		QSVLTQPPS.VSGAPGQRVTISCTGS	SSNIG...AGYD

FIG. 10 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	FR4-IMGT
PYWFQQKPGQAPRTLIY	DT.....T	NRHSWTP.ARFSGSL..LGAKAALTLSGVQPEDEADYYC	LLSYSGDRV	FGGGTKLTVL
PYWFQQKPGQAPRTLIY	DT.....T	NRHSWTP.ARFSGSL..LGAKAALTLSGVQPEDEADYYC	LLSYSGDRV	FGGETKLTVL
PYWFQQKPGQAPRTLIY	DT.....T	NRHSWTP.ARFSGSL..LGAKAALTLSGVQPEDEADYYC	LLSYSGDRV	FGGGTKLTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL

FIG. 10 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

Sequence ID	V-GENE and allele	J-GENE and allele		FR1-IMGT	CDR1-IMGT
CTLA4pmpl-Rd2-E2-G10	LV1-40*01 F	LJ1*01 F		QSVLTHPPSVSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-F1	LV1-40*01 F	LJ1*01 F		QSVLTQPPSVSGAPGQRVTISCTGS	SSNIG...AGYD
CTLA4pmpl-Rd2-E2-C10	LV2-14*01 F	LJ1*01 F		QSALTQPASVSGSPGQSITISCTGT	SGDVG...AHDY
CTLA4pmpl-Rd2-E2-F2	LV2-14*01 F	LJ1*01 F		QSALTQPASVSGSPGQSITISCTGT	SGDVG...AHDY
CTLA4pmpl-Rd2-E2-E2	LV2-14*01 F	LJ1*01 F		QSALTQPASVSGSPGQSITISCTGT	SGDVG...AHDY
CTLA4pmpl-Rd2-E2-G6	LV2-14*01 F	LJ1*01 F		QSALTQPASVSGSPGQSITISCTGT	SGDVG...AHDY
CTLA4pmpl-Rd2-E2-D3	LV2-14*01 F	LJ1*01 F		QSALTQPASVSGSPGQSITISCTGT	SGDVG...AHDY
CTLA4pmpl-Rd2-E2-H3	LV2-14*01 F	LJ1*01 F		QSALTQPASVSGSPGQSITISCTGT	SGDVG...AHDY
CTLA4pmpl-Rd2-E2-H12	LV2-14*01 F	LJ1*01 F		QSALTQPASVSGSPGQSITISCTGT	SGDVG...AHDY
CTLA4pmpl-Rd2-E2-H8	LV2-14*01 F	LJ1*01 F		QSALTQPASVSGSPGQSITISCTGT	SGDVG...AHDY
CTLA4pmpl-Rd2-E2-G5	LV1-47*02 F	LJ3*02 F		QPGLTQPPSASGTPGQRVTLSCSGS	SSNI....GSNY
CTLA4pmpl-Rd2-E2-H9	LV1-40*01 F	LJ1*01 F		QSVLTHPPSVSGAPGQRVTISCTGN	SSNIG...APYD

FIG. 10 CON'T

Alignment of CTLA4 PMPL Rd 2 plate E2 phage sequencing

FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	FR4-IMGT
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC	LSWDESLNAYV	FGSGTKVTVL
VSWYQQHPGKAPKLMIY	EG.....S	KRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSFAGTNNYV	FGTGTKVAVL
VSWYQQHPGKAPKLMIY	EG.....S	KRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSFAGTNNYV	FGTGTKVAVL
VSWYQQHPGKAPKLMIY	EG.....S	KRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSFAGTNNYV	FGTGTKVAVL
VSWYQQHPGKAPKLMIY	EG.....S	KRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSFAGTNNYV	FGTGTKVAVL
VSWYQQHPGKAPKLMIY	EG.....S	KRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSFAGTNNYV	FGTGTKVAVL
VSWYQQHPGKAPKLMIY	EG.....S	KRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSFAGTNNYV	FGTGTKVAVL
VSWYQQHPGKAPKLMIY	EG.....S	KRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSFAGTNNYV	FGTGTKVAVL
VFWYQQLPGTAPKLLIY	SN.....N	QRPSGVP.DRFSASK..SGTSASLAISGLRSEDEADYYC	AAWDDSLSGWV	FGGGTKLTVL
VHWYQQLPGTAPKLLIY	AN.....K	YRPSGVP.DRFSGSK..SGTSASLAISGLRSKDEADYYC	AAWDDSLGGLYV	FGTGTKVTVL

FIG. 10 CON'T

Sequence number		V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION
CTLA4pmpl-Rd2-E2-A7		Homsap IGHV3-30-3*01 F	Homsap IGHJ3*02 F	Homsap IGHD4-17*01 F	caggtgcagctggtgcagtctggggga...agtgtggt ccggcctgggaggtccctgcgactcgcctgtgcagcc tctggattcacttic.....aggagttacgctatgca ctgggtccgccagactccaggcaaggggctggagtg ggtggcagttatatcatatgat.....ggagacaacactt ttatgcagacgccgtgaag...ggccggttcaccatct ccagagacaattccaagaacacgctgtatctgcaaat gaacagcctgagagctgaggacacggctgtgtatta ctgtgcgaaactcgggatgactacgtatgctttgatat ctggggccaagggaaccctggtcaccgtctcctcag
CTLA4pmpl-Rd2-E2-D4		Homsap IGHV1-46*01 F, or Homsap IGHV1-46*02 F or Homsap IGHV1-46*03 F	Homsap IGHJ4*02 F	Homsap IGHD2-21*01 F	caggtgcagctggtgcagtctggagct...gaggtgaa gaagcctgggcctcagtgaagcttcctgcaaggga tctggatacaccttc.....atcaccgactatataca ctgggtgcggcaggcccctggacaagggcttgagtg gatgggaagactcatccccagt.....gatggaagtac aatttacgcacagaagttccgg...ggcagagtcacca tgaccagggacacgtccacgagaacggtctacatgg agctgagcagcctgcgatcagaggacacggccctat attattgtgcgagagatggtagtcattacgacttttgaca actggggccagggcaccctggtcaccgtctcctcag
CTLA4pmpl-Rd2-E2-G9		Homsap IGHV1-46*01 F, or Homsap IGHV1-46*02 F or Homsap IGHV1-46*03 F	Homsap IGHJ4*02 F	Homsap IGHD2-21*01 F	caggtgcagctggtgcagtctggagct...gaggtgaa gaagcctgggcctcagtgaagcttcctgcaaggga tctggatacaccttc.....atcaccgactatataca ctgggtgcggcaggcccctggacaagggcttgagtg gatgggaagactcatccccagt.....gatggaagtac aatttacgcacagaagttccgg...ggcagagtcacca tgaccagggacacgtccacgagaacggtctacatgg agctgagcagcctgcgatcagaggacacggccctat attattgtgcgagagatggtagtcattacgacttttgaca actggggccagggcaccctggtcaccgtctcctcag
CTLA4pmpl-Rd2-E2-A10		Homsap IGHV1-69*04 F, or Homsap IGHV1-69*09 F or Homsap IGHV1-69*11 F	Homsap IGHJ4*02 F		caggtacagctgcagcagtcaggggct...gaggtga agaagcctgggtcctcggtgaaggtctcctgcaaggc ttctggaggcaccttc.....agcagctatgctatca gctgggtgcgacaggcccctggacaagggcttgagt ggatgggaaggatcatccctatc.....ctttggtatagc aaactacgcacagaagttccag...ggcagagtcacg attaccgcggacgaatccacgagcacagcctacatg gagctgagcagcctgagatctgaggacacggccgtg tattactgtgcgagagattgggactactggggccagg gcaccctggtcaccgtctcctcag

FIG. 11

V-J-REGION	V-REGION	FR1-IMGT	CDR1-IMGT	FR2-IMGT
	caggtgcagctggtgcagtctggggga...agtgtgg tccggcctgggaggtcccttgcgactctgcctgtgcag cctctggattcactttc.....aggagttacgctatg cactgggtccgccaggctccaggcaaggggctgga gtgggtggcagttatatcatatgat.....ggagacaa cacttttatgcagaacgccgtgaag...ggcccgttca ccatctccagagacaattccaagaacacgctgtatct gcaaatgaacagcctgagagctgaggacacggct gtgtattactgtgcga	caggtgcagctggtgc agtctgggga...agtg tggtccggcctgggag gtccctgcgactctgcct gtgcagccttct	ggattcactttc... .....aggagtt acgct	atgcactgggtc cgccaggctcc aggcaagggg ctggagtgggtg gcagtt
	caggtgcagctggtgcagtctggagct...gaggtga agaagcctggggcctcagtgaagcttttcctgcaagg gatctggatacaccttc.....atcaccgactatat acactgggtgcggcaggcccctggacaagggcttg agtggatgggaagactcatccccagt.....gatgga agtacaatttacgcacagaagttccgg...ggcagag tcaccatgaccagggacacgtccacgagaacggtc tacatggagctgagcagcctgcgatcagaggacac ggccctatattattgtgcgagaga	caggtgcagctggtgc agtctggagct...gagg tgaagaagcctggggc ctcagtgaagcttttcctg caagggatct	ggatacaccttc. .....atcacc gactat	atacactgggtg cggcaggcccc tggacaagggc ttgagtggatgg gaaga
	caggtgcagctggtgcagtctggagct...gaggtga agaagcctggggcctcagtgaagcttttcctgcaagg gatctggatacaccttc.....atcaccgactatat acactgggtgcggcaggcccctggacaagggcttg agtggatgggaagactcatccccagt.....gatgga agtacaatttacgcacagaagttccgg...ggcagag tcaccatgaccagggacacgtccacgagaacggtc tacatggagctgagcagcctgcgatcagaggacac ggccctatattattgtgcgagaga	caggtgcagctggtgc agtctggagct...gagg tgaagaagcctggggc ctcagtgaagcttttcctg caagggatct	ggatacaccttc. .....atcacc gactat	atacactgggtg cggcaggcccc tggacaagggc ttgagtggatgg gaaga
	caggtacagctgcagcagtcaggggct...gaggtg aagaagcctgggtcctcggtgaaggctcctgcaag gcttctggaggcaccttc.....agcagctatgct atcagctgggtgcgacaggccccttggacaagggct tgagtggatgggaaggatcatccctatc.....ctttggt atagcaaactacgcacagaagttccag...ggcaga gtcacgattaccgcggacgaatccacgagcacagc ctacatggagctgagcagcctgagatctgaggaca cggccgtgtattactgtgcgagaga	caggtacagctgcagc agtcaggggct...gag gtgaagaagcctgggt cctcggtgaaggtctcct gcaaggcttct	ggaggcaccttc .....agcag ctatgct	atcagctgggtg cgacaggcccc tggacaagggc ttgagtggatgg gaagg

FIG. 11
CON'T

CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
atatcatatgat... ...ggagacaac act	ttttatgcagacg ccgtgaag...g gccggttcacca tctccagagaca attccaagaac acgctgtatctgc aaatgaacagc ctgagagctga ggacacggctg tgtattactgt	gcgaaactcgggg tgactacgtatgctt tgatatc	tgtgcgaaactcg gggtgactacgta tgctttgatatctg g	atgcttttgatat ctggggccaa ggaaccctggt cacgtctcctc ag	tggggccaagg aaccctggtcac cgtctcctcag
ctcatcccagt.. ....gatggaagta ca	atttacgcacag aagttccgg...g gcagagtcacc atgaccagggа cacgtccacga gaacggtctac atggagctgag cagcctgcgatc agaggacacg gccctatattatt gt	gcgagagatggta gtcattacgacttg acaac	tgtgcgagagat ggtagtcattacg acttgacaactg g	acgactttgac aactggggcc agggcaccctg gtcaccgtctcc tcag	tggggccaggg caccctggtcac cgtctcctcag
ctcatcccagt.. ....gatggaagta ca	atttacgcacag aagttccgg...g gcagagtcacc atgaccagggа cacgtccacga gaacggtctac atggagctgag cagcctgcgatc agaggacacg gccctatattatt gt	gcgagagatggta gtcattacgacttg acaac	tgtgcgagagat ggtagtcattacg acttgacaactg g	acgactttgac aactggggcc agggcaccctg gtcaccgtctcc tcag	tggggccaggg caccctggtcac cgtctcctcag
atcatccctatc... ...cttggtatagc a	aactacgcaca gaagttccag... ggcagagtcac gattaccgcgg acgaatccacg agcacagccta catggagctga gcagcctgaga tctgaggacac ggccgtgtatta ctgt	gcgagagattggg actac	tgtgcgagagatt gggactactgg	gactactgggg ccagggcacc ctggtcaccgtc tcctcag	tggggccaggg caccctggtcac cgtctcctcag

FIG. 11
CON'T

Sequence number		V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION
CTLA4pmpl-Rd2-E2-A12		Homsap IGHV3-23*04 F	Homsap IGHJ4*02 F	Homsap IGHD1-7*01 F	caggtgcagctggtgcagtctgggga...ggcttggt acagcctgggggtccctgagactctcctgtgcagcct ctggattcaccttt.....agcagctatgccatgagc tgggtccgccaggctccagggaagggctggagtg ggtctcagctattagtggtagt.....ggtggtagcacat actacgcagactccgtgaag...ggccggttcaccatc tccagagacaattccaagaacacgctgtatctgcaaa tgaacagcctgagagctgaggacacggctgtgtatta ctgtgcgagagaagagggtataactggaactggctt gactactggggccagggcaccctggtcaccgtctcct cag
CTLA4pmpl-Rd2-E2-E5		Homsap IGHV3-23*04 F	Homsap IGHJ4*02 F	Homsap IGHD1-7*01 F	caggtgcagctggtgcagtctgggga...ggcttggt acagcctgggggtccctgagactctcctgtgcagcct ctggattcaccttt.....agcagctatgccatgagc tgggtccgccaggctccagggaagggctggagtg ggtctcaictattactggtaat.....ggtggtagcacata ctacgcagactccgtgaag...ggccggttcaccatctc cagagacaattccaagaacacgctgtatctgcaaatg aacagcctgagagctgaggacacggctgtgtattact gtgcgagagaagagggtataactggaactggctttga ctactggggccagggcaccctggtcaccgtctcctca g
CTLA4pmpl-Rd2-E2-H5		Homsap IGHV1-46*01 F, or Homsap IGHV1-46*03 F	Homsap IGHJ6*02 F	Homsap IGHD5-24*01 ORF	gaggtgcagctggtggagtctggggct...gaggtgaa gaagcctgggggcctcagtgaaggtttcctgcaaggca tctggatacacctic.....accagctactatatgca ctgggtgcgacaggccctggacaagggcttgagtg gatgggaataatcaaccctagt.....ggtggtagcac aagctacgcacagaagttccag...ggcagagtcacc atgaccagggacatgtccacgagcacagtctacatg gagctgagcagcctgagatctgaggacacggctgtg tattactgtgcgagagaggagatggccccgttcctttcg aactacggtatggacgtctgggggccaagggacaatg gtcaccgtctcttca
CTLA4pmpl-Rd2-E2-C4		Homsap IGHV1-46*01 F, or Homsap IGHV1-46*03 F	Homsap IGHJ6*02 F	Homsap IGHD1-1*01 F	gaggtgcagctggtgcagtctgggggct...gaggtgaa gaagcctgggggcctcagtgaaggtttcctgcaaggca tctggatacacctic.....accagctactatatgca ctgggtgcgacaggccctggacaagggcttgagtg gatgggaataatcaaccctagt.....ggtggtagcac aagctacgcacagaagttccag...ggcagagtcacc atgaccagggacacgtccacgagcacagtctacatg gagctgagcagcctgagatctgaggacacggccgtg tattactgtgcgagagaactaaaacgcggggattact actactactacggtatggacgtctggggccaagggac cacggtcaccgtctcctca

FIG. 11 CON'T

V-J-REGION	V-REGION	FR1-IMGT	CDR1-IMGT	FR2-IMGT
	caggtgcagctggtgcagtctggggga...ggcttgg tacagcctgggggtccctgagactctcctgtgcagc ctctggattcaccttt.....agcagctatgccatg agctgggtccgccaggctccagggaagggctgg agtgggtctcagctattagtggtagt.....ggtggtag cacatactacgcagactccgtgaag...ggccggttc accatctccagagacaattccaagaacacgctgtat ctgcaaatgaacagcctgagagctgaggacacgg ctgtgtattactgtgcgagaga	caggtgcagctggtgc agtctgggga...ggct tggtacagcctgggg gtccctgagactctcctg tgcagcctct	ggattcacctttt... .....agcagct atgcc	atgagctgggtc cgccaggctcc agggaagggg ctggagtgggtc tcagct
	caggtgcagctggtgcagtctggggga...ggcttgg tacagcctgggggtccctgagactctcctgtgcagc ctctggattcaccttt.....agcagctatgccatg agctgggtccgccaggctccagggaagggctgg agtgggtctcatctattactggtaat.....ggtggtagc acatactacgcagactccgtgaag...ggccggttca ccatctccagagacaattccaagaacacgctgtatct gcaaatgaacagcctgagagctgaggacacggct gtgtattactgtgcgagaga	caggtgcagctggtgc agtctgggga...ggct tggtacagcctgggg gtccctgagactctcctg tgcagcctct	ggattcacctttt... .....agcagct atgcc	atgagctgggtc cgccaggctcc agggaagggg ctggagtgggtc tcatct
	gaggtgcagctggtggagtctgggggct...gaggtga agaagcctgggggcctcagtgaaggtttcctgcaagg catctggatacaccttc.....accagctactatat gcactgggtgcgacaggccccctggacaagggcttg agtggatgggaataatcaaccctagt.....ggtggta gcacaagctacgcacagaagttccag...ggcaga gtcaccatgaccagggacatgtccacgagcacagt ctacatggagctgagcagcctgagatctgaggaca cggctgtgtattactgtgcgagaga	gaggtgcagctggtgg agtctgggggct...gagg tgaagaagcctgggggc ctcagtgaaggtttcctg caaggcatct	ggatacaccttc. .....accag ctactat	atgcactgggtg cgacaggcccc tggacaagggc ttgagtggatgg gaata
	gaggtgcagctggtgcagtctgggggct...gaggtga agaagcctgggggcctcagtgaaggtttcctgcaagg catctggatacaccttc.....accagctactatat gcactgggtgcgacaggccccctggacaagggcttg agtggatgggaataatcaaccctagt.....ggtggta gcacaagctacgcacagaagttccag...ggcaga gtcaccatgaccagggacacgtccacgagcacagt ctacatggagctgagcagcctgagatctgaggaca cggccgtgtattactgtgcgagaga	gaggtgcagctggtgc agtctgggggct...gagg tgaagaagcctgggggc ctcagtgaaggtttcctg caaggcatct	ggatacaccttc. .....accag ctactat	atgcactgggtg cgacaggcccc tggacaagggc ttgagtggatgg gaata

FIG. 11
CON'T

CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
attagtggtagt... ...ggtggtagca ca	tactacgcagac tccgtgaag...g gccggttcacca tctccagagaca attccaagaac acgctgtatctgc aaatgaacagc ctgagagctga ggacacggctg tgtattactgt	gcgagagaagag ggtataactggaac tggctttgactac	tgtgcgagagaa gagggtataact ggaactggctttg actactgg	ctttgactactg gggccagggc accctggtcac cgtctcctcag	tggggccaggg caccctggtcac cgtctcctcag
attactggtaat... ...ggtggtagca ca	tactacgcagac tccgtgaag...g gccggttcacca tctccagagaca attccaagaac acgctgtatctgc aaatgaacagc ctgagagctga ggacacggctg tgtattactgt	gcgagagaagag ggtataactggaac tggctttgactac	tgtgcgagagaa gagggtataact ggaactggctttg actactgg	ctttgactactg gggccagggc accctggtcac cgtctcctcag	tggggccaggg caccctggtcac cgtctcctcag
atcaaccctagt. .....ggtggtagc aca	agctacgcaca gaagttccag... ggcagagtcac catgaccaggg acatgtccacga gcacagtctaca tggagctgagc agcctgagatct gaggacacgg ctgtgtattactgt	gcgagagaggag atggccccgttcctttt cgaactacggtatg gacgtc	tgtgcgagagag gagatggccccg ttccttttcgaacta cggtatggacgtc tgg	actacggtatg gacgtctgggg ccaagggaca atggtcaccgtc tcttca	tggggccaagg gacaatggtcac cgtctcttca
atcaaccctagt. .....ggtggtagc aca	agctacgcaca gaagttccag... ggcagagtcac catgaccaggg acacgtccacg agcacagtctac atggagctgag cagcctgagatc tgaggacacgg ccgtgtattactg t	gcgagagaactaa aacgcggggatta ctactactactacgg tatggacgtc	tgtgcgagagaa ctaaaacgcgggg gattactactacta ctacggtatggac gtctgg	attactactact actacggtatg gacgtctgggg ccaagggacc acggtcaccgt ctcctca	tggggccaagg gaccacggtcac cgtctcctca

FIG. 11
CON'T

Sequence number		V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION
CTLA4pmpl-Rd2-E2-A4		Homsap IGHV3-23*04 F	Homsap IGHJ3*02 F	Homsap IGHD6-19*01 F	caggtgcagctggtgcagtctgggga...ggcttggt acagcctgggggtccctgagactctcctgtgcagcct ctggattcacgttt.....agcagctatgtcatgagtt gggtccgccaggctccagggaaggggctggagtgg gtctcaagtattagtggtagt.....ggtggtagcacaga ctacgcagactccgtgaag...ggccggttccccatctc cagagacaattccaagaacacattgtatctggaaatg aacagcctgagagctgaggacacggctgtatattact gtgcgagaggaggcagtgcctggtcgcttgatatctg gggccaagggaccacggtcaccgtctcctcag
CTLA4pmpl-Rd2-E2-H10		Homsap IGHV1-18*01 F	Homsap IGHJ6*04 F	Homsap IGHD2-15*01 F	caggtgcagctggtgcagtctggaggt...gaggtgaa gaagcctggggcctcagtgaaggtctcctgcaaggct tctggtgacaccttt.....agcaggtatggatca ccctgggtgcgtcaggccccctggacaagggcttgagtg gatgggatggatgagcaccgtc.....actggaaaca caaactccgcgcagaagttccag...ggcagagtcttc ttgacccgagacacatccacgagcacagcctacttgg agctgaggagcctgagacctgacgacacggccgtct attactgtgcgagaggactatgtcgtgatagcagctgc ctaacccccctactactattacggtatggacgtctgggg caaaggcaccctggtcaccgtctcctcag
CTLA4pmpl-Rd2-E2-F1		Homsap IGHV1-18*01 F	Homsap IGHJ6*02 F, or Homsap IGHJ6*03 F	Homsap IGHD1-14*01 ORF	caggtacagctgcagcagtcaggaact...gaggtga agaagcctgggcctcagtgaaagtctcctgcaagg cttctggttacatcttt.....acgagttatggtttcact tgggtgcggcaggcccccggacaaggccttgagtgg atgggatggatcagtcttac.....aatggtaacacag actatgcacaaaagttcgag...ggcagagtcaccat gaccacagacacatccacgaccacagcctatatgga gttgaggggtctgaaatctgacgacacggccatgtatt attgtgcgagaggtccgcaaatggacgtctggggcc aagggaccacggtcaccgtctcctca
CTLA4pmpl-Rd2-E2-H8		Homsap IGHV3-53*01 F, or Homsap IGHV3-53*03 F	Homsap IGHJ1*01 F	Homsap IGHD5-24*01 ORF	gaggtgcagctggtgcagtctggagga...ggcttgat ccagccgggggggtccctgagactctcctgcgcagc ctctgggttcaccgtc.....agcagcgagtacatg acctgggtccgccaggctccagggaagggggctgga gtgggtctcaaatatttatacaagt.....ggtcccac ctactacgcagactctgtgaag...ggccgattcaccat ctccagggacaacgccaagaactcactgtatctgca aatgaacagcctgagagccgaggacacggccgtgt attactgtgcgagagtagggaatggaggtggctacaa tttgtggggccagggcaccctggtcaccgtctcctcag

FIG. 11 CON'T

V-J-REGION	V-REGION	FR1-IMGT	CDR1-IMGT	FR2-IMGT
	caggtgcagctggtgcagtctggggga...ggcttgg tacagcctgggggtccctgagactctcctgtgcagc ctctggattcacgttt.....agcagctatgtcatga gttgggtccgccaggctccagggaaggggctggag tgggtctcaagtattagtggtagt.....ggtggtagca cagactacgcagactccgtgaag...ggccggttccc catctccagagacaattccaagaacacattgtatctg gaaatgaacagcctgagagctgaggacacggctgt atattactgtgcgagag	caggtgcagctggtgc agtctgggga...ggct tggtacagcctggggg gtcctgagactctcctg tgcagcctct	ggatttcacgttt... .....agcagct atgtc	atgagttgggtc cgccaggctcc agggaagggg ctggagtgggtc tcaagt
	caggtgcagctggtgcagtctggaggt...gaggtga agaagcctggggcctcagtgaaggtctcctgcaag gcttctggtgacaccttt.....agcaggtatggg atcacctgggtgcgtcaggcccctggacaagggctt gagtggatgggatggatgagcaccgtc.....actgg aaacacaaactccgcgcagaagttccag...ggca gagtcttcttgacccgagacacatccacgagcacag cctacttggagctgaggagcctgagacctgacgac acggccgtctattactgtgcgagag	caggtgcagctggtgc agtctggaggt...gagg tgaagaagcctggggc ctcagtgaaggtctcctg caaggcttct	ggtgacaccttt.. .....agcagg tatggg	atcacctgggtg cgtcaggcccct ggacaagggct tgagtggatggg atgg
	caggtacagctgcagcagtcaggaact...gaggtg aagaagcctggggcctcagtgaaagtctcctgcaa ggcttctggttacatctttt.....acgagttatggttt cacttgggtgcggcaggcccccggacaaggccttg agtggatgggatggatcagttcttac.....aatggtaa cacagactatgcacaaaagttcgag...ggcagagt caccatgaccacagacacatccacgaccacagcct atatggagttgaggggtctgaaatctgacgacacgg ccatgtattattgtgcgagag	caggtacagctgcagc agtcaggaact...gag gtgaagaagcctgggg cctcagtgaaagtctcct gcaaggcttct	ggttacatctttt.... .....acgagtta tggt	ttcacttgggtgc ggcaggccccc ggacaagggctt gagtggatggg atgg
	gaggtgcagctggtgcagtctggagga...ggcttga tccagccgggggggtccctgagactctcctgcgcag cctctgggttcaccgtc.....agcagcgagtac atgacctgggtccgccaggctccagggaaggggct ggagtgggtctcaaatatttatacaagt.....ggtc ccacctactacgcagactctgtgaag...ggccgattc accatctccagggacaacgccaagaactcactgtat ctgcaaatgaacagcctgagagccgaggacacgg ccgtgtattactgtgcgagag	gaggtgcagctggtgc agtctggagga...ggct tgatccagccgggggg gtcctgagactctcctg cgcagcctct	gggttcaccgtc. .....agcag cgagtac	atgacctgggtc cgccaggctcc agggaagggg ctggagtgggtc tcaaat

FIG. 11
CON'T

CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
attagtggtagt... ...ggtggtagca ca	gactacgcaga ctccgtgaag... ggccggttcccc atctccagagac aattccaagaa cacattgtatctg gaaatgaacag cctgagagctg aggacacggct gtatattactgt	gcgagaggaggc agtgcctggtcgctt gatatc	tgtgcgagagga ggcagtgcctggt cgcttgatatctgg	ttgatatctggg gccaagggac cacggtcaccg tctcctcag	tggggccaagg gaccacggtcac cgtctcctcag
atgagcaccgtc .....actggaaa caca	aactccgcgca gaagttccag... ggcagagtcttc ttgacccgagac acatccacgag cacagcctactt ggagctgagga gcctgagacctg acgacacggcc gtctattactgt	gcgagaggactat gtcgtgatagcagc tgcctaacccccctac tactattacggtatg gacgtc	tgtgcgagagga ctatgtcgtgatag cagctgcctaacc ccctactactatta cggtatggacgtc tgg	ctactactattac ggtatggacgt ctggggcaaa ggcaccctggt caccgtctcctc ag	tggggcaaagg caccctggtcac cgtctcctcag
atcagttcttac... ...aatggtaaca ca	gactatgcaca aaagttcgag... ggcagagtcac catgaccacag acacatccacg accacagcctat atggagttgagg ggtctgaaatct gacgacacggc catgtattattgt	gcgagaggtccgc aaatggacgtc	tgtgcgagaggtc cgcaaatggacg tctgg	atggacgtctg gggccaaggg accacggtcac cgtctcctca	tggggccaagg gaccacggtcac cgtctcctca
atttatacaagt... .....ggtcccacc	tactacgcagac tctgtgaag...g gccgattcacca tctccagggaca acgccaagaac tcactgtatctgc aaatgaacagc ctgagagccga ggacacggccg tgtattactgt	gcgagagtagggа atggaggtggctac aattttg	tgtgcgagagta gggaatggaggt ggctacaatttgtg g	tggggccagg gcaccctggtc accgtctcctca g	tggggccaggg caccctggtcac cgtctcctcag

FIG. 11
CON'T

Sequence number		V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION
CTLA4pmpl-Rd2-E2-G5		Homsap IGHV1-18*01 F	Homsap IGHJ6*02 F	Homsap IGHD2-15*01 F	gaggtgcagctggtggagtctggagcc...gaggtga gaaagcccggagagtctctgacgatctcctgcaagg cttctggttacacctt.....accagctatggtatca gctgggtgcgacaggcccctggacaagggcttgagt ggatgggatggatcagcgcttac.....aatggtaaca caaactatgcacagaagctccag...ggcagagtcac catgaccacagacacatccacgagcacagcctacat ggagctgaggagcctgagatctgacgacacggccgt gtattactgtgcaacagatctatggcccatatattgtagt ggtggtagctgctacgaaacgagctactacggtatgg acgtctggggccaaggcaccctggtcaccgtctcttca
CTLA4pmpl-Rd2-E2-H9		Homsap IGHV3-23*04 F	Homsap IGHJ1*01 F	Homsap IGHD4-23*01 ORF	gaggtgcagctggtggagtctgggggа...ggcttggtt cagccgggggggtccctaagactgccctgtgcagcct ctggattcacgttt.....agcagctatgccatgag ctgggtccgccaggctccagggaaggggctggagtg ggtctctgttataagtggtagt.....ggcactaatacac actacgcagactccgtgaag...ggccggttcaccatc tccagagacaatttcaagaacacggtatatctgcaag tgaacagcccgagagccgaggacacggccgtctatt attgtgttagagagttcggtggtccctcaaactactggg gccagggcaccctggtcaccgtctcctcag

FIG. 11
CON'T

V-J-REGION	V-REGION	FR1-IMGT	CDR1-IMGT	FR2-IMGT
	gaggtgcagctggtggagtctggagcc...gaggtg agaaagcccggagagtctctgacgatctcctgcaa ggcttctggttacacctttaccagctatggta tcagctgggtgcgacaggcccctggacaagggctt gagtggatgggatggatcagcgcttac.....aatggt aacacaaactatgcacagaagctccag...ggcag agtcaccatgaccacagacacatccacgagcaca gcctacatggagctgaggagcctgagatctgacga cacggccgtgtattactgtgcaacaga	gaggtgcagctggtgg agtctggagcc...gag gtgagaaagcccgga gagtctctgacgatctcc tgcaaggcttct	ggttacacctttaccagct atggt	atcagctgggtg cgacaggcccc tggacaagggc ttgagtggatgg gatgg
	gaggtgcagctggtggagtctgggggga...ggcttgg ttcagccgggggggtccctaagactgccctgtgcag cctctggattcacgtttagcagctatgccat gagctgggtccgccaggctccagggaaggggctg gagtgggtctctgttataagtggtagt.....ggcacta atacacactacgcagactccgtgaag...ggccggtt caccatctccagagacaatttcaagaacacggtata tctgcaagtgaacagcccgagagccgaggacacg gccgtctattattgtg	gaggtgcagctggtgg agtctgggggga...ggct tggttcagccgggggg gtccctaagactgccct gtgcagcctct	ggattcacgtttagcagct atgcc	atgagctgggtc cgccaggctcc agggaagggg ctggagtgggtc tctgtt

FIG. 11
CON'T

CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
atcagcgcttac.....aatggtaacaca	aactatgcacagaagctccag...ggcagagtcaccatgaccacagacacatccacgagcacagcctacatggagctgaggagcctgagatctgacgacacggccgtgtattactgt	gcaacagatctatggcccatatattgtagtggtagctgctacgaaacgaaacgagctacttacggtatggacgtc	tgtgcaacagatctatggcccatatattgtagtggtagctgctacgaaacgagctactacggtatggacgtctgg	ctactacggtatggacgtctgggccaaggcaccctggtcaccgtctcttca	tggggccaagggcaccctggtcaccgtctcttca
ataagtggtagt.....ggcactaataca	cactacgcagactccgtgaag...ggccggttcaccatctccagagacaattttcaagaacacggtatatctgcaagtgaacagcccgagagccgaggacacggccgtctattattgt	gttagagagttcggtggtccctcaaactac	tgtgttagagagttcggtggtccctcaaactactgg	actggggccagggcaccctggtcaccgtctcctcag	tggggccagggcaccctggtcaccgtctcctcag

FIG. 11
CON'T

Sequence number	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION
CTLA4pmpl-Rd2-E2-A7	productive	Homsap IGLV2-11*01 F	Homsap IGLJ1*01 F			caytctgccctgactcagccctcgctca...gtgtccgg gtctcctggacagtcagtcaccatctcctgcactgga accagcagtgatgttggt.....ggttataagtatgtctc tcctggtaccaacaccaccaggcaaagcccccca aactcatgattatgatgtc.....agtga ggggcctcagcggtctcct...gatcgctctctggctc caag.....tctggcaacacggccctccctgaccatctc tgggctccaggctgaggatgaggctgattattactgc agctcatatgcaggcagcaaca	caytctgccctgactcagccctcgctca...gtgtccgg gtctcctggacagtcagtcaccatctcctgcactgga accagcagtgatgttggt.....ggttataagtatgtctc tcctggtaccaacaccaccaggcaaagcccccca aactcatgattatgatgtc.....agtga ggggcctcagcggtctcct...gatcgctctctggctc caag.....tctggcaacacggccctccctgaccatctc tgggctccaggctgaggatgaggctgattattactgc agctcatatgcaggcagcaaca
CTLA4pmpl-Rd2-E2-D4	productive	Homsap IGLV2-11*01 F, or Homsap IGLV3*01 F or Homsap IGLV3*02 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F or Homsap IGLJ3*02 F			caycctgtgctgactcagccctcgctca...gtgtccgg gtctcctggacagtcagtcaccatctcctgcactggacc agcagtgatgttggt.....ggttatgactatgtctcctg gtaccaacaccaccaggcaaagcccccaaactcat cattatgaggtc.....aataagcggccct cagcgtctcct...gatcgctctctggctccaag.....tc tggcaacacgcctcctgaccgtctctgggtccaag gctgaggatgaggctgattattactgcagctcatattgg agcagcgacttggttcttcggcggaggaccaagt tgaccgtcctag	caycctgtgctgactcagccctcgctca...gtgtccgg gtctcctggacagtcagtcaccatctcctgcactgga accagcagtgatgttggt.....ggttataactatgtctc tcctggtaccaacaccaccaggcaaagcccccca aactcatgattatgaggtc.....aataa gcggccctcagcggtctcct...gatcgctctctggctc caag.....tctggcaacacggccctccctgaccgtctc tggcctccaggctgaggatgaggctgattattactgc agctcatattcgagcagcaagcagtt

FIG. 11 CONT

FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
cagtctgcctgactca gcctgcctca...gtgtcc gggtcctctgacagtc agtcaccatctcctgca ctggaacc	agcagtgaatgttg gt.....ggttat aagtat	gtctcctggtacc aacaccaccca ggcaaagcccc caaactcatgatt tat	gatgtc..... .....agt	gagcggcctcagggtcct...gatc gcttctctggctccaag.....tctggcaa caggcgctcctgaccatctctgggctc caggcggaggatgaggctgattattact gc	agctcatatgcagg cagcaacagtcatttt tgttc	tgcagctcatatg cagcagcaac agtcatttgttctttc	ttttgtctttggc actggacca aagtcaccgtc ctag	ttcggccatggg accaagtcacc gtcctag
cagcctgtctgactca gcctgcctca...gtgtcc gggtcctctgacagtc agtcaccatctcctgca ctggaacc	agcagtgaatgttg gt.....ggttat aactat	gtctcctggtacc aacaacaccca ggcaaggcccc caaactcatcatt tat	gaggtc..... .....aat	aagcggcctcagggtcct...gatc gcttctctggctccaag.....tctggcaa cacggctcctgaccgtctctgggctc caggctgaggatgaggctgattattact gc	agctcatattgagc agcagcacttggtc	tgcagctcatattc gagcagcagca cttggtcttc	ggtcttcggcg gggggaccaa gttgacgtcct ag	ttcggcgggggg accaagttgacc gtcctag

FIG. 11 CONT

Sequence number	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION
CTLA4pmpl-Rd2-E2-G9	productive	Homsap IGLV2-11*01 F, or Homsap IGLV3-1*01 F or Homsap IGLV3*02 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F			cagcctgtgctgactcagccctcgcttca...gtgtccggt ctcctggacagtcagtcaccatctcctgcactggaacc agcagtgatgttggt.....ggttatgactatgtctcctg gtaccaacaacaccaggcaaagcccccaaactcat catttatgaggtc.....aatcggcggccct caggggtccct...gatcgcttctctggctccaag.....tc tggcaacaggcctcactgtctgggctccag gctgaggatgaggctgattattactgcagctcatatgcag agcagcgacacttcgtattcttcggcggagaccaagtt tgaccgtcctag	cagcctgtgctgactcagccctcgcttca...gtgtccgg gtctcctggacagtcagtcaccatctcctgcactgga accagcagtgatgttggt.....ggttatgactatgtctc tcctggtaccaacaacaccaggcaaagcccccca aactcatcatttatgaggtc.....aatcaa gggggtccctcagggttcct...gatcgttctctggctc caag.....tctggcaacacggccttcactgaccgtctc tgggctcaggctgaggatgaggctgattattactgc agctcatattcgagcagcgacacttt
CTLA4pmpl-Rd2-E2-A10	productive	Homsap IGLV8-61*01 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F			cagactgtggtgactcaggagccatcg...ttctcagtg gccctgggggacagtcacactcactttgccttgag ctctggctcagctctct.....agtaactatgcccagc tgattccagcagagcccaggccaggccacaca ctcatctacaatacg.....gacatagttct caatgggtccct...gatcgttctctggctctatc....ctt ggaaacaaagcagcctcaccatcacgggggccca gccaaatgatgaatctgaatactctgtgtctatatg ggtagcggcaattcgatttcggcggagaccaagg tgaccgtcctag	cagactgtggtgactcaggagccatcg...ttctcagtt ggccctgggggacagtcacactcactttgccttgag agctctggctctctct.....agtaactatgcccagc cagtgattccagcagagcccaggccaggccaca cgcacactcatctacaatacg.....gac atacgttctcatgggttcct...gatcgttctctggct ctctc.....ctttggaaacaaagcagcctcaccatca cgggggccagccaaatgatgaatctgaatactact gtgctctatatggtagcggcaattc

FIG. 11 CONT

FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
cagcctgtgctgactca gccctgcctca...gtgtcc ggctcctctgacagtc agtcaccatcctctgca ctggaacc	agcagtgatgttg gt.....ggttat aactat	gtacctggtacc aacaacaccca ggcaaggcccc caaaatcatcatt tat	gaggtc..... .....aat	aagcggcctcaggggtcact...gatc gctttctggctccaag.....tctggcaa cacggcctcctgaccgtctctgggctc caggctgaggatgaggctgattattact gc	agctcatattgagc agcagcacttgctc	tgcagctcatattc gagcagcagca cttggtcttc	ggtcttcggcg gggggaccaa gttgacggtcct ag	ttcggcgggggg accaagttgacc gtcctag
cagactgtgtgactca ggagccatcg...ttctca gtggcctctgggggga cagtcacactcacttctgtg ccttgagc	tctgctcggtctc t.....agtaact atcac	cccagctggttc cagcagaccac aggccaggcgc cacgcacatc atctac	aatacа..... .....gac	atacgttctcatcgggtcact...gatcgg ttctctggctctctc.....cttggaaacaa agcagcctcaccatcacgggggccc agccaaatgatgaatctgaatactactgt t	gctctctatatgggt atcggcatttcgat a	tgtgctctatatg ggtagcggcattt cgatattc	tattcggcgga gggaccaagg tgaccgtcctag	ttcggcgaggg accaagtgac cgtcctag

FIG. 11 CONT

Sequence number	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION
CTLA4pmpl-Rd2.E2.A12	productive	Homsap IGLV8-61*01 F	Homsap IGLJ3*02 F			cagactgtggtgactcaggagccatcg...ttctcagt ccctgaggacagtcactcattgggcttgagc tctggctcagtctct.....actagttactacccagctg gtaccagcagaccccaggccaggtccctgtgctcgt catctacgaggacagcaagcgaccccagggatccct gagcgattctctggctccagctcagggacatcagc ctcacaatcactggggcccaggctgaggatgag gctgactattactgtgtcctgtacatgggcgatggc atcttcggcggagggaccaagctgaccgtcctag	cagactgtggtgactcaggagccatcg...ttctcagt gtccctgaggacagtcactcattgggcttgagc tctggctcagtctct.....actagttactacccc agtatggtaccagcagaccccaggccaggtccctgc gcacactcatctacgacacaaaaaccgaccctcc ggggtctctgatcgattctctggctccagctcagg acatcgctctcaccatcactggggcccaggctgag gacgaggctgactattactgtgtcctgtacatgggc atcttcggcggagggaccaagctgaccgtcctag	cagactgtggtgactcaggagccatcg...ttctcagt gtccctgaggacagtcactcattgggcttgagc agtctggtaccagcagaccccaggccaggtccctgc gcacactcatctacgacacaaaaaccgaccctcc ggggtctctgatcgattctctggctccagctcagg acatcgctctcaccatcactggggcccaggctgag gacgaggctgactattactgtgtcctgtacatgggc atcttcggcggagggaccaagctgaccgtcctag

FIG. 11 CONT

FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
cagactgtggtgactca ggagccatcg...ttctca gtgtcccctggaggac agtcacacticattgtgg cttgagc	tctggctcagtctcc t.....actagtt actac	cccagctggtac cagcagacccc aggccaggctc cacgcacatc atctac	accaca..... .....aac	actggctcttctgggtcccct...gatcgct tctctggtccatc.....cttggaacaa agctgcctcaccatcacgggggccc aggcagatgatgaatctgattactgt	gtcctatatatggct agtggcatttgggtg	tgtgtcctatatatg ggtagtggcattt gggtgttc	gggtgttcggc ggagggacca agctgaccgtc ctag	ttcggcggaggg accaagctgacc gtcctag

FIG. 11 CONT

Sequence number	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION
CTLA4pmpl-Rd2-E2-E5	productive	Homsap IGLV8-61*01 F	Homsap IGLJ3*02 F			catactgtggtgactcaggagccatcc...ttctcagtga ccactgaggagacagtcaccatcacttgtggttgagc tctgatcaatatgt.....actagttactaccaatctg gtaccagcaaccaccaggcctcccaggccatcact caatatgctaccaa.....aacaatcgaccgat cctggggtcct...gatcgattctctggctccatc....ctt cgggaacaaagatgacctcaccatcactcaggggcca ggaagatgatgctgattattactgtgtcctatatatg ggtagtggcattttggtgttgggggaaggaccaaact gaccgtcctag	catactgtggtgactcaggagccatcc...ttctcagtg accactgaggagacagtcaccatcacttgtggttgg agtctgatcaatatgt.....actagttactaccaa atctgatgctaccaa.....aacaatcgaccgat cctggggtcctcaatctct.....actagttactaccc gtaccagcaaccaccaggcctcccaggccatcact caat

FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
catactgtggtgactca ggagccatcc...ttttca gtgaccctggagccga cagtcaacacacattgtg gcttgagc	tctggctcaatctc t.....actagtt actac	ccatctgtgtac cagcacacccc agccaggctc cagcaactc atctac	accaca..... .....aac	actccatctctgtgggtccct...gatcgtt tctctgctccatc.....cttggaacaa agtgccctcaccatcaccggtgccc aggaagatgatgaatctgattactgt	gtcctatatagtgt agtggcattttgctg	tgtgtcctatatatg ggtagtggcattt gggtgttc	gggtgttcggc ggaaggacca aactgaccgtc ctag	ttcggcggaagg accaactgacc gtcctag
aatttatgctgactcacc ccaatct...gtgtcgga gtctccgggaagacg gtaaccatctcctgcac cggcagc	actgacagcctt. .....gccag caactat	gtgcagtggtac cagcagcgccc gggcagtgccc ccaccactgtga tctat	gaaaat..... .....aac	caaagaccctcgtgggtccct...gatc gattctgtggtccatcgacggctcctcc aactctgcctcctaccatctctgact ggagactgaggacgaggctgactact actgt	cagtctatgatggc acccccgtg	tgtcagtcctatga tggcaccccggt gttc	ggtgttcggca caggaccaa actgaccgtcct cc	ttcggcacaggg accaactgacc gtcctcc

FIG. 11 CON'T

Sequence number	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION
CTLA4pmpl-Rd2-E2.C4	productive	Homsap IGLV6-57*04 (F)	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F			cagcctgtgctgactcagccgccactct...gtgtcggagt ctccgggaagacggtcaccatctcctgcacccgca gcggtggcagcttt.....gccgacaactatgtgca gtggtaccaacagccccggcaggtgcccgtgctcatt atgatgtaagcaat.....cgccgaagcgc cctttgggtcccct...gatcgattctctggctccatcgac agctcctccaactctgcctccaccatcactgggctg aagctcaggctgaggatgaggctgattactactgtcta tgatagcagcgtcgtgtattcggcggagggaccc aagctgaccgtcctag	cagcctgtgctgactcagccgccactct...gtgtcggga gtctccgggaagacggtcaccatctcctgcacccg cagcggtggcagctt.....gccgacaactatgt gcagtggtaccaacagcccccggcaggtgcccgtgctcatc acctatgatgtaagcaat.....cgcc aaagaccctttgggtcccct...gatcgattctctggct ccatctccaactctgcctccaccatcactgggctg ctctggactcaggctgaggatgaggctgattactgtcta ctgtcagtctatgatagcagcgtcgtc	gacatccagatgacccagtctccatctttgtctgtgtctgc atctatgcgagacagagtcaccatcacttgcgggcc gagtcaggatatt.....agcaactggttag cctggtatcagcagaaaccagggaaagcccctaa actcctgatctatggtgca.....tccaatttg tgcgaagtgggggtccct...tcaggttcagcggcagt ggatctgggacagaattcactctcacaatcagcagcct gcagcctgatgattttgcaacttattactgtcaac agggtaacgttccc

FIG. 11 CONT

FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
caggtgtggtgactca gggagcactct...gtgtcg gagtctcgggggaaga cggtcaccatctcctgc accgcgagc	ggtggagcgctttt... .....gccgac .....aaccat	gtgcagtggtac caacagcgccc ggccagtgccc ccacccttatgat ctat	gaacat..... .....cac	caaagaccctttgggtcct...gatcg attctctgcctccatcgacagtctcctcca actctgcctcctcaccatctctgcatctg aagatgaggaccgagcctgactacta ctgt	cagtcttatgatagc agcactccgtggt a	tgtcagtctatgat agcagcaatccc gtggtattc	gtggtattcggc ggagggaccca agctgaccgtc ctag	ttcggcggagggg accaagctgacc gtcctag
gacatccagatgaccc agtctccatctttgtctgt gcatctataggagaca gagtcaccatcacttgtc gggcgagt	caggatatt..... .....agcaa ctcg	ttagcctggtatc agcagaaacca gggaaagcccc taaactcctgatc tat	ggtgca..... .....tcc	aattttcgcagtgggtcct...tcaag gttcagcggcggtgga.....tctggtac gtatttcactctcactatcagtagcctac agcctgcagattttgcgactactattgt	caacagggtaaca gttccgatcacc	tgtcaacagggta acagtttccgat caccttc	gatcacttcgg ccaaggtacg cgatcggagat taaac	ttcggccaaggg acgcgactgga gattaaac

FIG. 11 CON'T

Sequence number	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION
CTLA4pmpl-Rd2.E2.H10	productive	Homsap IGLV7-46*01 F	Homsap IGLJ3*02 F			cagactgtggtgactcaggagccctca...ctgactgtg tcccctggaggacatcattaactctgtgctcca gcactggagctgtcacc.....actgtcattatcct actgttccagcaaaagcctggccaggctcctcc cactgattatgatgca.....atcacaaa cactctggacccct...gccggttctcaggctc... ....ctttgggcaaaacttgcctgacctttcgggtgcg cagcctgaagtggaggctgactattactgcctctcc tatagtggtgctcgggtgttcggcggagggaccaagct gaccgtcctca	cagactgtggtgactcaggagccctca...ctgactgt gtcccctggaggacatcattaactctgtgctc cagcactggagctgtcacc.....actgtcattatc cctactgttccagcaaaagcctggccaggctcccc actgactgattatgatgca.....actc acaaacactctggacccct...gccggttctcagg ctcgtc....ctttgggcaaactgcctgacctt tcgggtgcagcctgaagtggaggctgactact gcctgtcctatagtggtgctcgg

FIG. 11 CONT

FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
caractgtgtgactca ggagcctca...ctgac tgtgtcccaggaagg acagtactcacctgt ggcaccagc	actggaggtgtc acc.....actg gtcattat	ccctatggttcc agcaaaagcct ggccaggcccc cacgacatgat ttat	gatgca..... .....act	caaaaactctgtgaccct..gccc ggttctcaggtccgtc.....ctgggg caaagtgccctgaccttgggtgcg cagcctgaagatagggctgactattact gc	ctgctctctatagtg gtgctgggatg	tgcctgctcccta tagtggtgctcgg gtgttc	gtgttcggcgg agggaccaag ctgaccgtcctc a	ttcggcggagggg accaagctgacc gtcctca

FIG. 11 CONT

Sequence number	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION
CTLA4pmpl-Rd2-E2-F1	productive	Homsap IGLV1-40*01 F	Homsap IGLJ1*01 F			cagtctgtgctgactcagccaccctca...gtgtctgggg cccccagggcagaggtcaccatctctgcactggga gcagcctccaacatcggg.....gcaggttatgatgta cactggtaccagcagctccaggaaacagcccccaaa ctcctcatctatggtaac.....aggagtcg gccctcagggtcct...gaccgattctctggctcca g.....tctggcaactcagcctccatcactgggg ctccagtctgaagatgaggctgattattactgtcatcatg ggatgaaagcctgaatgcttatgtcttttggatctggcac caagctcaccgtcctag	cagtctgtgctgactcagccaccctca...gtgtctggg gcccagggcagaggtcaccatctctgcactgga gcagcctccaacatcggg.....gcaggttatgat gtacactggtaccagcagctccaggaaacagcccc caaactcctcatctatggtaac.....ag cagtcggccctcagggtcct...gaccgattctctg gctccaag.....tctggcaactcagcctccatctgcca tcagtctggctcactctgaagatgaggctgattattat tgtctatcatggga
CTLA4pmpl-Rd2-E2-H8	productive	Homsap IGLV2-14*01 F, or Homsap IGLV2-14*03 F	Homsap IGLJ1*01 F			cagtctgcctgactcagcctgcctcc...gtgtcaggct ctcctggacagtcgatcaccatcttctgcactggaacc agcggtgaccttggt.....ggccatgacaatgtctcgt ggtaccaacaacaccggcaaagcccccaaactc atgattatgaggc.....agtaagcggc cctcaggggttct...aatcgcttctctggctccaag..... .tctggcaacacggcctcctgaccgtctctgggctcca ggctgaggatgaggctgattactatcagtctattgac ggtcgcgtcctag	cagtctgcctgactcagcctgcctcc...gtgtcagg ctctctggacagtcgatcaccatcttctgcactgga accagcggtgaccttggt.....ggccatgacaatgtc tctcgtggtaccaacaacaccggcaaagcccccc aaactcatgattatgaggc.....agt aagcggcctcaggggttct...aatcgcttctctggc tccaag.....tctggcaacacggcctcctgaccgtc tctgggctccaggctgaggatgaggctgattactact gcagcctcattgcaggaaccaaca

FIG. 11 CON'T

FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
cagtcrtgtgtgactcag ccaccctca...gtgtctg gggcccaggcagaga gggtcaccatctcctgc actggagc	agctccaacatc ggg.....gca ggttatgat	gtacactggtac cagcagctcca ggaacagcccc caaactcctcat ctat	ggtaac..... .....agc	agtcggcctcaggggtccct...gacc gattctctggctccaag.....tctggcac ctcagcctcctgccatcagtgggctc cagctgaagatgaggctgattattattg t	ctatcatggatga aagcctgaatgctt atgtc	tgtctatcatggga tgaaagcctgaat gcttatgtattt	ttatgtcttttggat ctggaccaa ggtcaccgtcct gg	tttggatctgggа ccaaggtcaccg tcctgg
cagtctgcctgactca gcctgcctcc...gtgtca ggctctctgtgcacgtc gatcaccatcctctgca ctggaacc	agcggtgacgtt ggt.....gggc attgatdat	gtctcgtggtacc aacaacaccgg ggcaagcccc caaactcatgatt tat	gagggc..... .....agt	aagcggcctcaggggttttct...aatcg ctctctggctccaag.....tctggcac acggcctcctgacggtctctggctcc aggctgaggatgaggctgattactactg c	agctcattttgcagg aaccaacaattacg tc	tgcagctcaattttgc aggaaccaaca attacgtcttc	ttacgtcttcgg aactggtacc aaggtcgccgt cctag	ttcggaactggg accaggtcgcc gtcctag

FIG. 11 CONT

Sequence number	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION
CTLA4pmpl-Rd2-E2-G5	productive	Homsap IGLV1-47*02 F	Homsap IGLJ3*02 F			cagcctgggctgactcagccaccctca...ggtctctg ggaccccgggcagagggtcaccctctgttctgtggaa gcagctccaacatc.....ggaagtaattatgttc tggtaccagcagctcccaggaacggcccccaaactc ctcatctatagtaat.....aatcagaggcc ctcagggtccct...gaccgattctctggctcc aag.....tctggcacctcagcctccctgggctcag gtcctgaggatgaggctgattactgtgcagcatggg atgacagcctgagtggttgggtgttcggcggagggac caagtgaccgtcctag	cagtctgtgctgactcagccaccctca...gtgtctggg cccccagggcagagggtcaccatctcctgcactggga acagctccaacatcggg.....gcaacttatgata cactgtaccagcagttccaggaacagcccccaaa actcctcattatgctaac.....aagtatcgg cctctaggggtccct...gaccgattctctggctccaag. .....tctggcacctcagcctccctgccatcagtgggct ccggtccaaagatgaggctgattactgtgcagcct gggatgacagcctgggtgttattgttcggaactg ggaccaagtcaccgtcctac	caggtgcagctgcaggagtcgggcccaggactggtgaag ccttcggagaccctgtccctcacctgcactgtctct ggtggctccatcagtagttactactggagctggatccg gcagcccccagggaaggggctggagtggattgggagt atctattatagtgggagcacctactacaacccgtccctc aagagtcgagtcaccatatcagtagagacacgtccaag aaccagttctccctgaagctgagctctgtgaccgccgc ggacacggccgtgtattactgtgcgagacaggtcgtg gctacttttgactactggggccagggaaccctggtcac cgtctcctca	gaggtgcagctggtggagtctgggggaggcttggtacag cctggggggtccctgagactctcctgtgcagcctct ggattcacctttagcagctatgccatgagctgggtccgc caggctccagggaaggggctggagtgggtctcagctat tttagtggtagtggtggtagcacatactacgcagactcc gtgaagggccggttcaccatctccagagacaattccaag aacacgctgtatctgcaaatgaacagcctgagagccgag gacacggccgtatattactgtgcgaaagatcgtagtgg ctacgattttgactactggggccagggaaccctggtcac cgtctcctca

FIG. 11 CON'T

FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
cagctgggtgatca gccacctca...gcgtc tgggaccccgggcag aggtcaccctctctgtt ctggaagc	agctccaacatc. .....ggaag taattat	gtattctgctacc agcagctccca ggaacggcccc caaactcctcat ctat	agtaat..... .....aat	cagaggcctcaggggtcct...gacc gattctgcctccaag.....tctggcac ctcagcctcctgccatcagtgggctc cggtccgaggatgaggctgattattact gt	gcagcatgggatg acagcctgagtggt tggatg	tgtgcagcatggg atgacagcctga gtggttgggtgttc	tggatgttcggc ggagggacca agctgaccgtc ctag	ttcggcggaggg accaagctgacc gtcctag
cagtctgctgactcac ccagcctca...gtgtctg ggcccccagggtcaga ggctcaccatctcctgc actgggaac	agctccaacatc ggg.....gca ccttatgat	gtaactgctac cagcagttcca ggaacagcccc caaactcctcatt tat	gctaac..... .....aag	tatcggcctcagggtcct...gaccg attctctgcctccaag.....tctggcacc tcagcctcctgccatcagtgggctcc ggtccaaggatgaggctgattactatg t	gcagcctgggatg acagcctgggtgt cttatgtc	tgtgcagcctggg atgacagcctgg gtggtcttatgtctt c	ttatgtcttcggа actggaccа agctcaccgtc ctac	ttcggaactggg accaagtgacc gtcctac

FIG. 11 CON'T

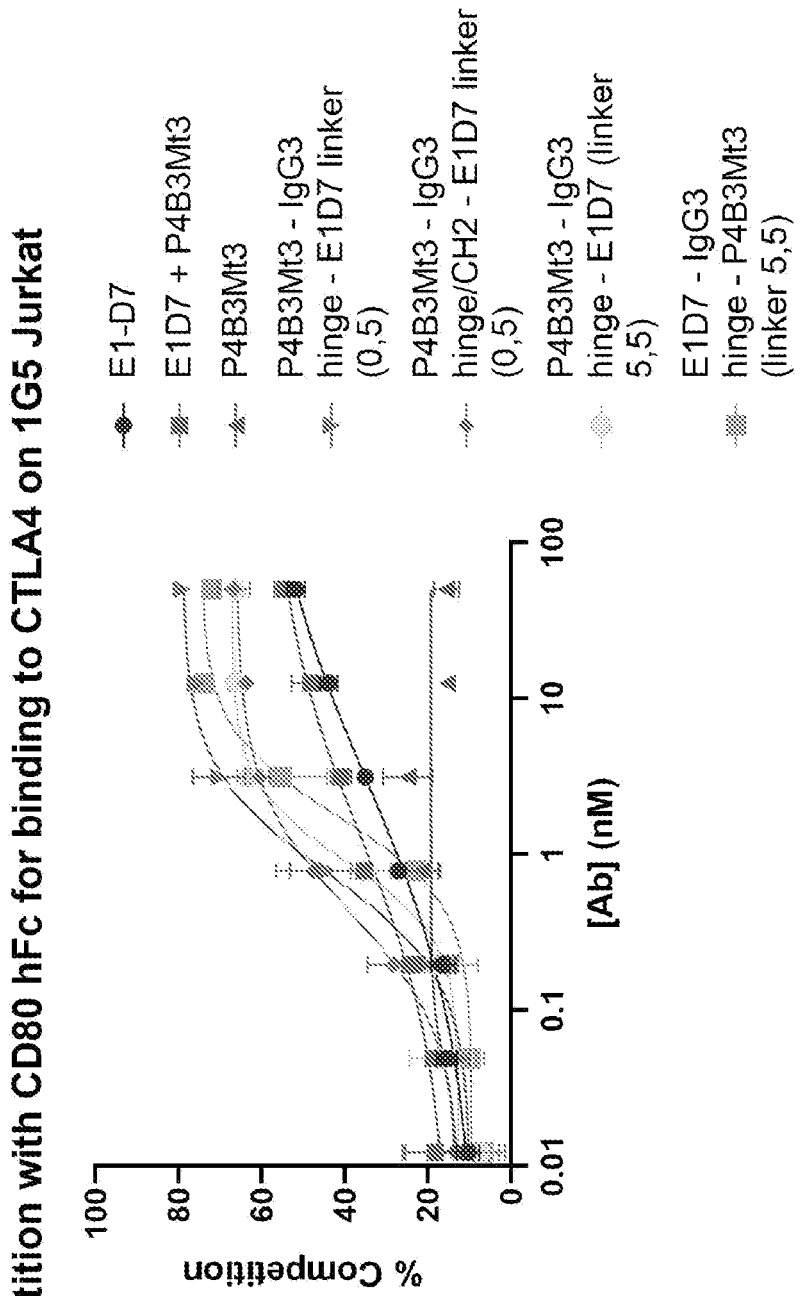

% Competition with CD80 hFc for binding to CTLA4 on 1G5 Jurkat
% Competition
100
80
60
40
20
0
0.01
0.1
1
10
100
[Ab] (nM)
E1-D7
E1D7 + P4B3Mt3
P4B3Mt3
P4B3Mt3 - IgG3 hinge - E1D7 linker (0,5)
P4B3Mt3 - IgG3 hinge/CH2 - E1D7 linker (0,5)
P4B3Mt3 - IgG3 hinge - E1D7 (linker 5,5)
E1D7 - IgG3 hinge - P4B3Mt3 (linker 5,5)

FIG. 12

FIG. 12
CON'T

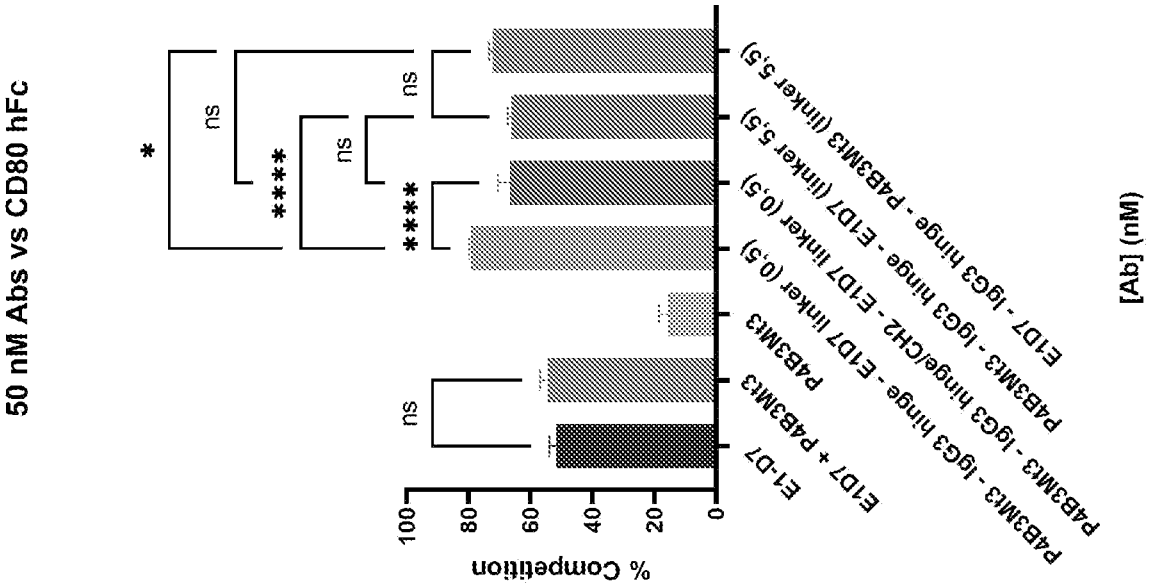

50 nM Abs vs CD80 hFc
% Competition
100
80
60
40
20
0
ns
*
ns
****
ns
****
ns
E1-D7
E1D7 + P4B3M13
P4B3M13
P4B3M13 - IgG3 hinge - E1D7 linker (0,5)
P4B3M13 - IgG3 hinge/CH2 - E1D7 linker (0,5)
P4B3M13 - IgG3 hinge - E1D7 (linker 5,5)
E1D7 - IgG3 hinge - P4B3M13 (linker 5,5)
[Ab] (nM)

FIG. 12
CON'T

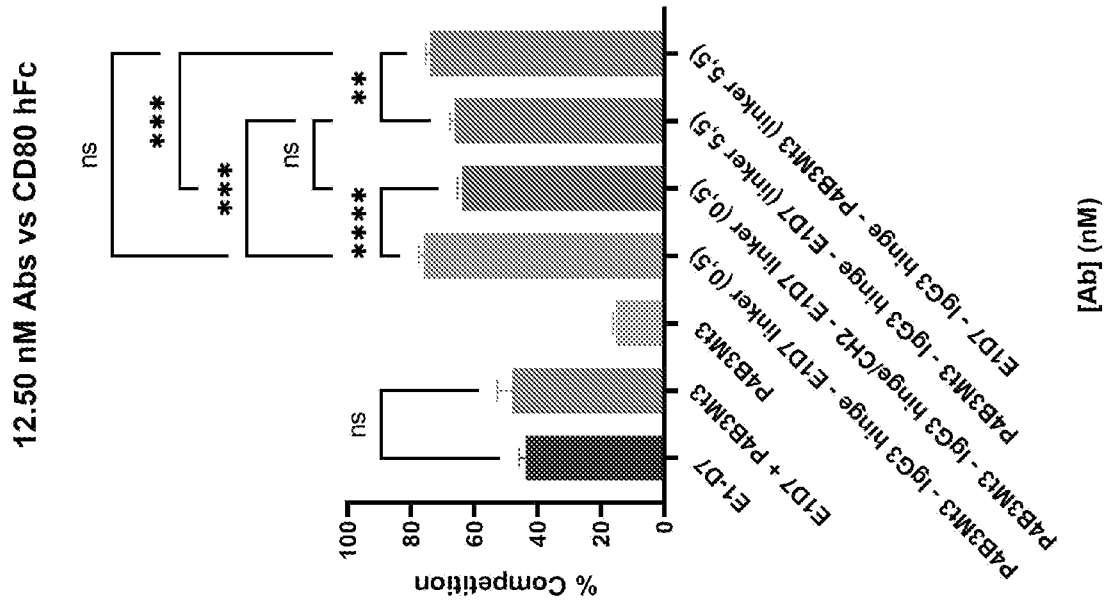

12.50 nM Abs vs CD80 hFc
% Competition
100
80
60
40
20
0
ns
****
***
ns
***
**
E1-D7
E1D7 + P4B3Mt3
P4B3Mt3
P4B3Mt3 - IgG3 hinge - E1D7 linker (0,5)
P4B3Mt3 - IgG3 hinge/CH2 - E1D7 linker (0,5)
P4B3Mt3 - IgG3 hinge - E1D7 (linker 5,5)
E1D7 - IgG3 hinge - P4B3Mt3 (linker 5,5)
[Ab] (nM)

FIG. 12
CON'T

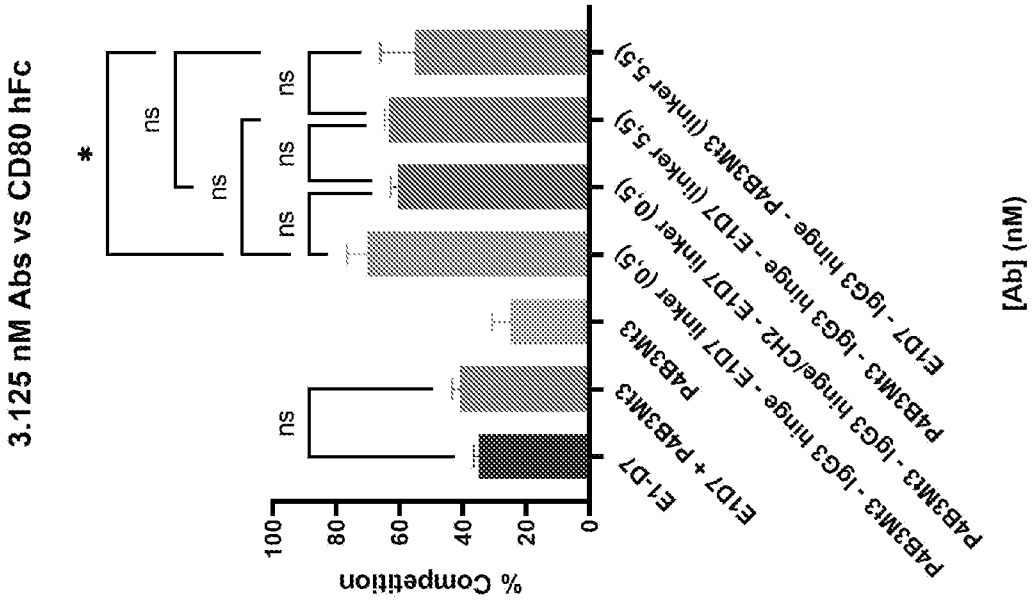

3.125 nM Abs vs CD80 hFc
% Competition
100
80
60
40
20
0
*
ns
ns
ns
ns
ns
E1-D7
E1D7 + P4B3Mt3
P4B3Mt3
P4B3Mt3 - IgG3 hinge - E1D7 linker (0,5)
P4B3Mt3 - IgG3 hinge/CH2 - E1D7 linker (0,5)
P4B3Mt3 - IgG3 hinge - E1D7 (linker 5,5)
E1D7 - IgG3 hinge - P4B3Mt3 (linker 5,5)
[Ab] (nM)

FIG. 12
CON'T

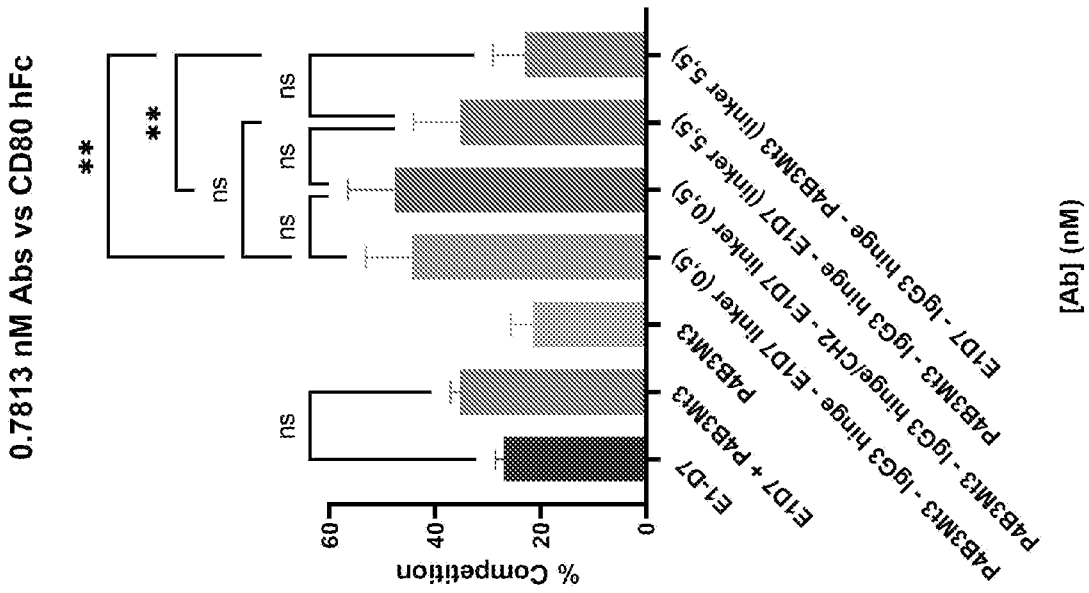
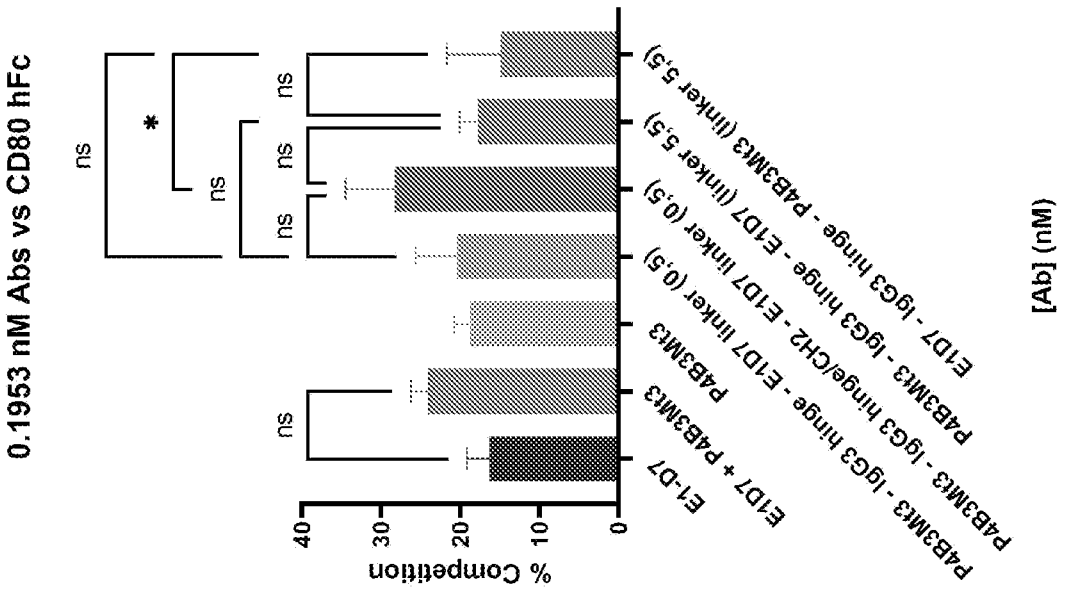

0.7813 nM Abs vs CD80 hFc
% Competition
0
20
40
60
ns
**
ns
**
ns
ns
ns
E1-D7
E1D7 + P4B3Mt3
P4B3Mt3
P4B3Mt3 - IgG3 hinge - E1D7 linker (0,5)
P4B3Mt3 - IgG3 hinge/CH2 - E1D7 linker (0,5)
E1D7 - IgG3 hinge - P4B3Mt3 (linker 5,5)
[Ab] (nM)

FIG. 12
CON'T


0.1953 nM Abs vs CD80 hFc
% Competition
0
10
20
30
40
ns
ns
ns
ns
ns
*
E1-D7
E1D7 + P4B3Mt3
P4B3Mt3
P4B3Mt3 - IgG3 hinge - E1D7 linker (0.5)
P4B3Mt3 - IgG3 hinge/CH2 - E1D7 linker (0.5)
P4B3Mt3 - IgG3 hinge - E1D7 (linker 5.5)
E1D7 - IgG3 hinge - P4B3Mt3 (linker 5.5)
[Ab] (nM)

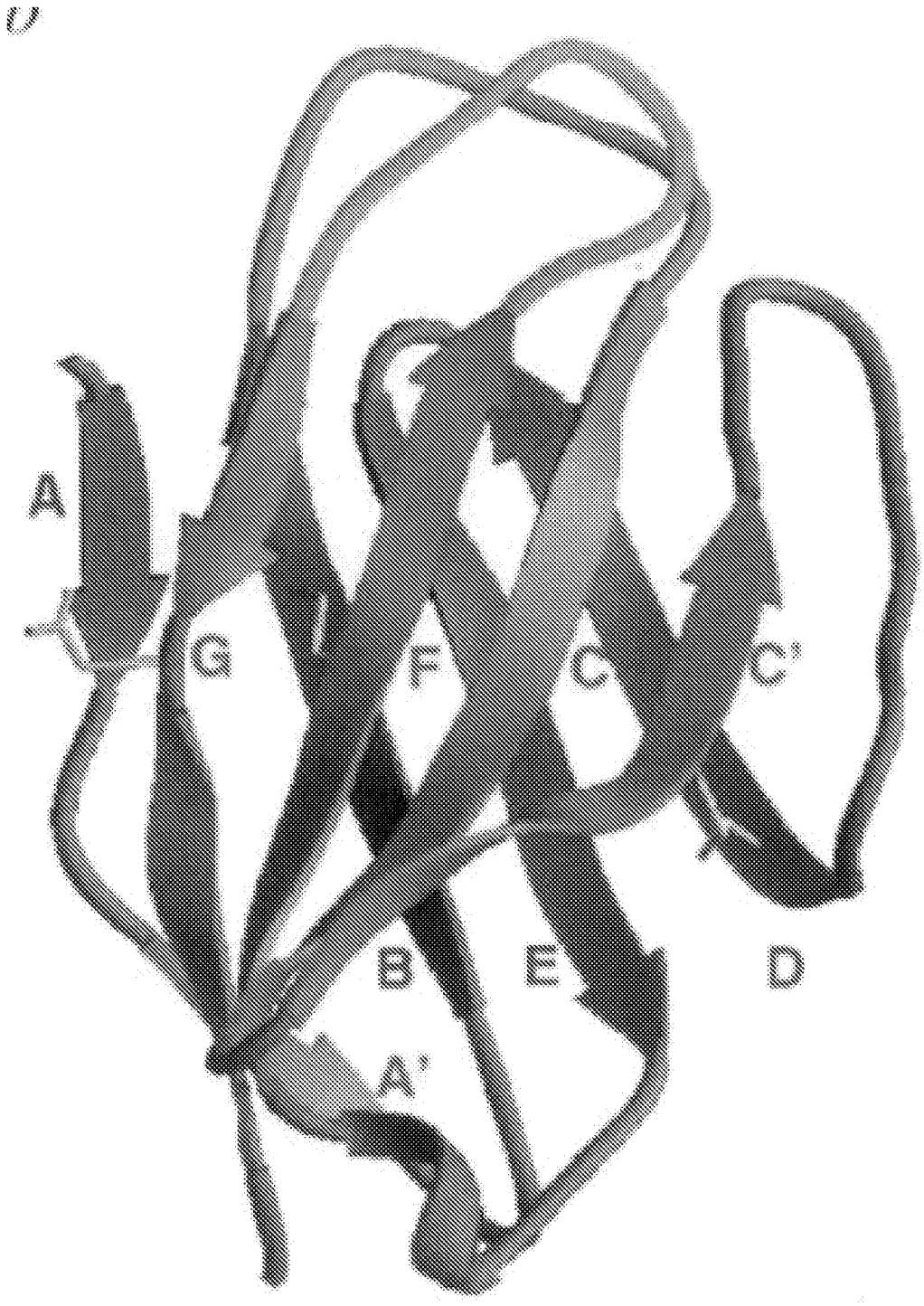


FIG. 13

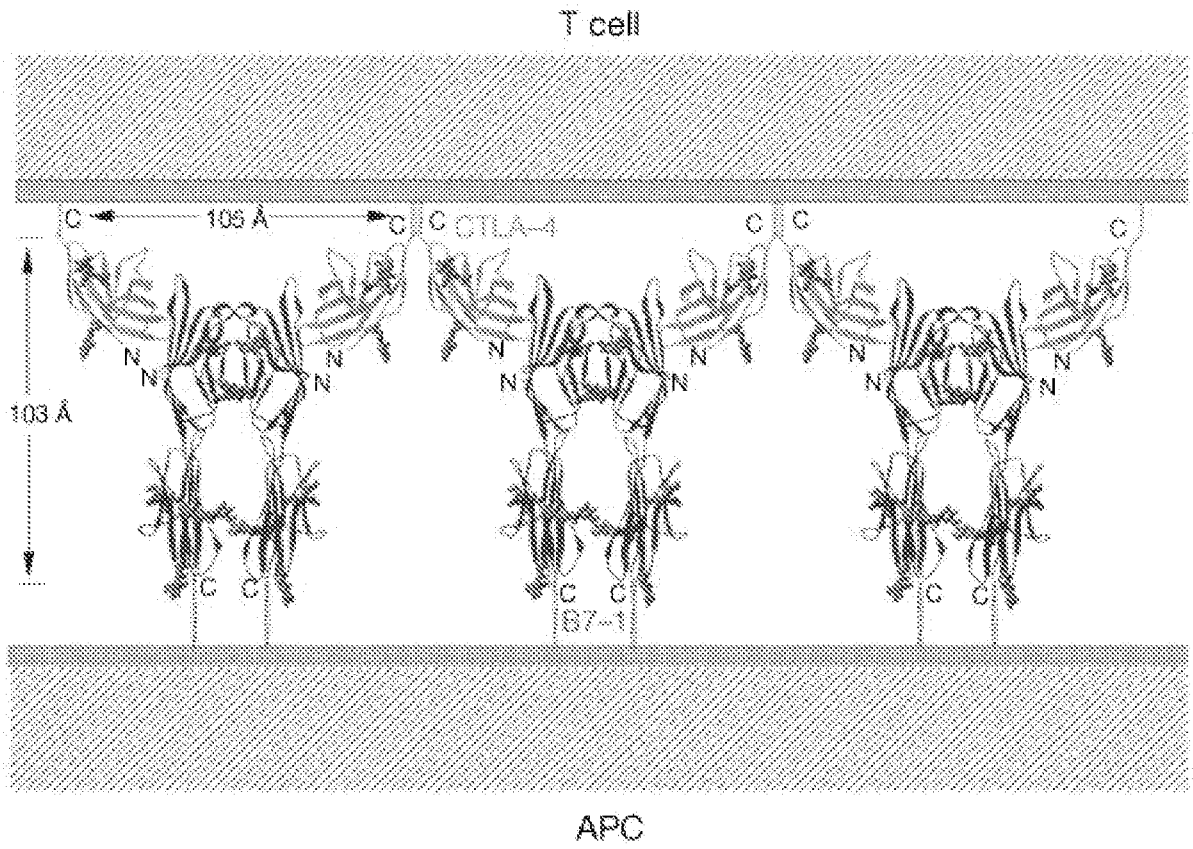


FIG. 14

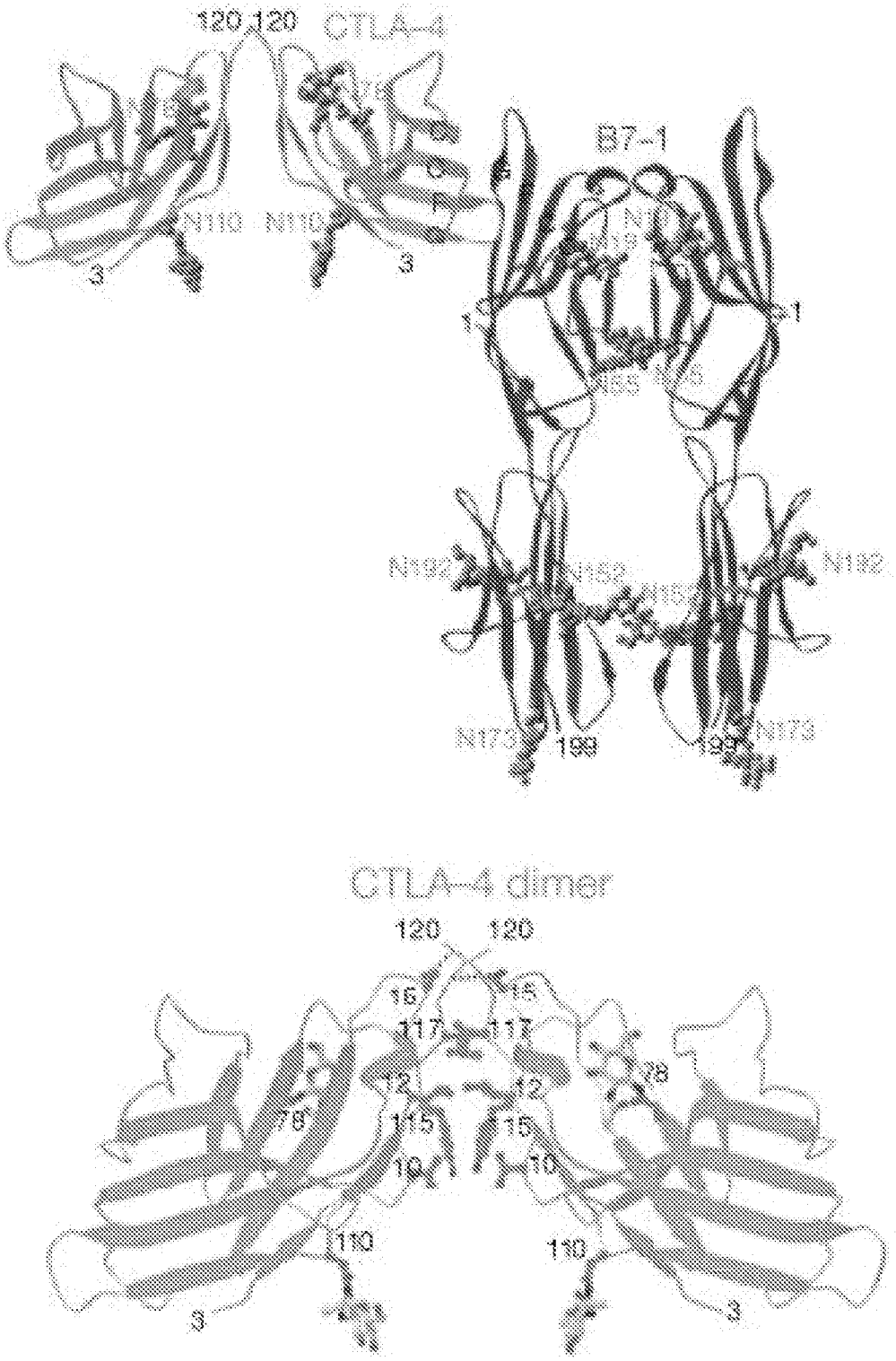
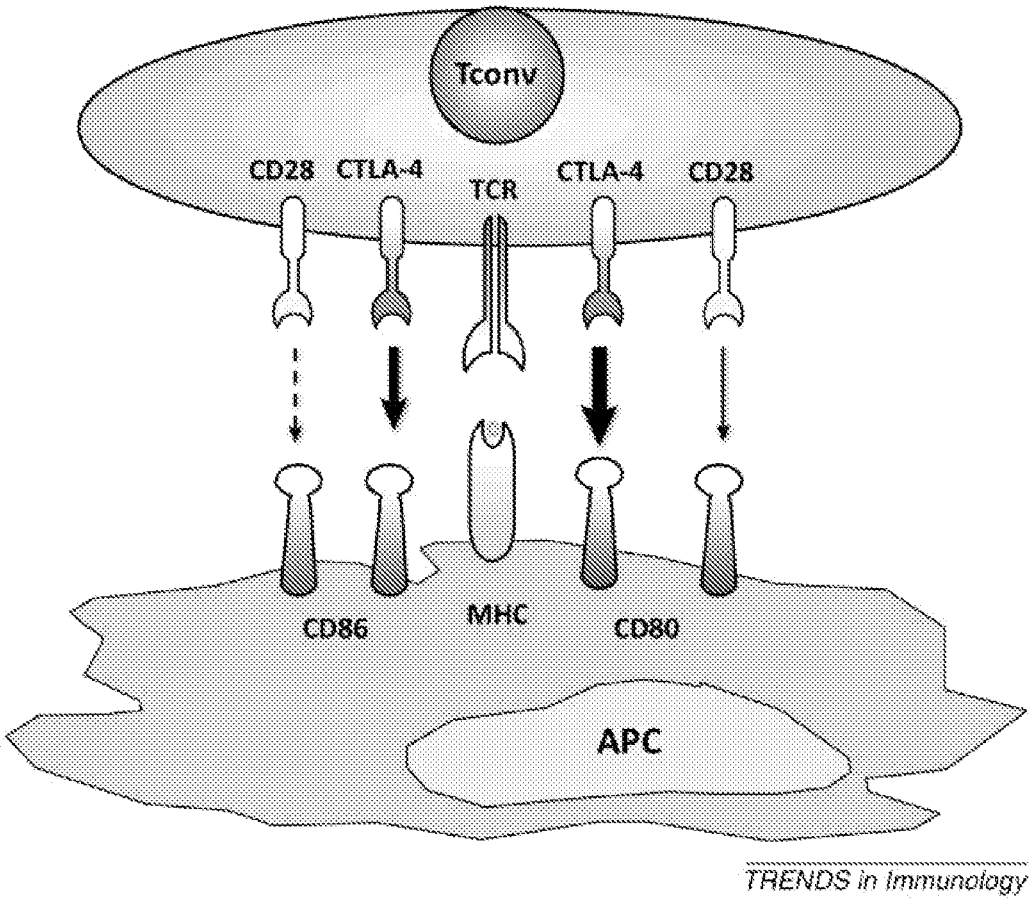


FIG. 14 (cont.)


Tconv
CD28
CTLA-4
TCR
CTLA-4
CD28
CD86
MHC
CD80
APC
TRENDS in Immunology

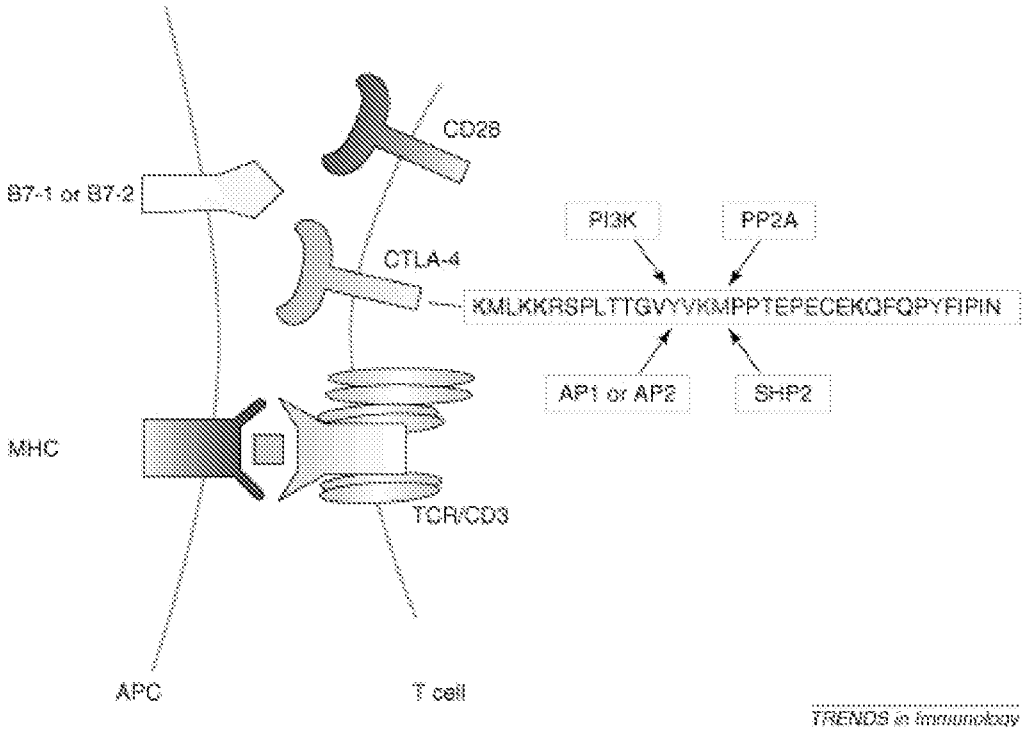
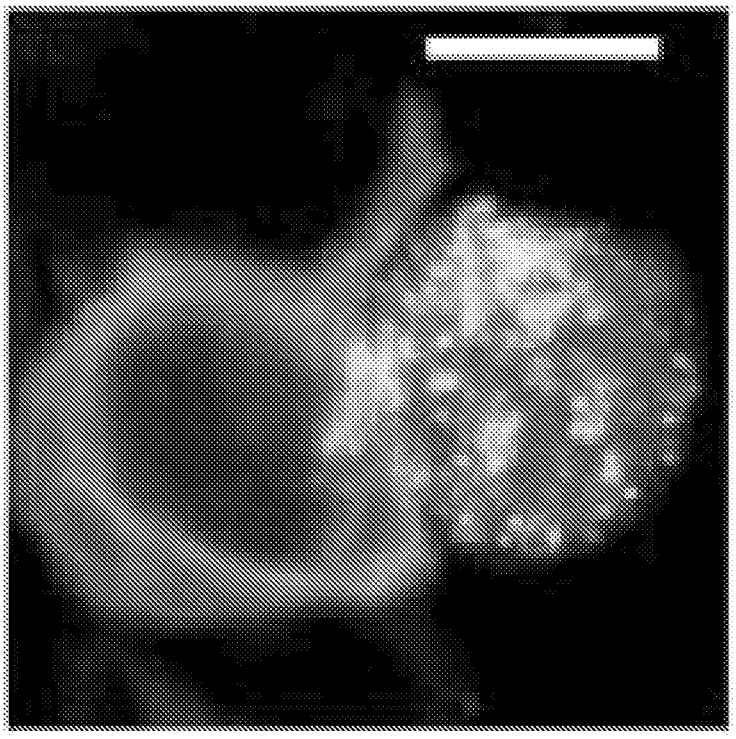

CD28
B7-1 or B7-2
CTLA-4
PI3K
PP2A
KMLKKRSPLTTGVYVKMPPTEPECEKQFQPYFIPIN
AP1 or AP2
SHP2
MHC
TCR/CD3
APC
T cell
TRENDS in Immunology

FIG. 15



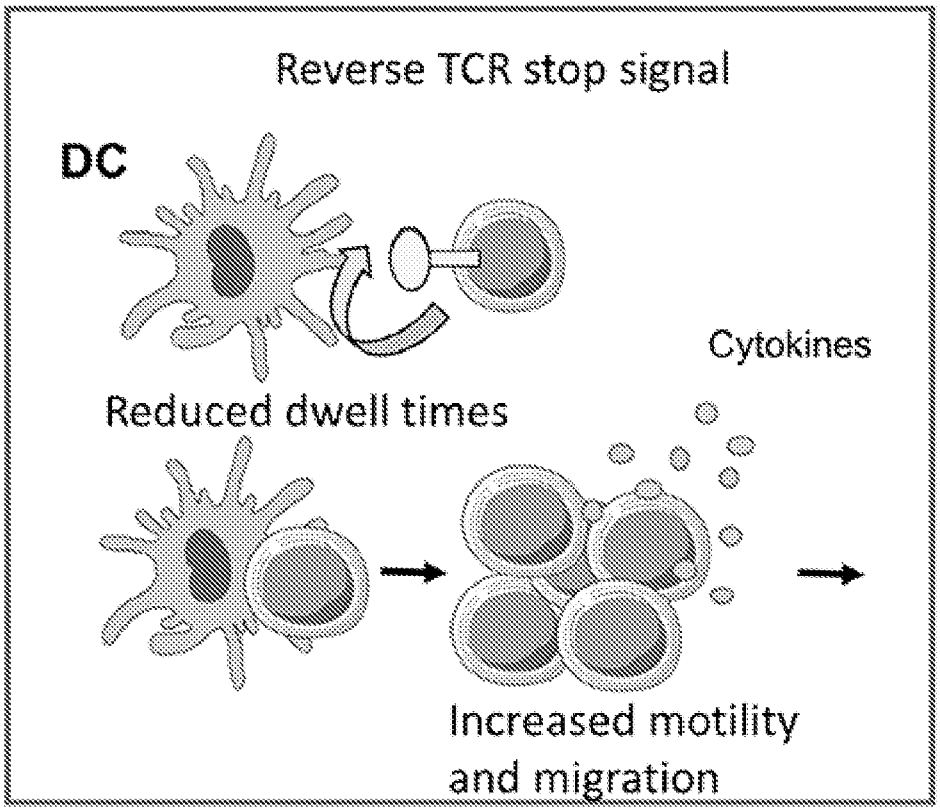

Reverse TCR stop signal
DC
Cytokines
Reduced dwell times
Increased motility
and migration

FIG. 15 (cont.)

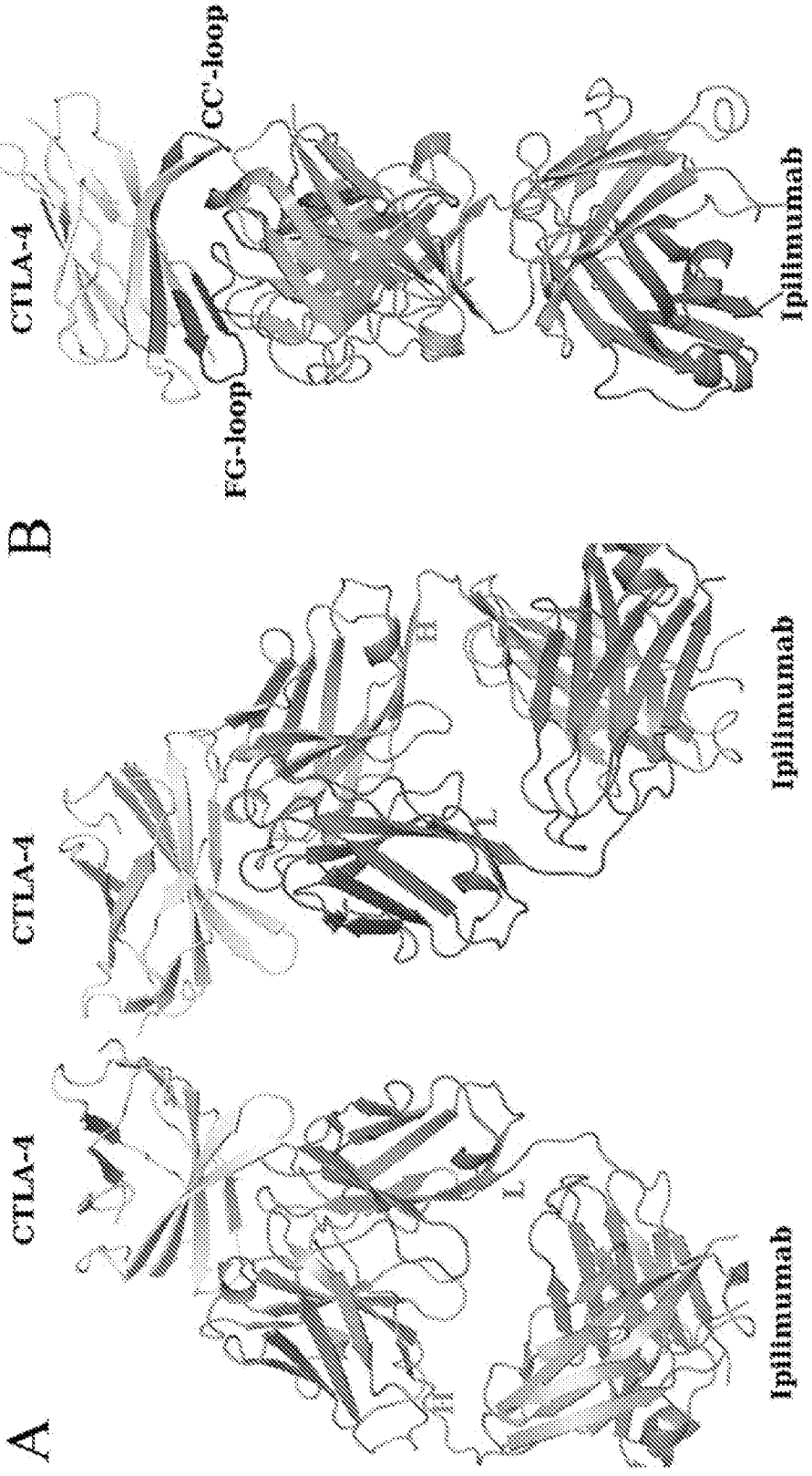

A
CTLA-4
Ipilimumab
CTLA-4
Ipilimumab
B
CTLA-4
CC'-loop
FG-loop
Ipilimumab

FIG. 16

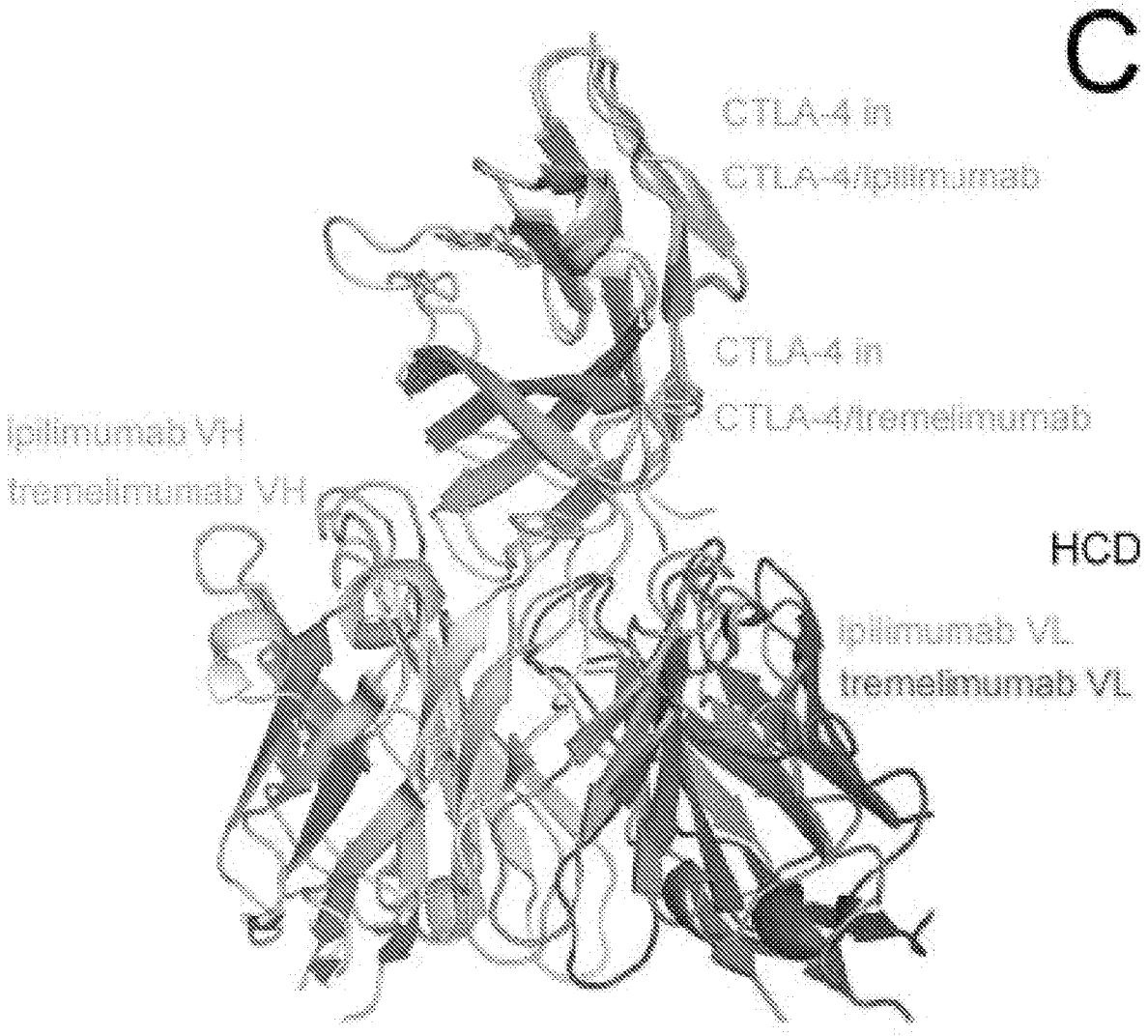

C
CTLA-4 in
CTLA-4/ipilimumab
CTLA-4 in
CTLA-4/tremelimumab
Ipilimumab VH
tremelimumab VH
HCD
Ipilimumab VL
tremelimumab VL

FIG. 16 (cont.)

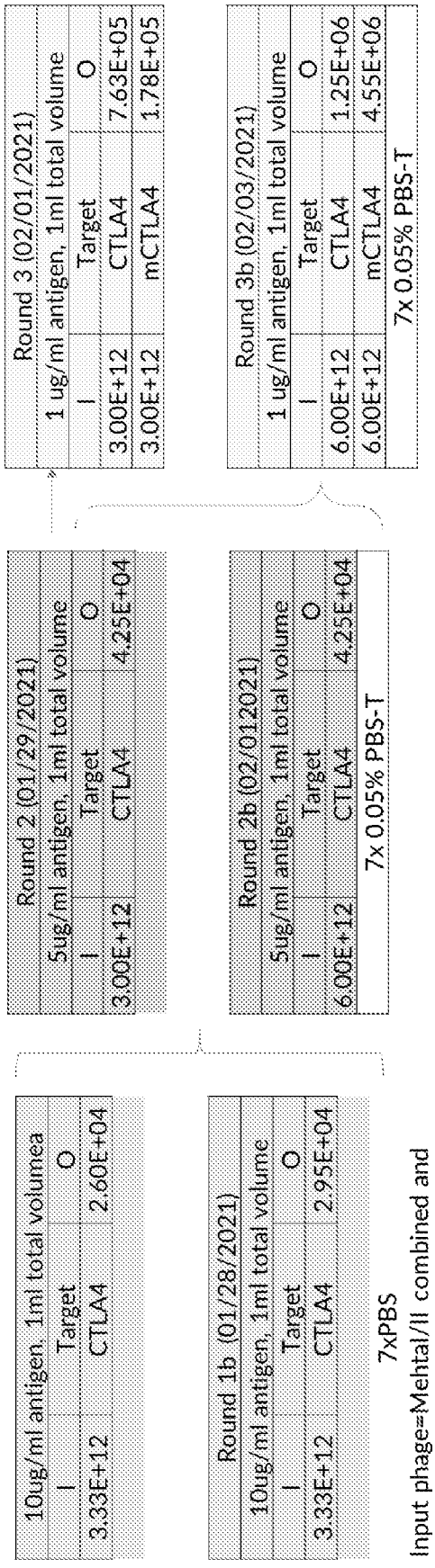

Round 3 (02/01/2021)
1 ug/ml antigen, 1ml total volume
I
Target
O
3.00E+12
CTLA4
7.63E+05
3.00E+12
mCTLA4
1.78E+05
Round 3b (02/03/2021)
1 ug/ml antigen, 1ml total volume
I
Target
O
6.00E+12
CTLA4
1.25E+06
6.00E+12
mCTLA4
4.55E+06
7x 0.05% PBS-T
Round 2 (01/29/2021)
5ug/ml antigen, 1ml total volume
I
Target
O
3.00E+12
CTLA4
4.25E+04
Round 2b (02/012021)
5ug/ml antigen, 1ml total volume
I
Target
O
6.00E+12
CTLA4
4.25E+04
7x 0.05% PBS-T
10ug/ml antigen, 1ml total volumea
I
Target
O
3.33E+12
CTLA4
2.60E+04
Round 1b (01/28/2021)
10ug/ml antigen, 1ml total volume
I
Target
O
3.33E+12
CTLA4
2.95E+04
7xPBS
Input phage=Mehtal/II combined and split

FIG. 17

Antibody	Conc. (nM)	Response	KD (M)	kon(1/Ms)	kdis(1/s)
E1-D7	20	1.1527	3.66E-10	4.64E+05	1.70E-04
T2-C10	20	0.3398	1.43E-11	4.23E+05	6.07E-06

*Sequencing following cloning from phage into scFv-Fc consolidated the 10 clones into the 2 above

FIG. 18

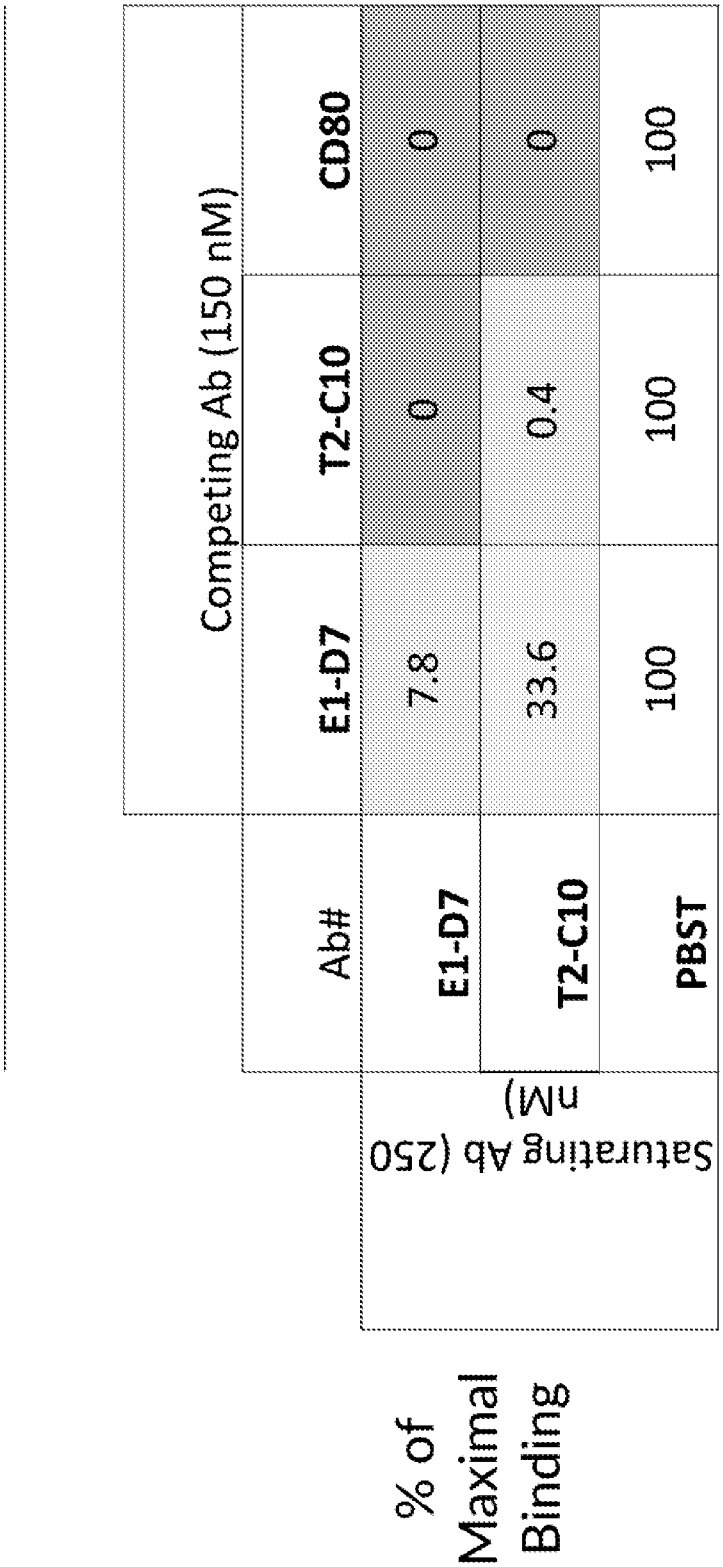

% of Maximal Binding
Saturating Ab (250 nM)
Ab#
E1-D7
T2-C10
PBST
Competing Ab (150 nM)
E1-D7
T2-C10
CD80
7.8
0
0
33.6
0.4
0
100
100
100
*negative values made 0
E1-D7 and T2-C10 both block CD80 binding to CTLA4

FIG. 19

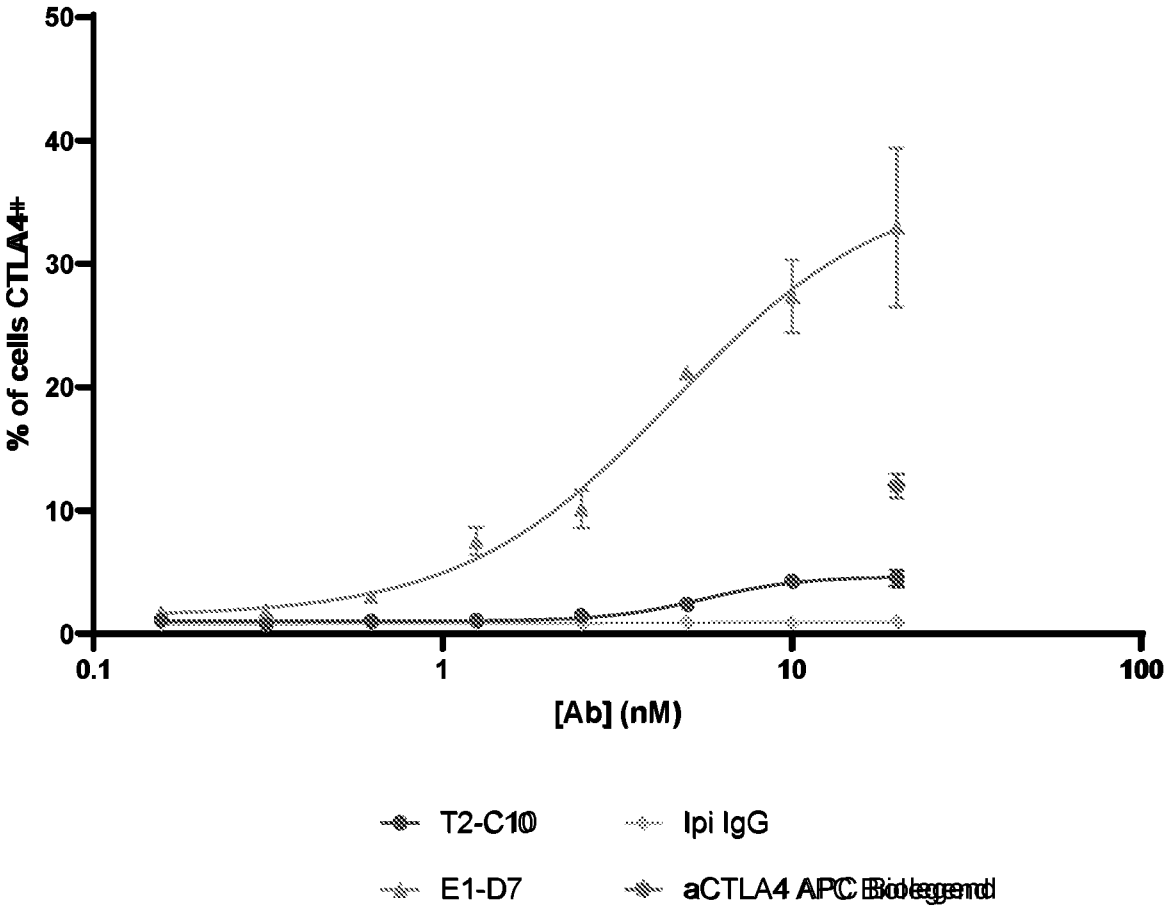

50
40
30
20
10
0
% of cells CTLA4+
0.1
1
10
100
[Ab] (nM)
T2-C10
Ipi IgG
E1-D7
aCTLA4 APC Biolegend

FIG. 20

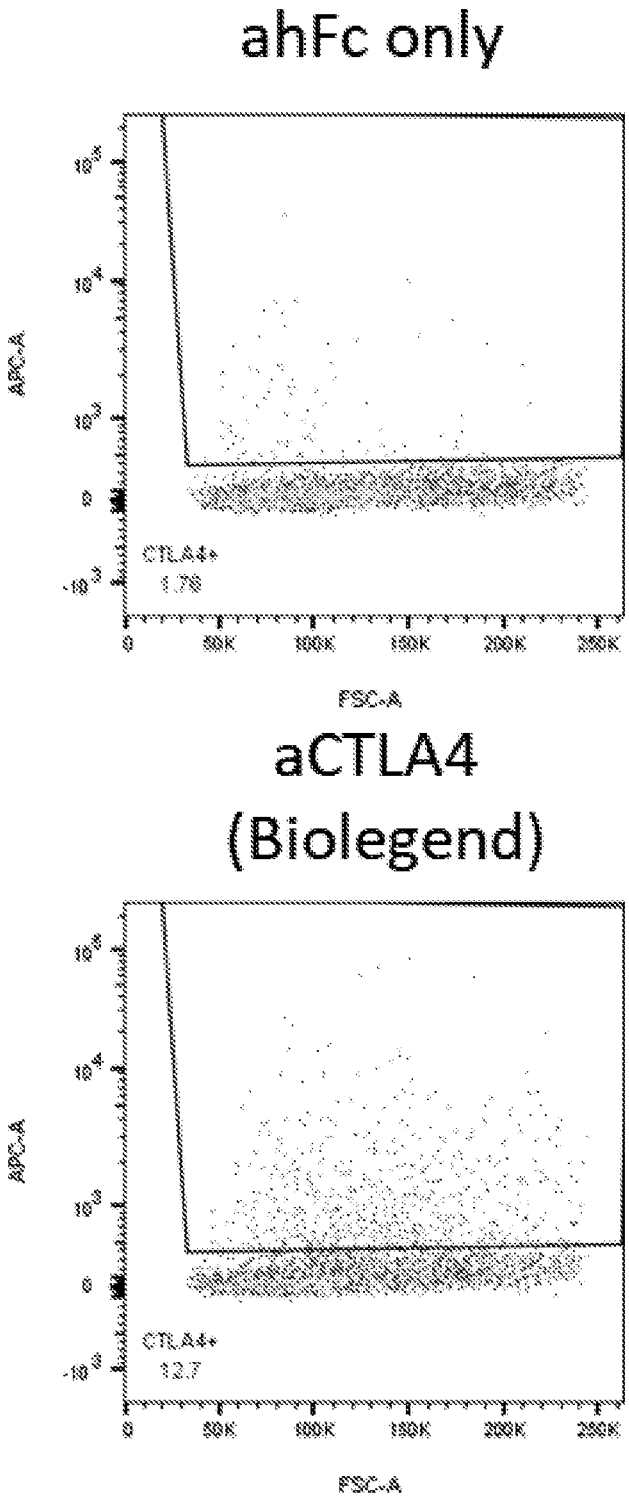

ahFc only
APC-A
FSC-A
CTLA4+
1.78
0
50K
100K
150K
200K
250K
aCTLA4
(Biolegend)
APC-A
FSC-A
CTLA4+
12.7
0
50K
100K
150K
200K
250K

FIG. 21

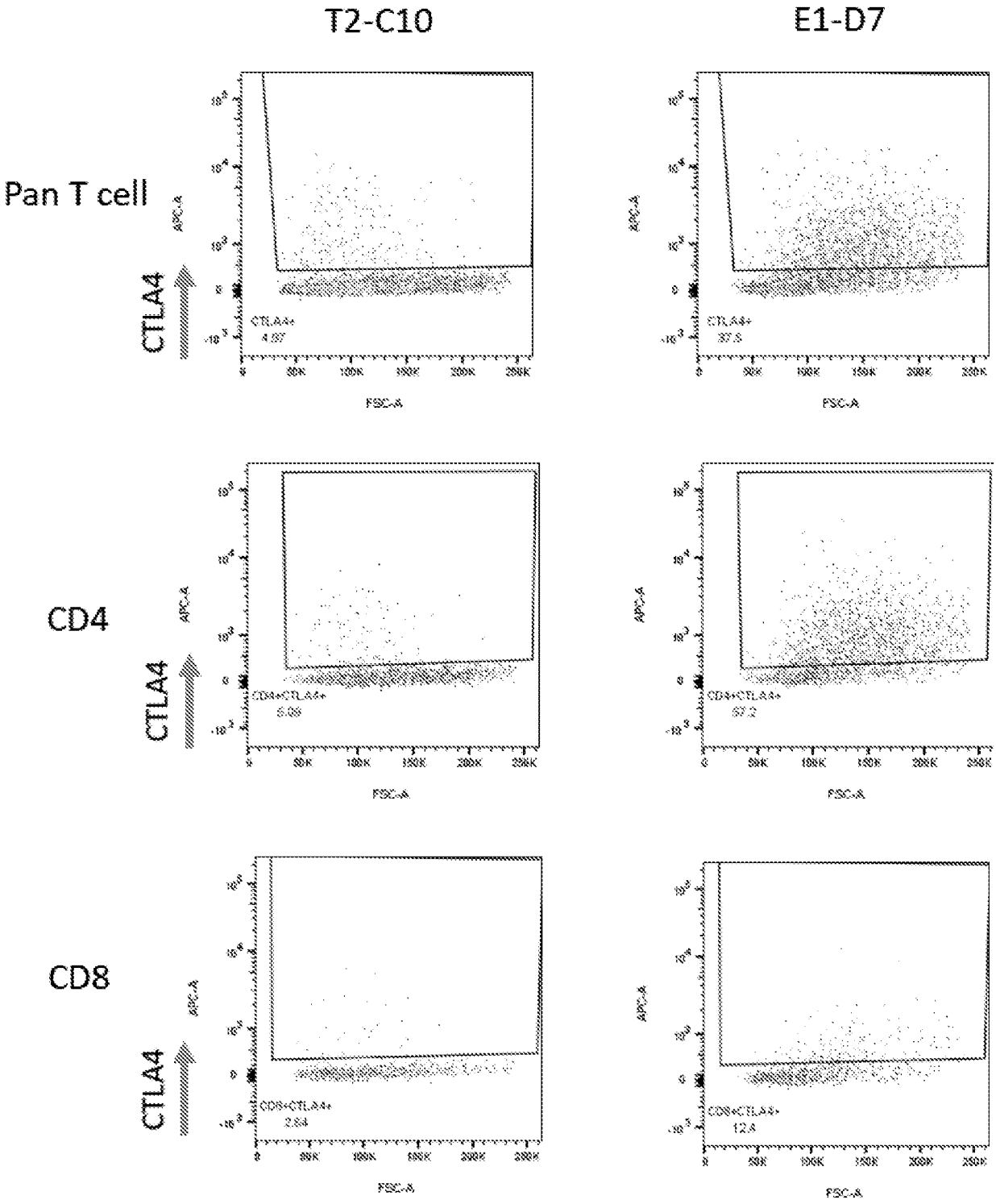

T2-C10
E1-D7
Pan T cell
CD4
CD8
CTLA4
APC-A
FSC-A
CTLA4+
4.87
CTLA4+
37.8
CD4+CTLA4+
6.08
CD4+CTLA4+
57.2
CD8+CTLA4+
2.64
CD8+CTLA4+
12.8

FIG. 21 (cont.)

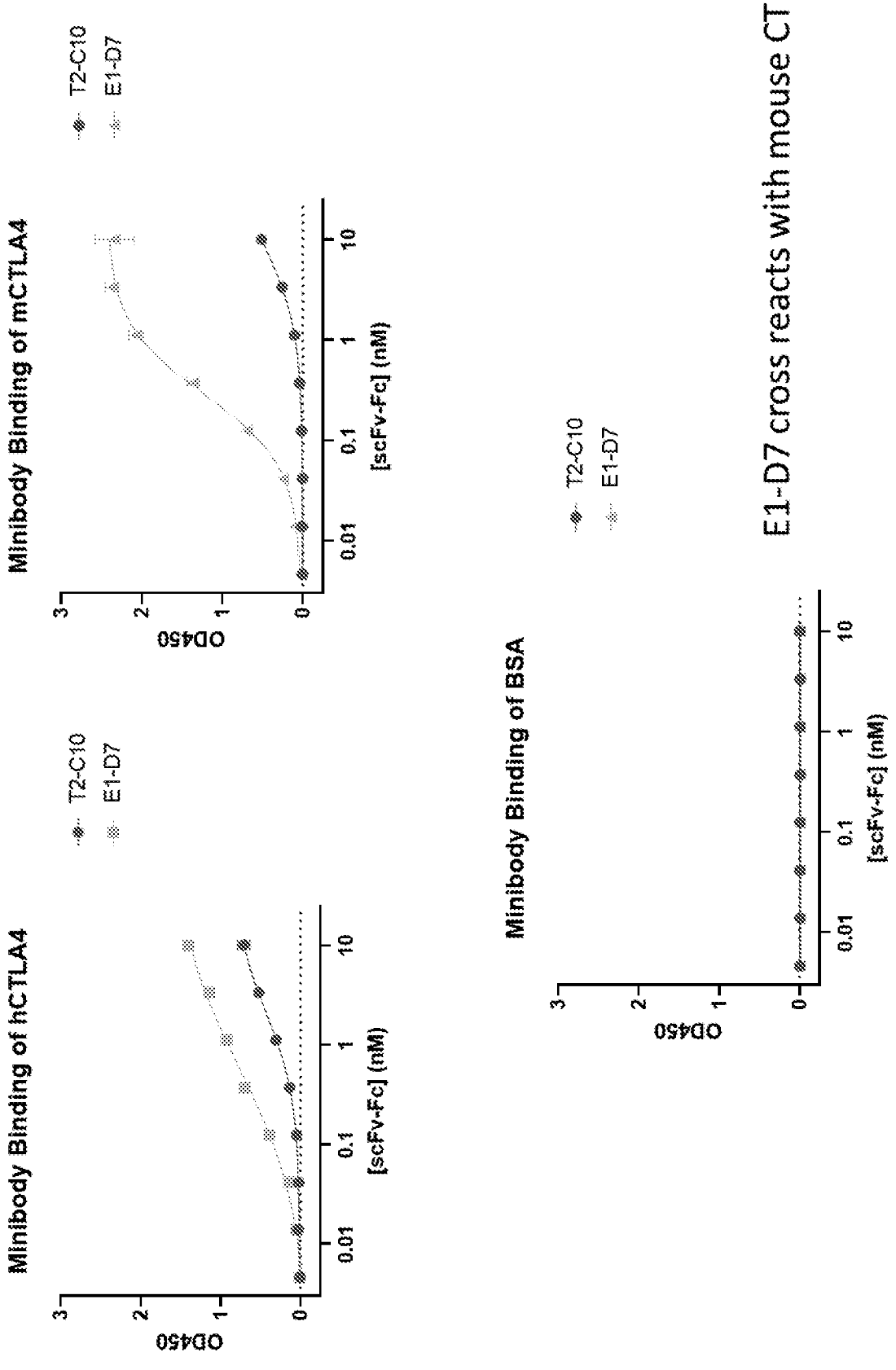

Minibody Binding of hCTLA4
T2-C10
E1-D7
OD450
[scFv-Fc] (nM)
Minibody Binding of mCTLA4
T2-C10
E1-D7
OD450
[scFv-Fc] (nM)
Minibody Binding of BSA
T2-C10
E1-D7
OD450
[scFv-Fc] (nM)
E1-D7 cross reacts with mouse CTLA4

FIG. 22

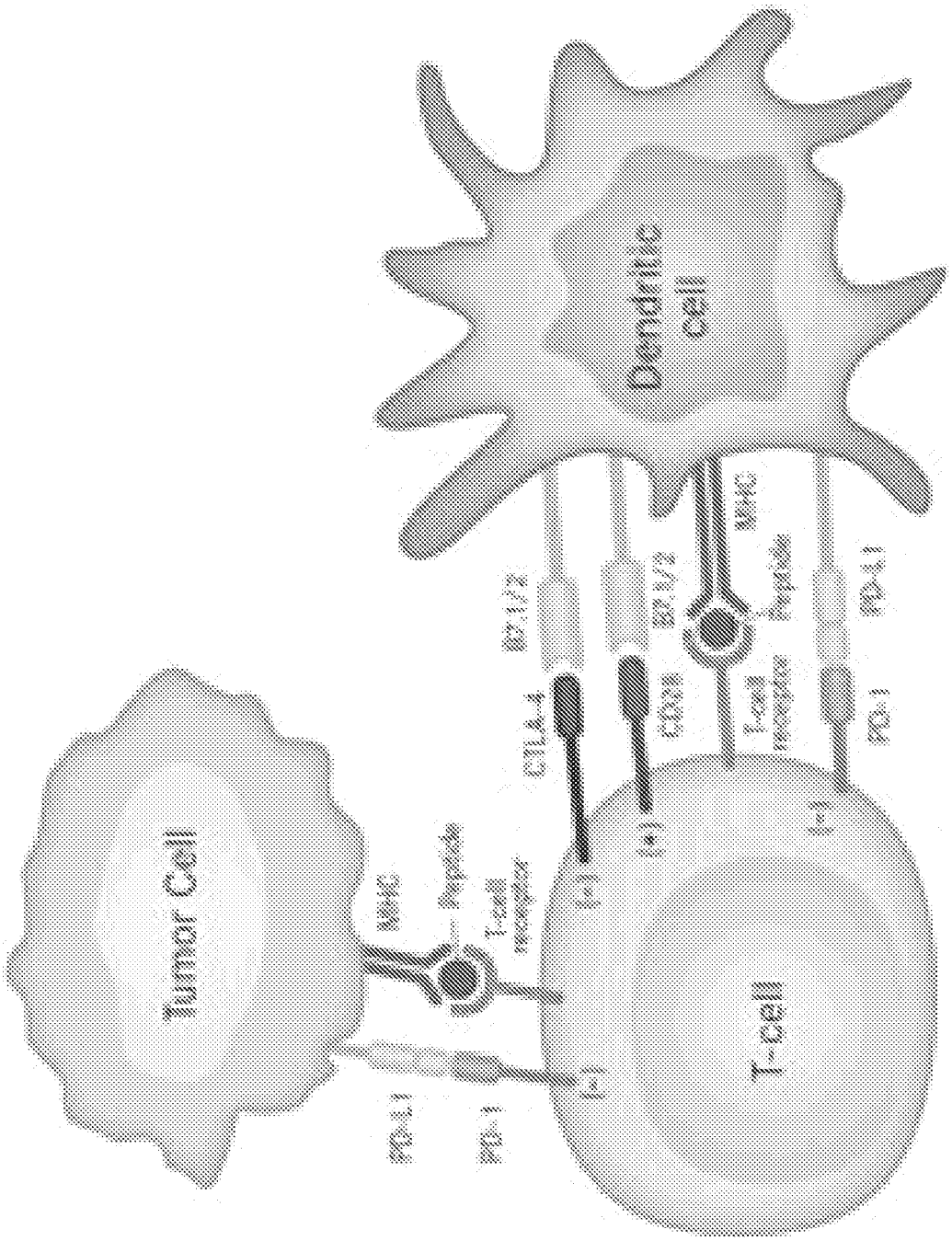

Tumor Cell
MHC
Peptide
T-cell receptor
PD-L1
PD-1
(-)
(-)
CTLA-4
B7.1/2
(+)
CD28
B7.1/2
MHC
Peptide
T-cell receptor
PD-L1
PD-1
(+)
(+)
Dendritic cell
T-cell

FIG. 23

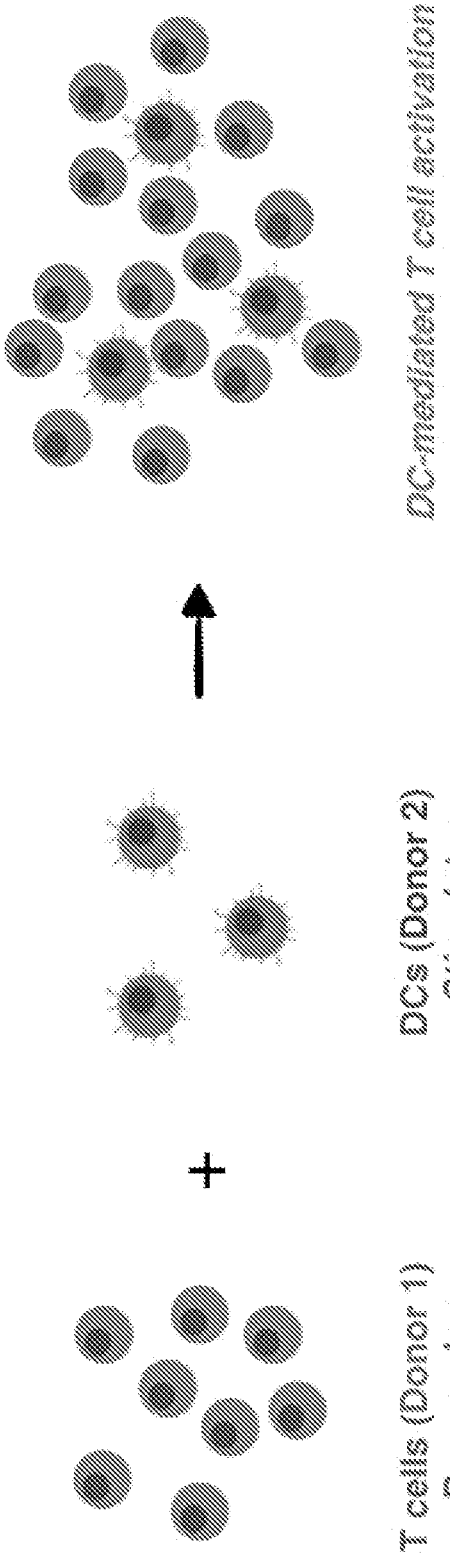

T cells (Donor 1)
Responder
DCs (Donor 2)
Stimulator
DC-mediated T cell activation

FIG. 24

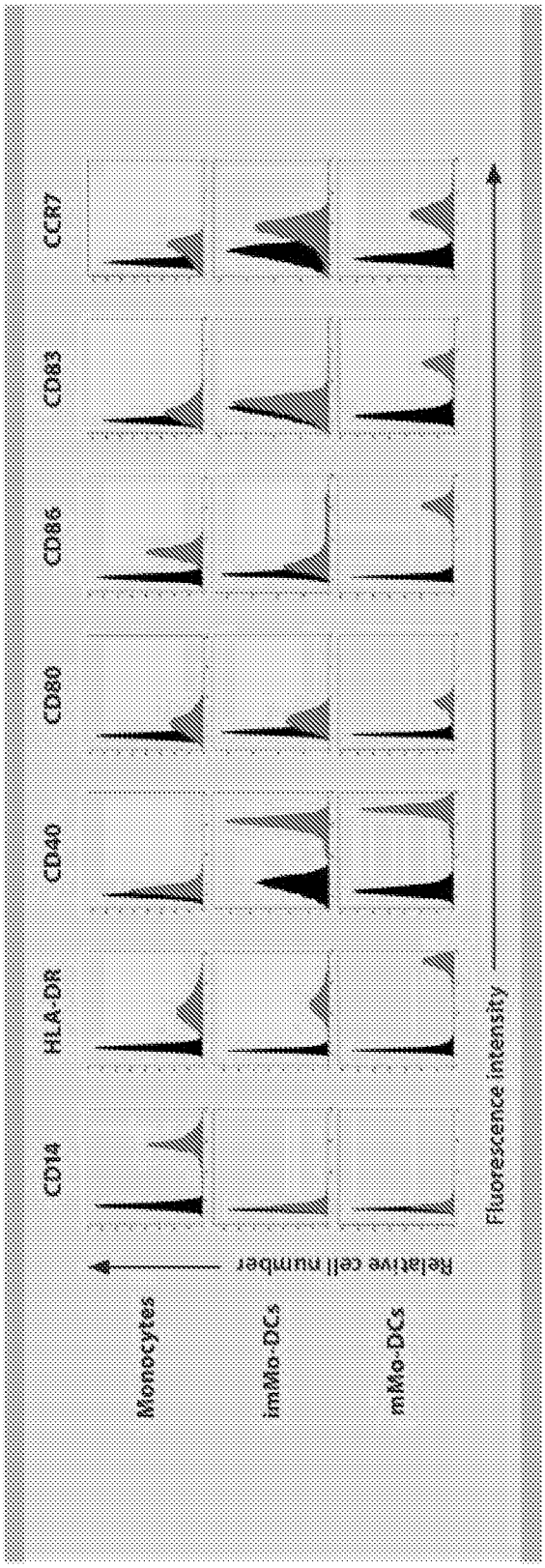

CD14
HLA-DR
CD40
CD80
CD86
CD83
CCR7
Monocytes
imMo-DCs
mMo-DCs
Relative cell number
Fluorescence intensity

FIG. 25

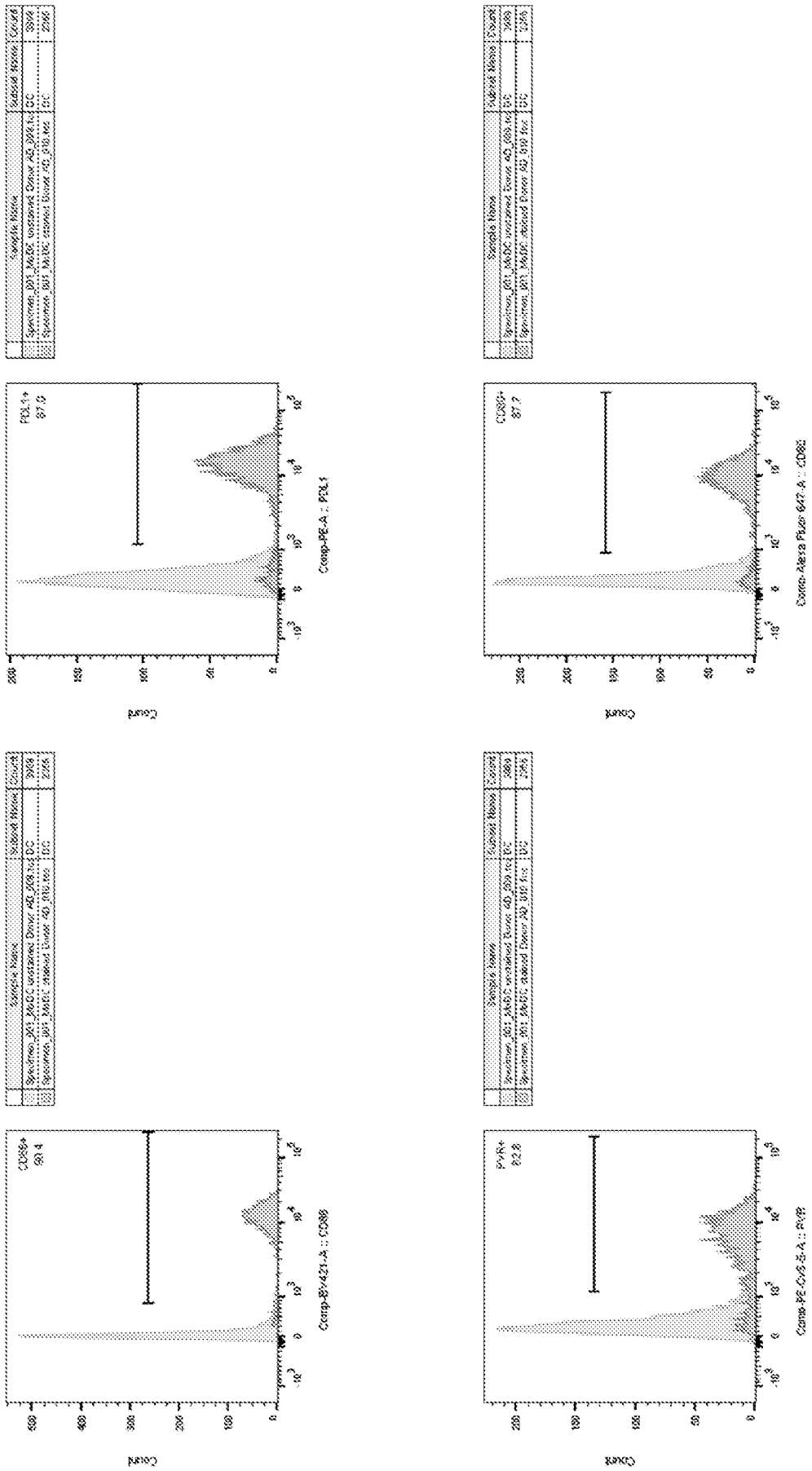


FIG. 26

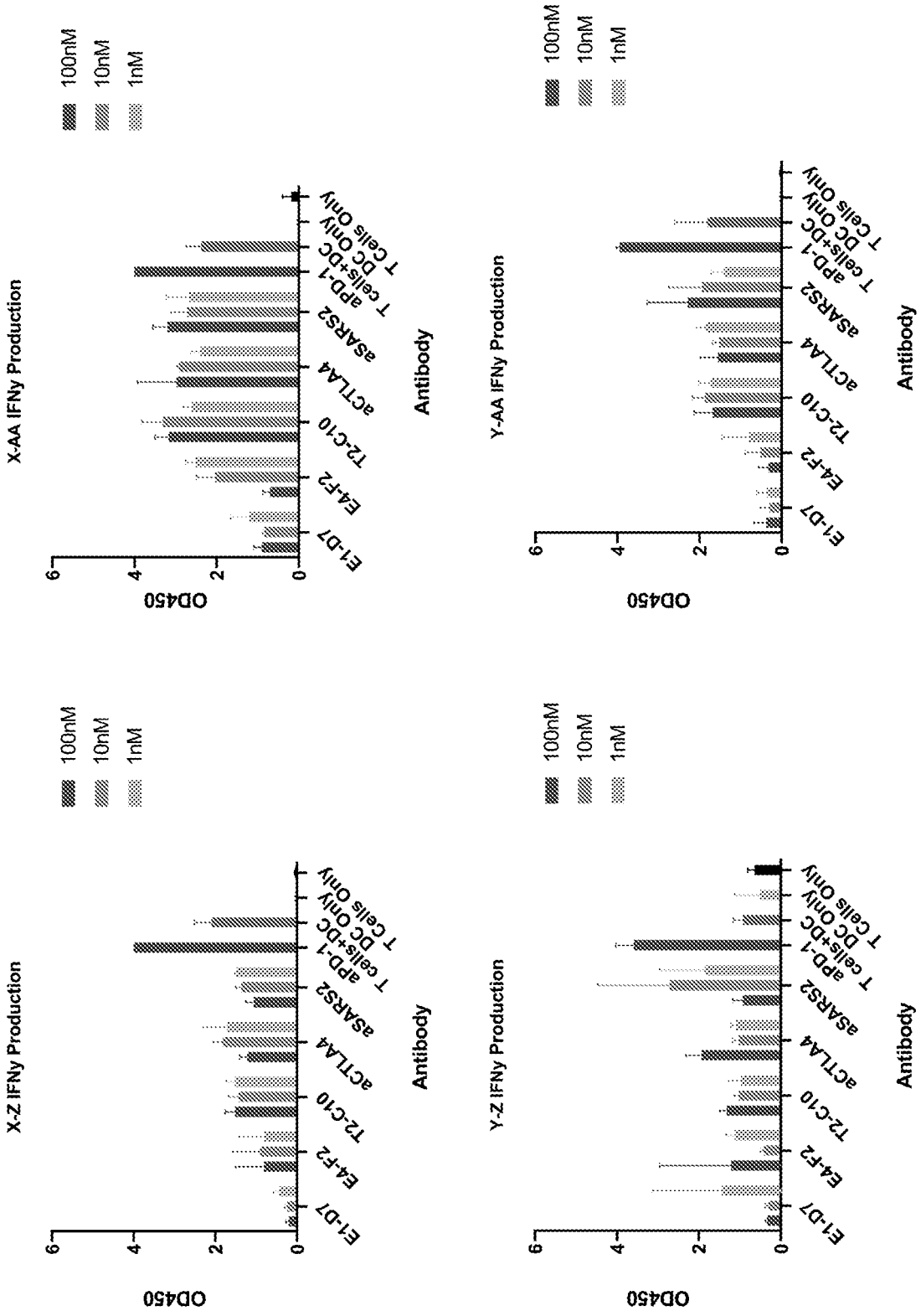

X-AA IFNy Production
100nM
10nM
1nM
OD450
0
2
4
6
E1-D7
E4-F2
T2-C10
aCTLA4
aSARS2
aPD-1
T cells+DC
DC Only
T Cells Only
Antibody
Y-AA IFNy Production
X-Z IFNy Production
Y-Z IFNy Production

FIG. 27

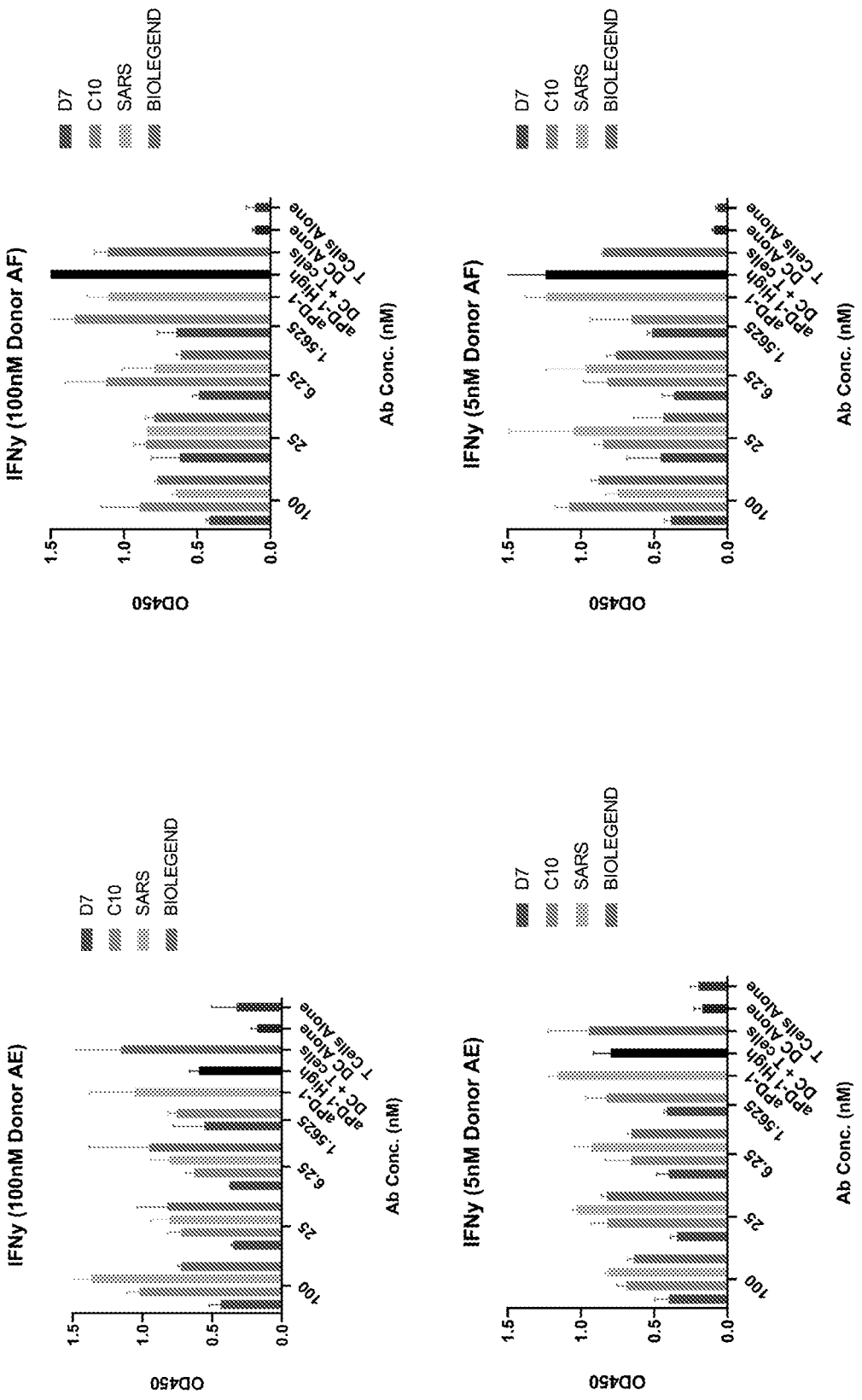
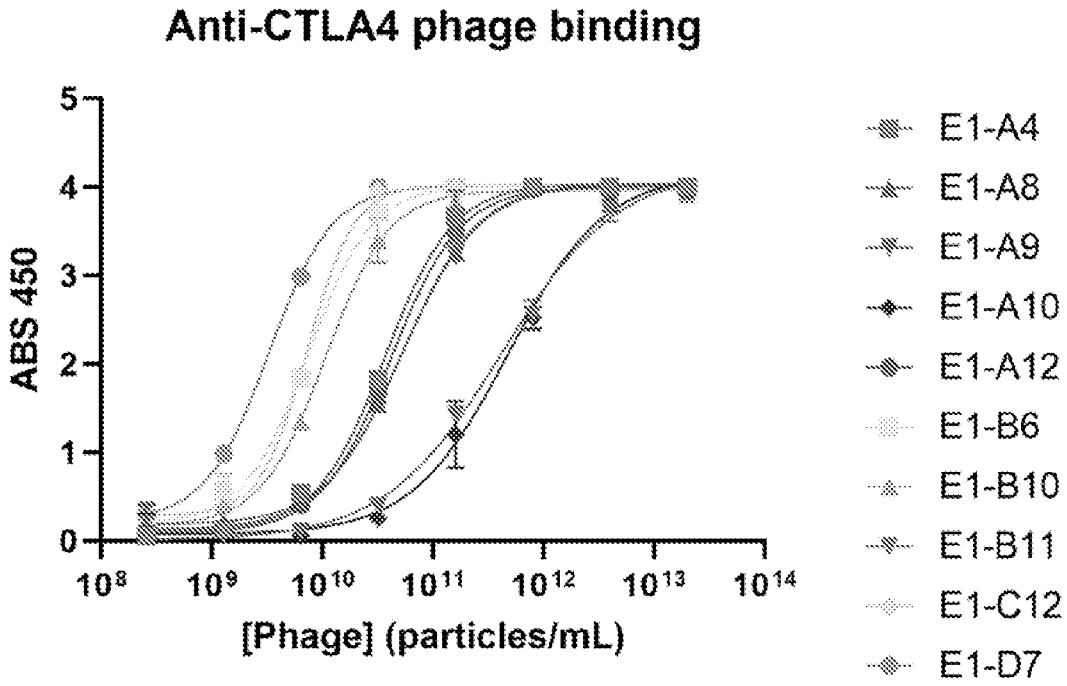

IFNy (100nM Donor AF)
IFNy (5nM Donor AF)
IFNy (100nM Donor AE)
IFNy (5nM Donor AE)
D7
C10
SARS
BIOLEGEND
OD450
Ab Conc. (nM)
100
25
6.25
1.5625
aPD-1
aPD-1 High DC + T cells
DC Alone
T Cells Alone

FIG. 28

Clone C9 tagged protein
Extracellular domain
Transmembrane domain
Intracellular domain
C9 epitope tag
Transient transfection to express membrane bound protein
Detergent based cell lysis
Capture tagged protein with anti-C9 functionalized magnetic bead
PMPL
Dialyze bead with captured protein into lipid mixture to form surrogate lipid bilayer

FIG. 29



Binding of unique clones from plate E1 were tested in an ELISA

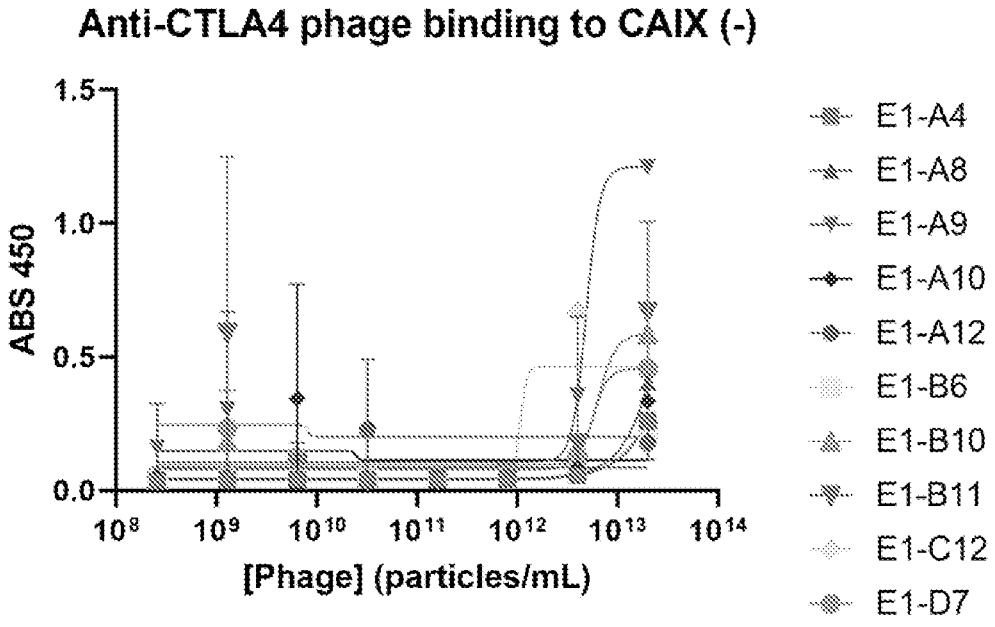


FIG. 30

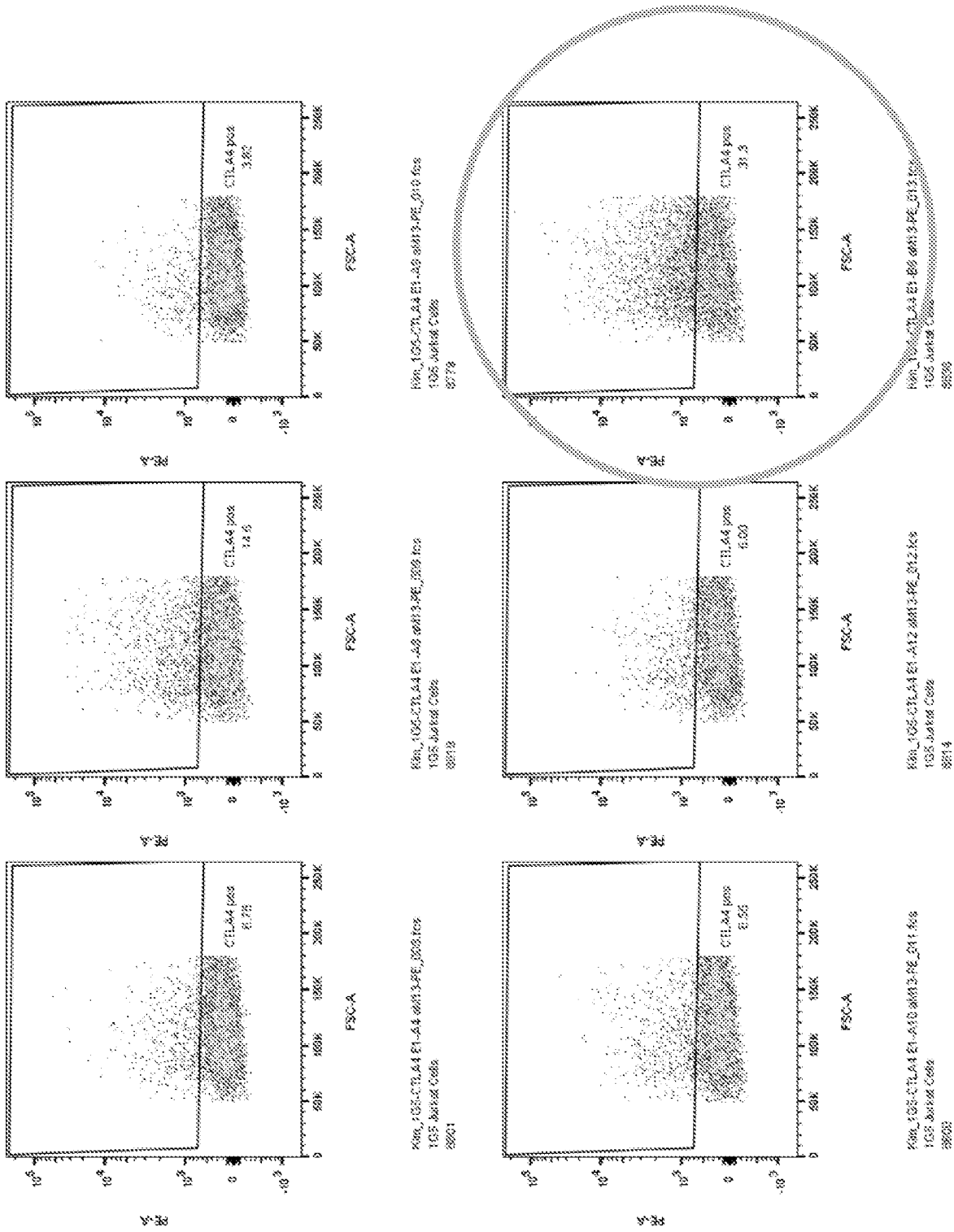


FIG. 31

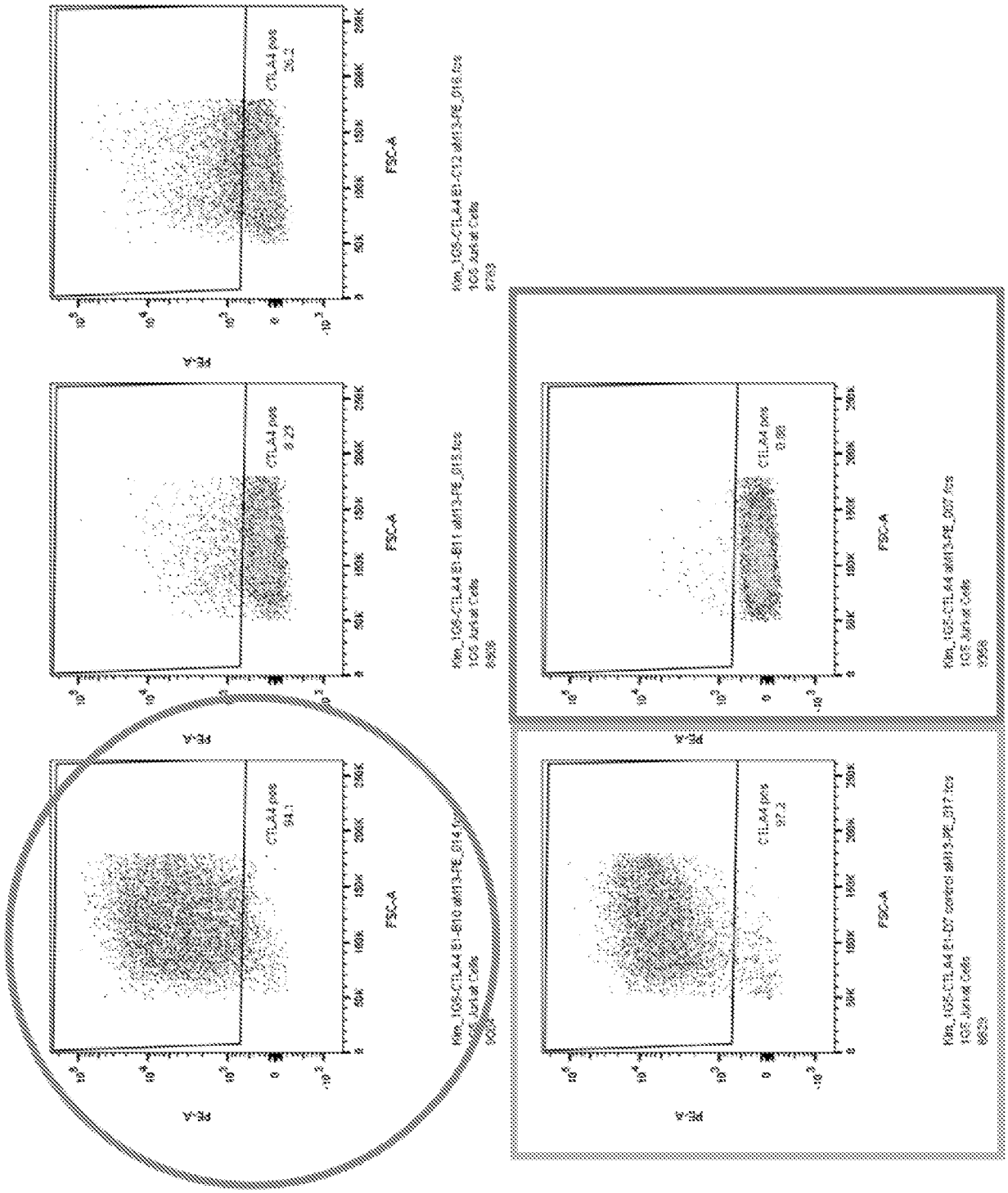


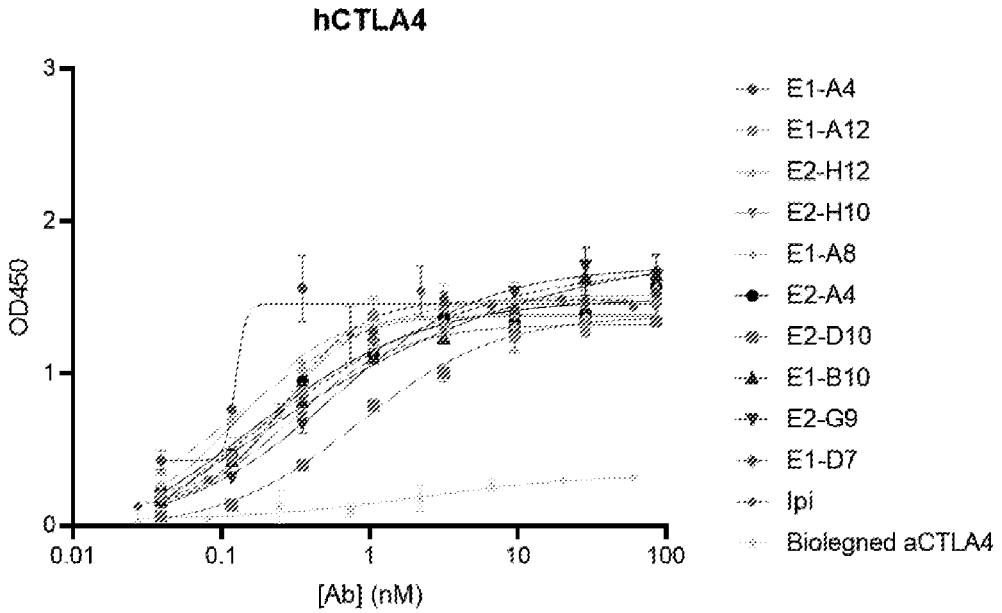
FIG. 31 (cont.)

Sample ID	Response when Loading at 2ug/mL	Response when Association time 30s
E2-H10	0.1429	0.1012
E1-A12	0.1338	0.1015
E1-A8	0.1269	0.052
E2-G9	0.1229	0.0759
maCD152 (commercial Ab)	0.1213	0.0758
E2-D10	0.1029	0.0786
E1-D7 (C)	0.1012	0.082
E2-A4	0.099	0.0505
E1-B10	0.0845	0.0677
E1-A4	0.0725	0.0615
E2-H12	0.0721	0.0617
E2-A10	0.0602	0.0418
E1-D7 (Purified)	0.0459	0.0365
E2-G5	0.0318	0.0365
E1-A9	0.0264	0.0286
E1-B11	0.023	0.0167
T2-C10 (C)	0.0223	0.0135
E1-B6	0.0107	0.009
E1-C12	0.0081	0.0095
CD80	0.0076	0.0096
E2-H2	0.0028	0.0006
E2-D11	0.0016	0.0026
E1-A10	-0.0003	-0.0017
E2-H5	-0.0032	-0.0008

Cutoff of 0.05 response at 30 sec was used as a cut off. Highlighted clones were re-expressed and purified for further characterization

FIG. 32

- Ranking of antibodies Based on Binding Affinity
  1) E2-G9
  2) E1-D7
  3) E1-B10
  4) E2-A4
  5) E2-H12
  6) E1-A4
  7) E1-A12
  8) E1-A8
  9) Ipilimumab
  10)E2-H10
  11)E2-D10
  12)Biolegend aCTLA4

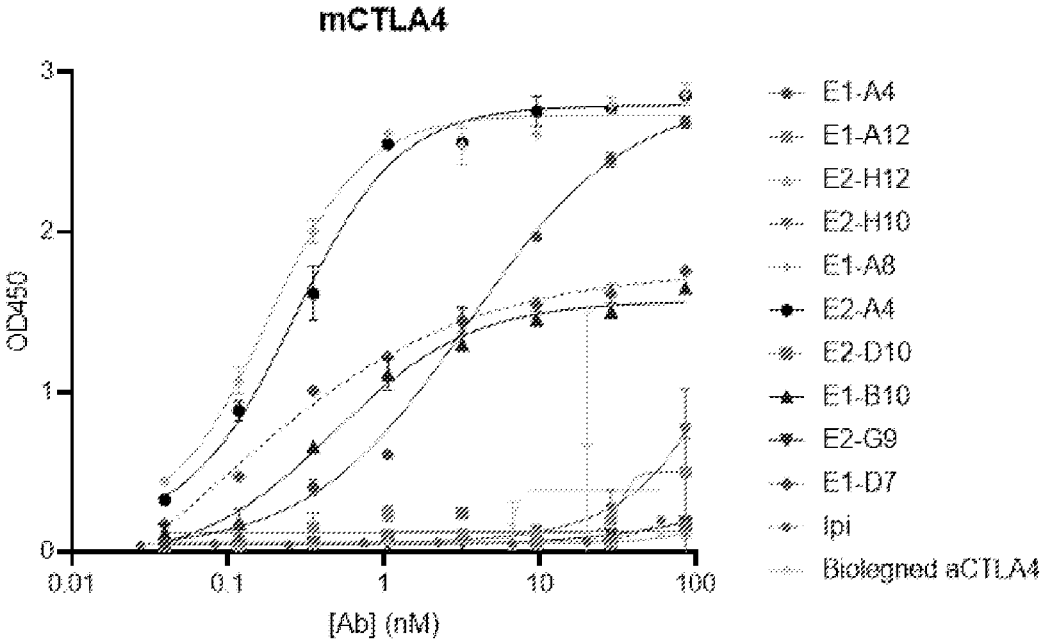


E1-A4 , E1-A8 and E2-G9 seem to have better saturation concentrations than other candidates (comparable to Ipilimumab)

BiolegendaCTLA4 shows very low binding affinity

FIG. 33

- Antibodies that show high Cross-Reactivity:
  - E1-A8
  - E2-A4
- Antibodies that show moderate levels of cross-reactivity:
  - E1-D7
  - E1-B10



- E1-D7 shows significant cross-reactivity with mouse CTLA4 consistent with Taylor's data
- Ipilimumab and BiolegendaCTLA4 show no cross-reactivity, consistent with literature
- E2-A4 and E1-B10 are derived from the same V gene and allele indicating they may be binding to the same epitope on CTLA4

FIG. 34

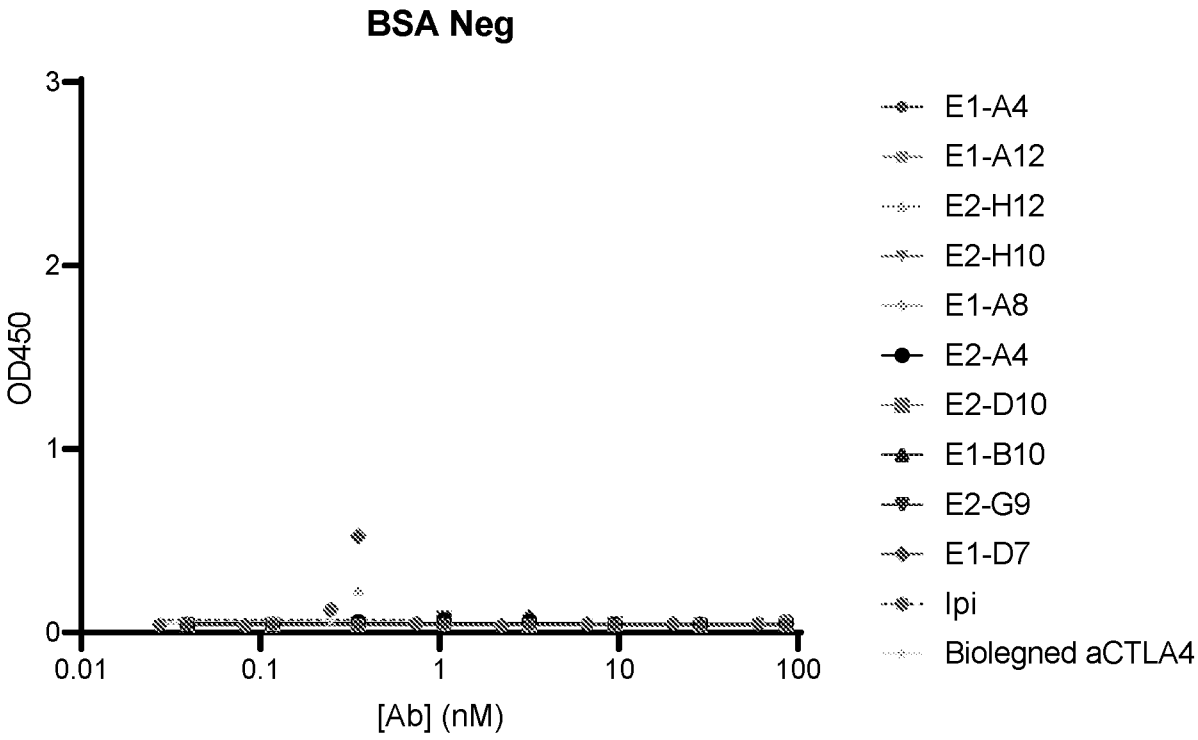

BSA Neg
OD450
3
2
1
0
0.01
0.1
1
10
100
[Ab] (nM)
E1-A4
E1-A12
E2-H12
E2-H10
E1-A8
E2-A4
E2-D10
E1-B10
E2-G9
E1-D7
Ipi
Biolegned aCTLA4

FIG. 35

	KD (M)	KD Error	Response (25nM)	Response (12.5 nM)	kon(1/Ms)	kdis(1/s)
E1-A4	3.92E-10	1.24E-11	0.76	0.43	6.29E+05	2.46E-04
E2-A4	1.25E-09	4.30E-11	0.76	0.41	6.88E+05	8.60E-04
E2-G9	1.02E-09	2.78E-11	0.71	0.45	1.09E+06	1.11E-03
E2-H12	1.26E-10	8.54E-12	0.69	0.39	5.39E+05	6.79E-05
E1-B10	3.83E-10	1.26E-11	0.64	0.35	5.02E+05	1.92E-04
E1-A8	1.31E-09	4.27E-11	0.64	0.34	5.59E+05	7.32E-04
E2-H10	2.15E-10	9.84E-12	0.63	0.34	4.75E+05	1.02E-04
E1-A12	1.98E-10	1.04E-11	0.61	0.30	4.22E+05	8.35E-05
Ipilimumab	<1.0E-12	1.11E-11	0.60	0.33	5.09E+05	<1.0E-07
E1-D7	3.56E-10	1.30E-11	0.59	0.32	4.83E+05	1.72E-04
E2-D10	2.94E-10	1.02E-11	0.45	0.24	5.41E+05	1.59E-04
Biolegend aCTLA4	<1.0E-12	2.59E-11	0.38	0.21	4.91E+05	<1.0E-07

FIG. 36

	Ab#	CD80	CD86	E1-D7	Ipilimumab	
	E1-A4	0.181	-0.061	0.072	0.214	
	E1-A12	0.150	-0.074	0.071	0.222	
	E1-B10	0.124	-0.053	0.054	0.166	
	E1-D7	0.095	-0.051	0.064	0.170	
	E1-A8	0.104	-0.033	0.021	0.082	
	E2-A4	0.133	-0.031	0.009	0.072	
	E2-D10	0.143	-0.089	0.110	0.315	
	E2-G9	0.107	-0.020	0.061	0.185	
	E2-H10	0.133	-0.070	0.074	0.211	
	E2-H12	0.177	-0.065	0.077	0.219	
	Ipilimumab	0.039	-0.030	0.000	0.015	
	T2-C10	0.186	-0.029	0.175	1.329	
	P8ST	0.885	0.259	0.922	1.266	

FIG. 37

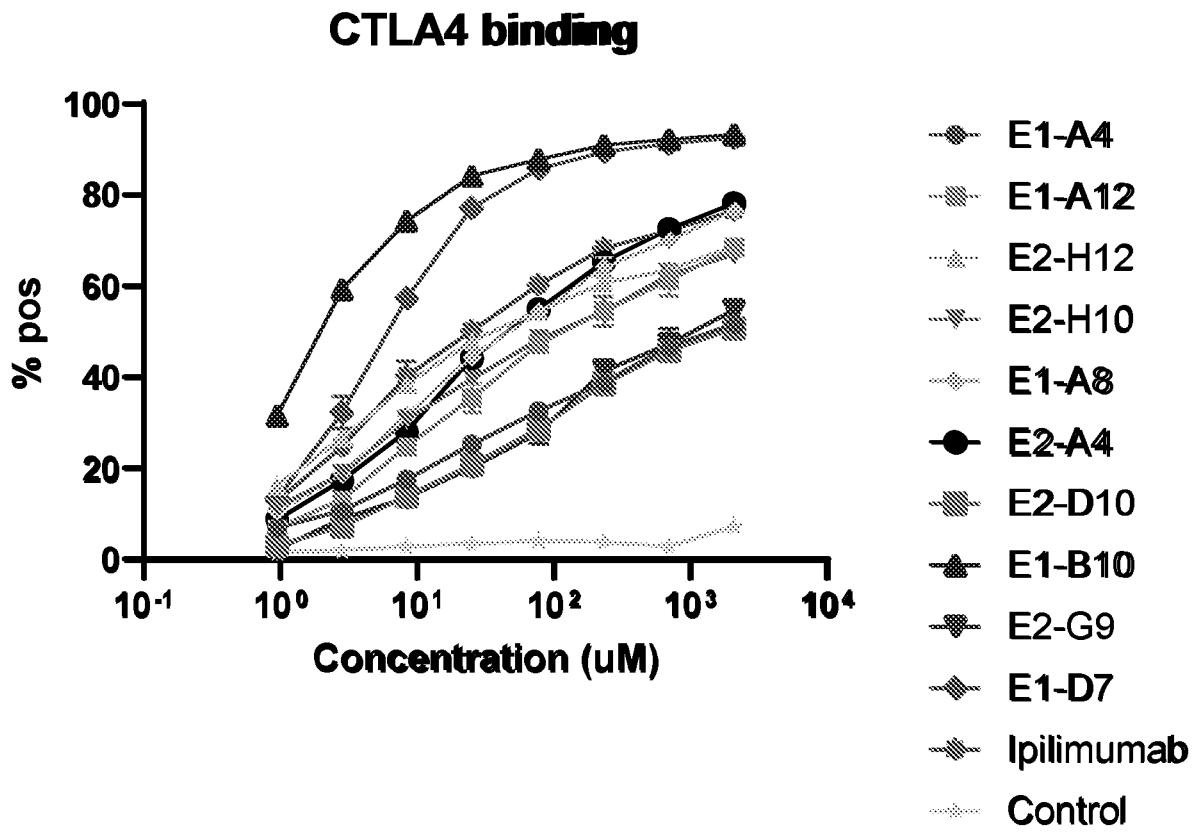

CTLA4 binding
% pos
100
80
60
40
20
0
10-1
100
101
102
103
104
Concentration (uM)
E1-A4
E1-A12
E2-H12
E2-H10
E1-A8
E2-A4
E2-D10
E1-B10
E2-G9
E1-D7
Ipilimumab
Control

FIG. 38

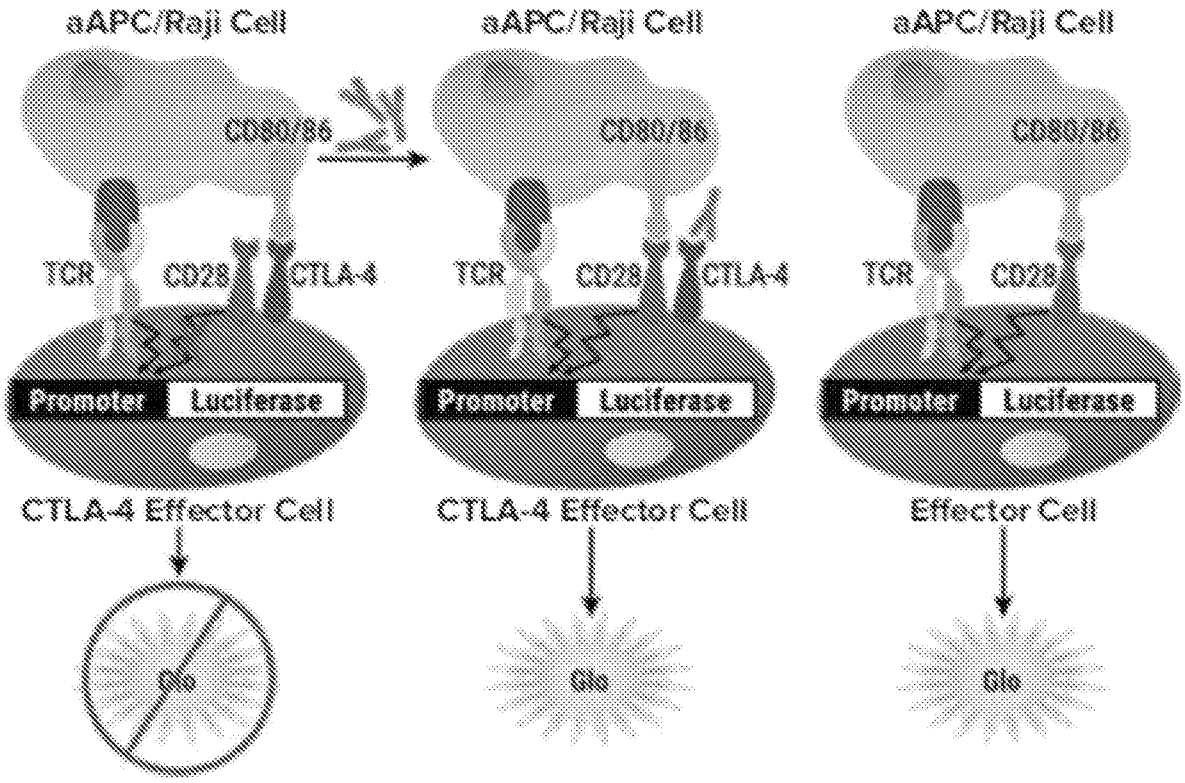

aAPC/Raji Cell
CD80/86
TCR
CD28
CTLA-4
Promoter
Luciferase
CTLA-4 Effector Cell
Glo
aAPC/Raji Cell
CD80/86
TCR
CD28
CTLA-4
Promoter
Luciferase
CTLA-4 Effector Cell
Glo
aAPC/Raji Cell
CD80/86
TCR
CD28
Promoter
Luciferase
Effector Cell
Glo

FIG. 39

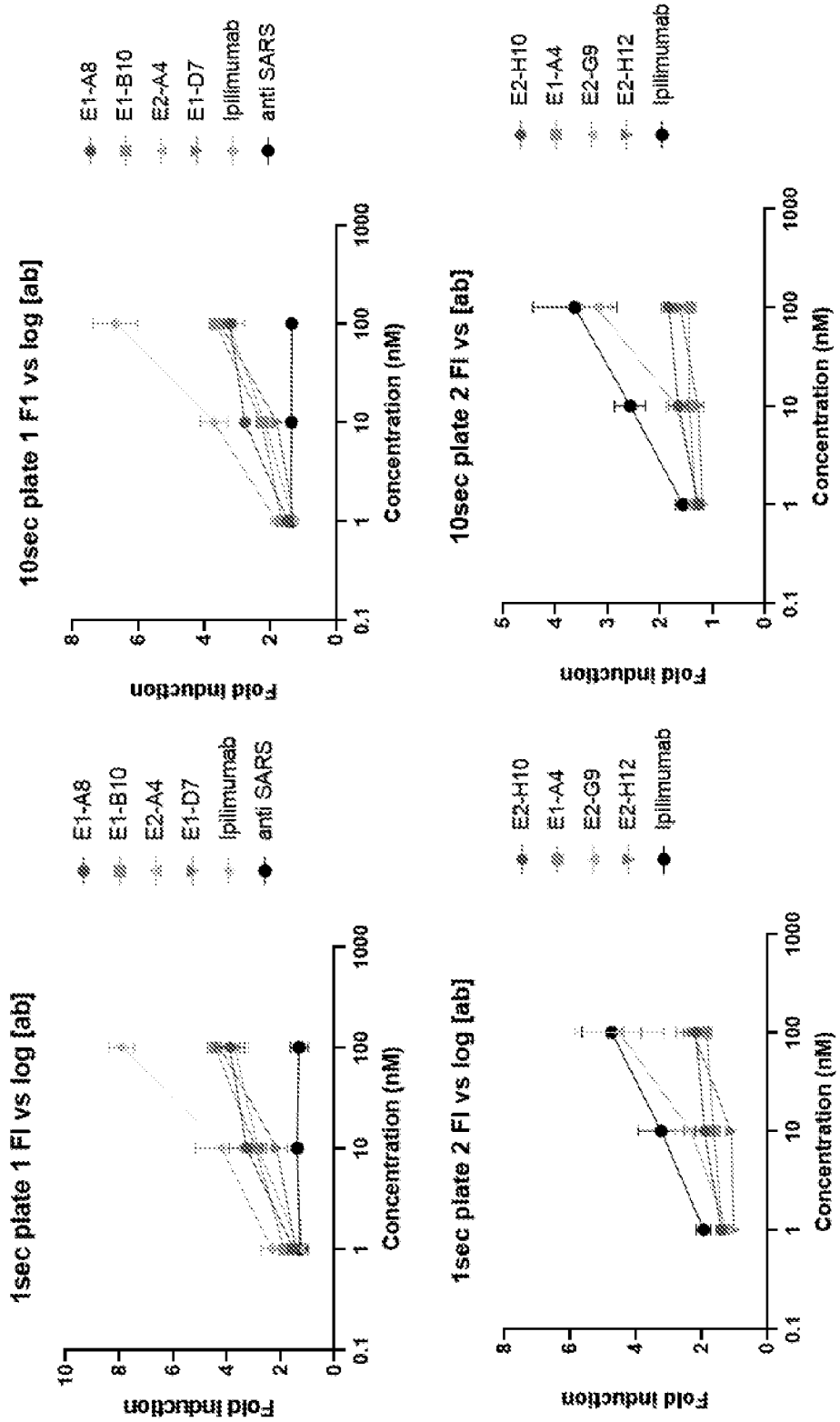

1sec plate 1 FI vs log [ab]
Fold Induction
Concentration (nM)
E1-A8
E1-B10
E2-A4
E1-D7
Ipilimumab
anti SARS
10sec plate 1 F1 vs log [ab]
Fold Induction
Concentration (nM)
E1-A8
E1-B10
E2-A4
E1-D7
Ipilimumab
anti SARS
1sec plate 2 FI vs log [ab]
Fold Induction
Concentration (nM)
E2-H10
E1-A4
E2-G9
E2-H12
Ipilimumab
10sec plate 2 FI vs [ab]
Fold Induction
Concentration (nM)
E2-H10
E1-A4
E2-G9
E2-H12
Ipilimumab

FIG. 40

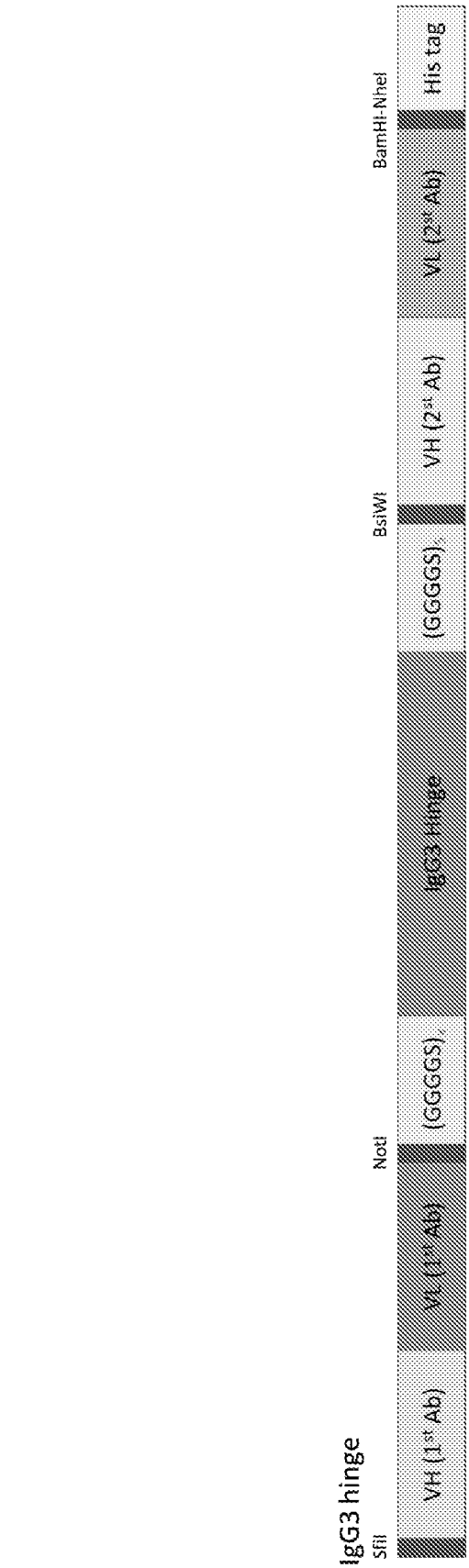

IgG3 hinge
SfiI
VH (1st Ab)
NotI
VL (1st Ab)
(GGGGS)
IgG3 Hinge
BsiWI
(GGGGS)
VH (2st Ab)
BamHI-NheI
VL (2st Ab)
His tag

FIG. 41

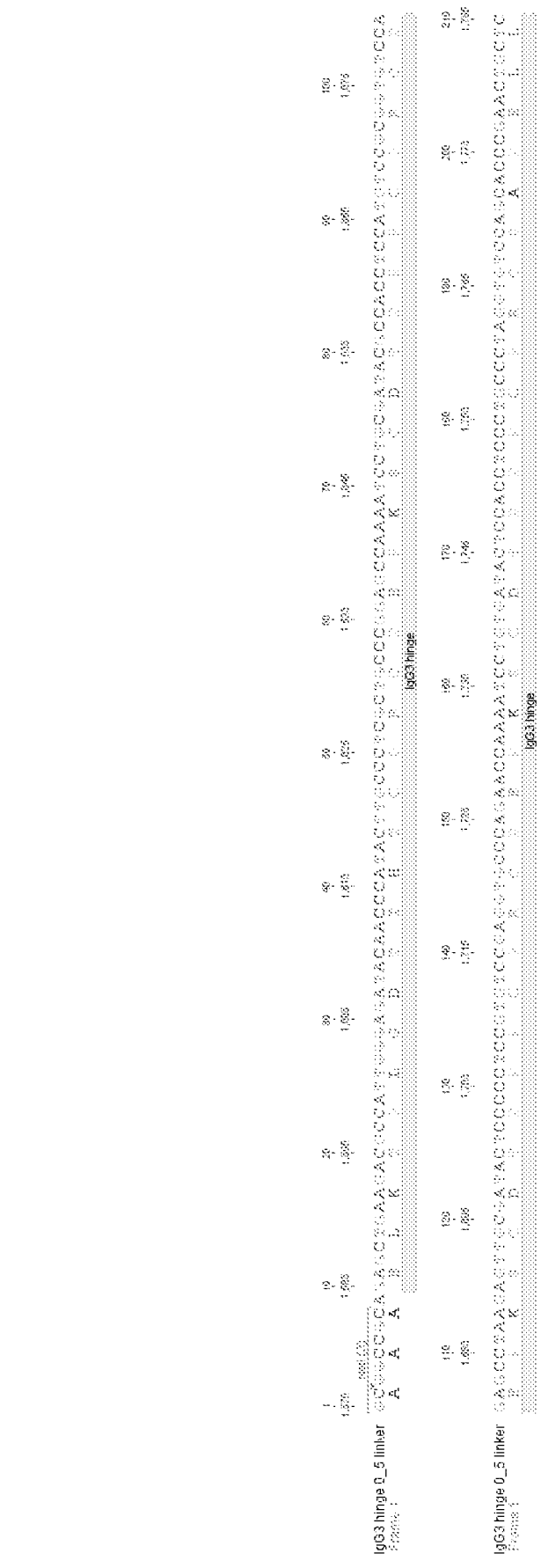


FIG. 42

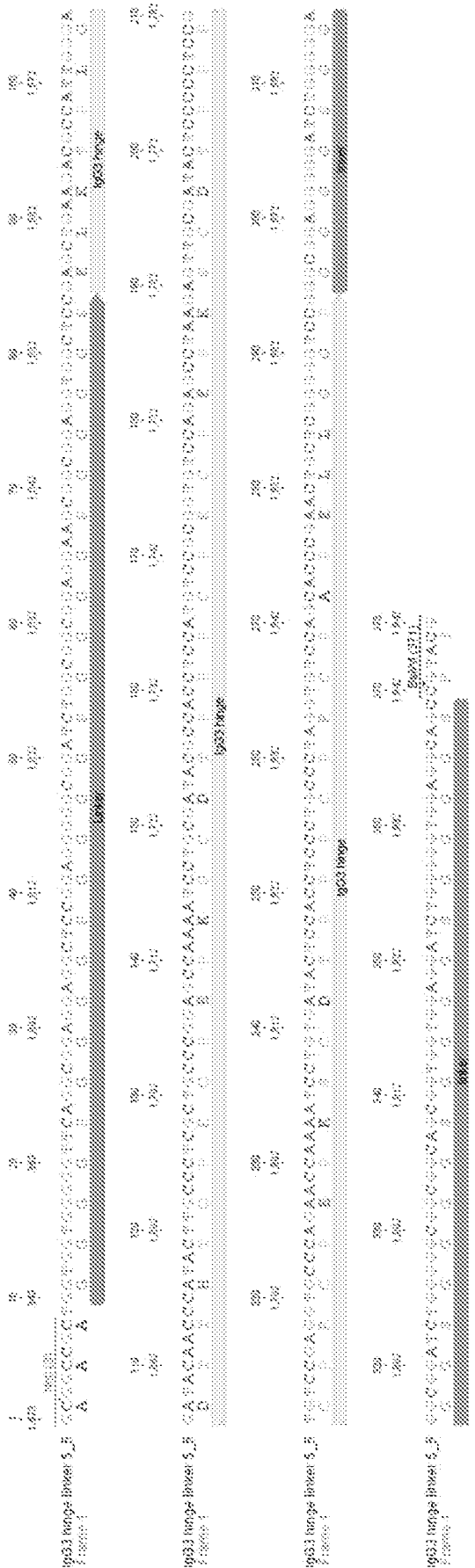


FIG. 42 (cont.)

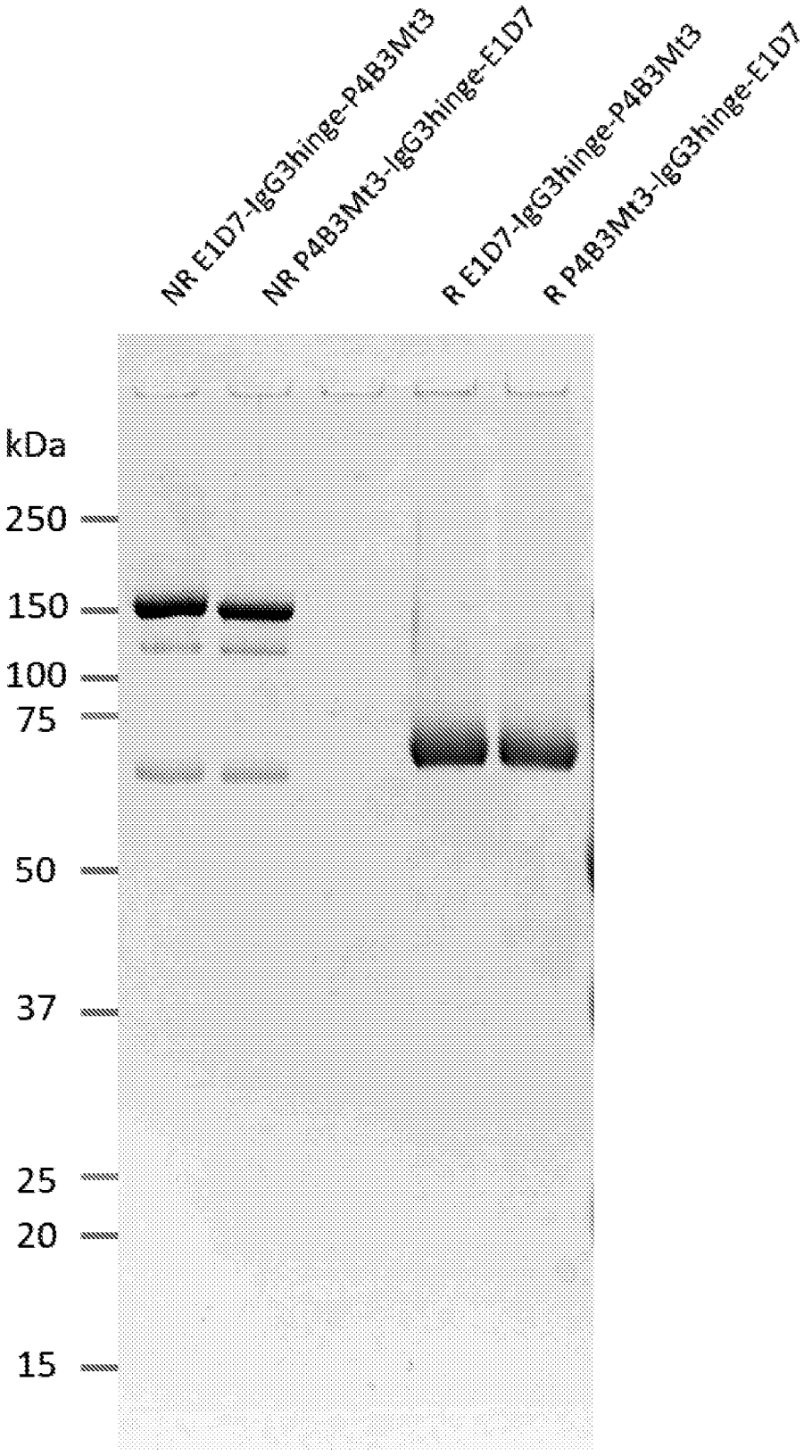

NR E1D7-IgG3hinge-P4B3Mt3
NR P4B3Mt3-IgG3hinge-E1D7
R E1D7-IgG3hinge-P4B3Mt3
R P4B3Mt3-IgG3hinge-E1D7
kDa
250
150
100
75
50
37
25
20
15

FIG. 43

CTLA4 biotin

Sample ID	Conc. (nM)	Response	KD (M)	kon(1/Ms)	kdis(1/s)
E1-D7 scFv-Fc	50	0.2902	6.21E-10	3.21E+06	1.99E-03
P4B3Mt3 scFv-Fc	50	-0.0097	-	-	-
P4B3Mt3 - IgG3 hinge - E1D7 linker (0,5)	50	0.2192	8.48E-10	1.43E+06	1.21E-03
P4B3Mt3 - IgG3 CH2 - E1D7 linker (0,5)	50	0.2939	4.11E-10	2.93E+06	1.20E-03
P4B3Mt3 - IgG3 hinge - E1D7 linker (5,5)	50	0.2291	8.84E-10	1.93E+06	1.71E-03
E1D7 - IgG3 hinge -P4B3Mt3 linker (5,5)	50	0.2585	4.53E-10	2.62E+06	1.19E-03

PD1 biotin

Sample ID	Conc. (nM)	Response	KD (M)	kon(1/Ms)	kdis(1/s)
E1-D7 scFv-Fc	50	0.0109	-	-	-
P4B3Mt3 scFv-Fc	50	1.183	<1.0E-12	3.96E+05	<1.0E-07
P4B3Mt3 - IgG3 hinge - E1D7 linker (0,5)	50	1.1275	<1.0E-12	2.47E+05	<1.0E-07
P4B3Mt3 - igG3 CH2 - E1D7 linker (0,5)	50	1.8981	<1.0E-12	6.70E+05	<1.0E-07
P4B3Mt3 - IgG3 hinge - E1D7 linker (5,5)	50	1.3714	<1.0E-12	3.48E+05	<1.0E-07
E1D7 - IgG3 hinge -P4B3Mt3 linker (5,5)	50	1.0476	<1.0E-12	3.64E+05	<1.0E-07

FIG. 44

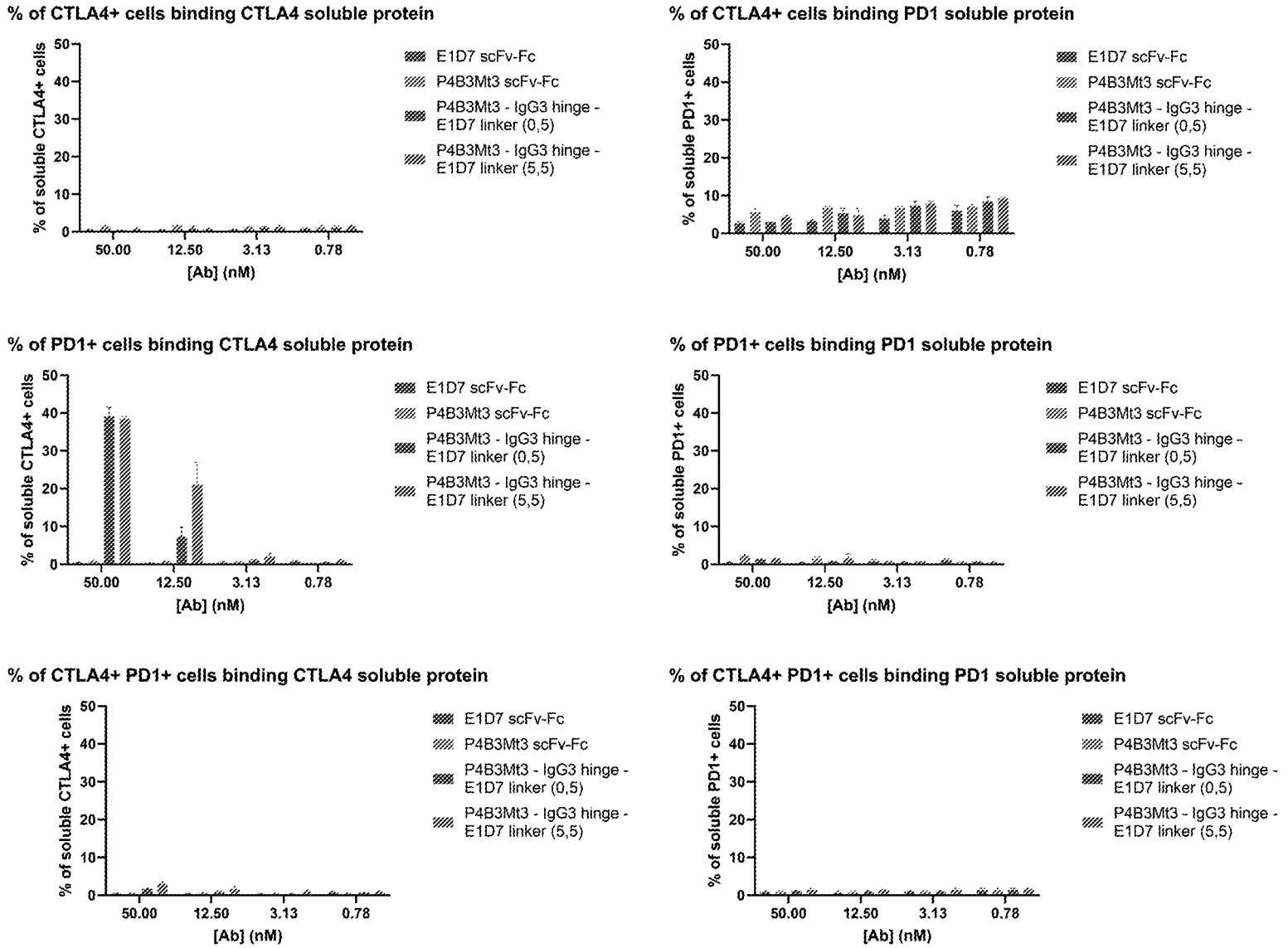

% of CTLA4+ cells binding CTLA4 soluble protein
% of soluble CTLA4+ cells
50
40
30
20
10
0
50.00
12.50
3.13
0.78
[Ab] (nM)
E1D7 scFv-Fc
P4B3Mt3 scFv-Fc
P4B3Mt3 - IgG3 hinge - E1D7 linker (0,5)
P4B3Mt3 - IgG3 hinge - E1D7 linker (5,5)
% of CTLA4+ cells binding PD1 soluble protein
% of soluble PD1+ cells
% of PD1+ cells binding CTLA4 soluble protein
% of PD1+ cells binding PD1 soluble protein
% of CTLA4+ PD1+ cells binding CTLA4 soluble protein
% of CTLA4+ PD1+ cells binding PD1 soluble protein

FIG. 45

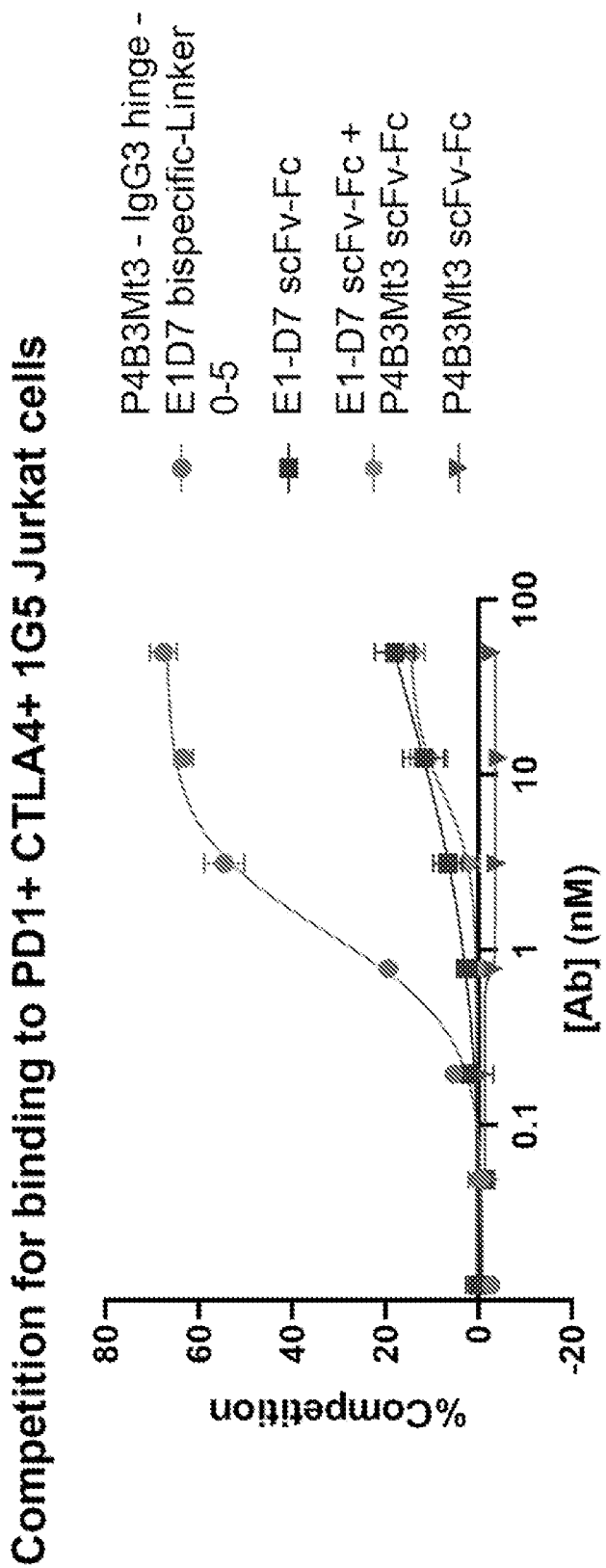

Competition for binding to PD1+ CTLA4+ 1G5 Jurkat cells
P4B3Mt3 - IgG3 hinge - E1D7 bispecific-Linker 0-5
E1-D7 scFv-Fc
E1-D7 scFv-Fc + P4B3Mt3 scFv-Fc
P4B3Mt3 scFv-Fc
%Competition
80
60
40
20
0
-20
0.1
1
10
100
[Ab] (nM)

FIG. 46

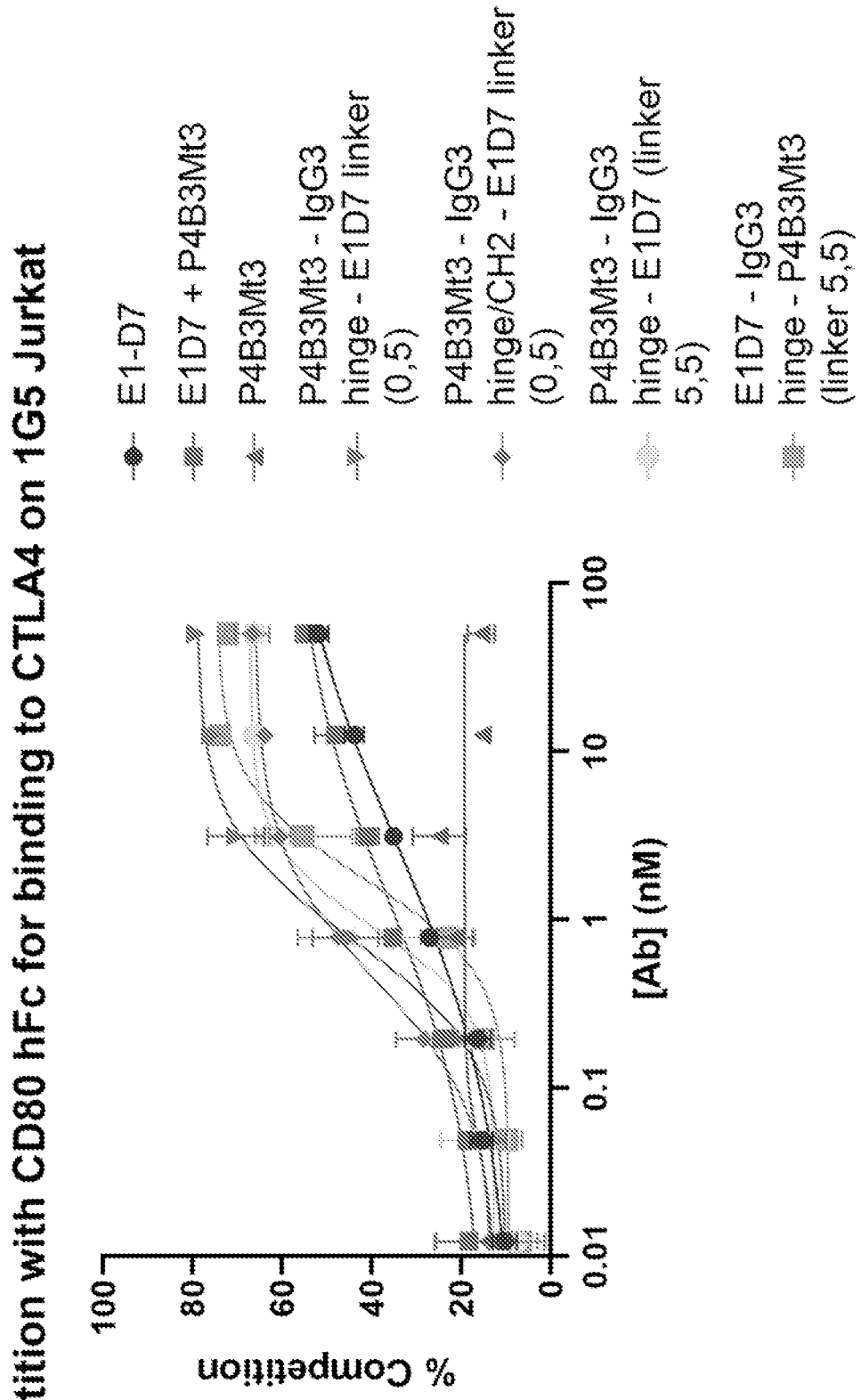

% Competition with CD80 hFc for binding to CTLA4 on 1G5 Jurkat
% Competition
100
80
60
40
20
0
0.01
0.1
1
10
100
[Ab] (nM)
E1-D7
E1D7 + P4B3Mt3
P4B3Mt3
P4B3Mt3 - IgG3 hinge - E1D7 linker (0,5)
P4B3Mt3 - IgG3 hinge/CH2 - E1D7 linker (0,5)
P4B3Mt3 - IgG3 hinge - E1D7 (linker 5,5)
E1D7 - IgG3 hinge - P4B3Mt3 (linker 5,5)

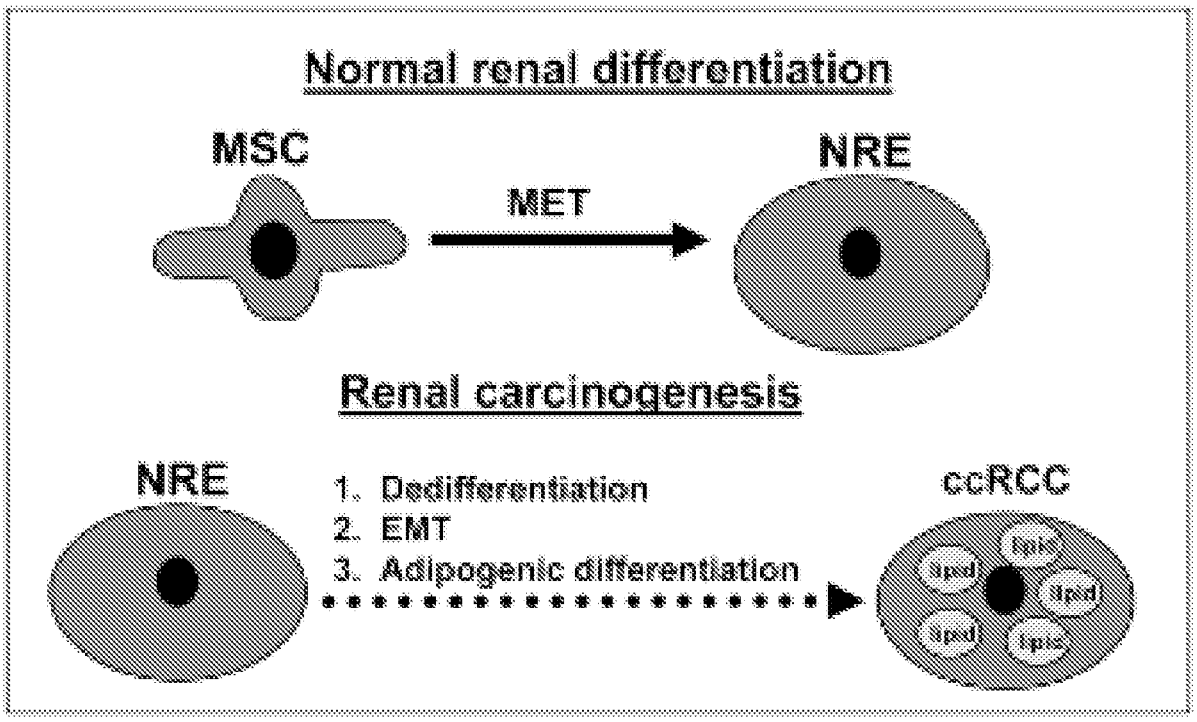
FIG. 47

A.

Tumor types	ccRCC
Morphology	
Incidence (%)	75%
Involved genes	3p loss (>90%) • *VHL* (52-90%) • *PBRM1* (33-41%) • *SETD2* (11%) • *BAP1* (10%) Others
Average Age	64 years

FIG. 48

B.



C.

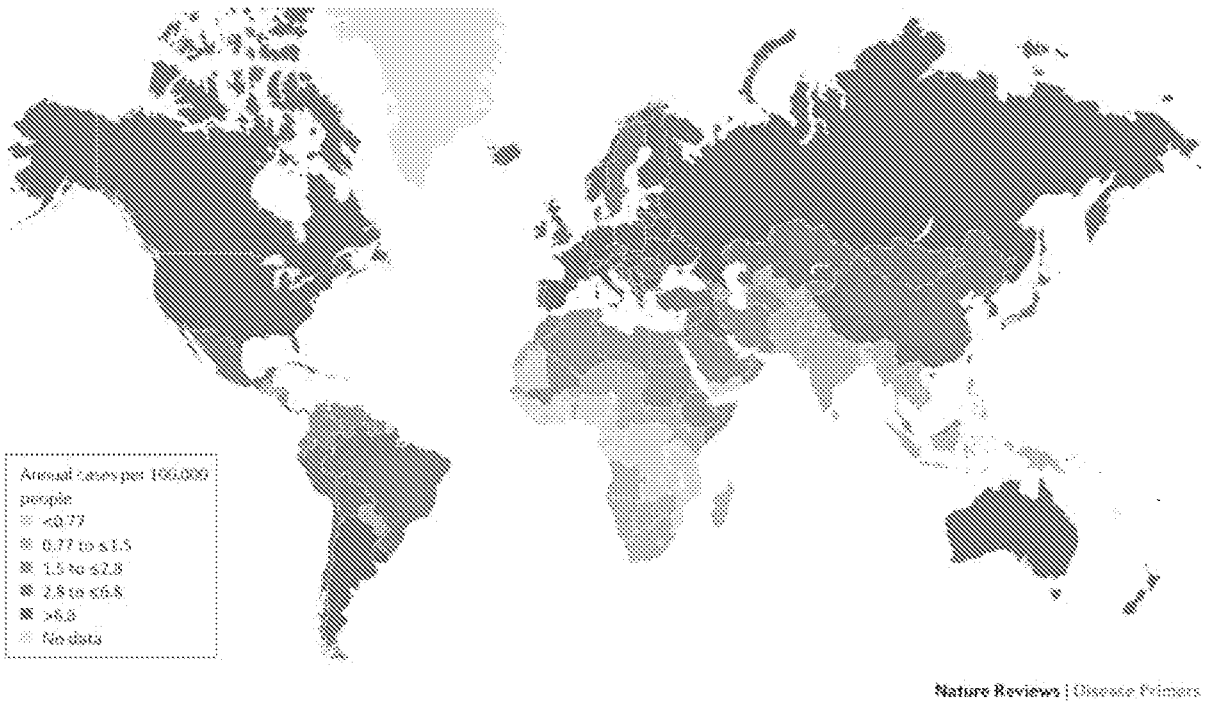


FIG. 48 (cont.)

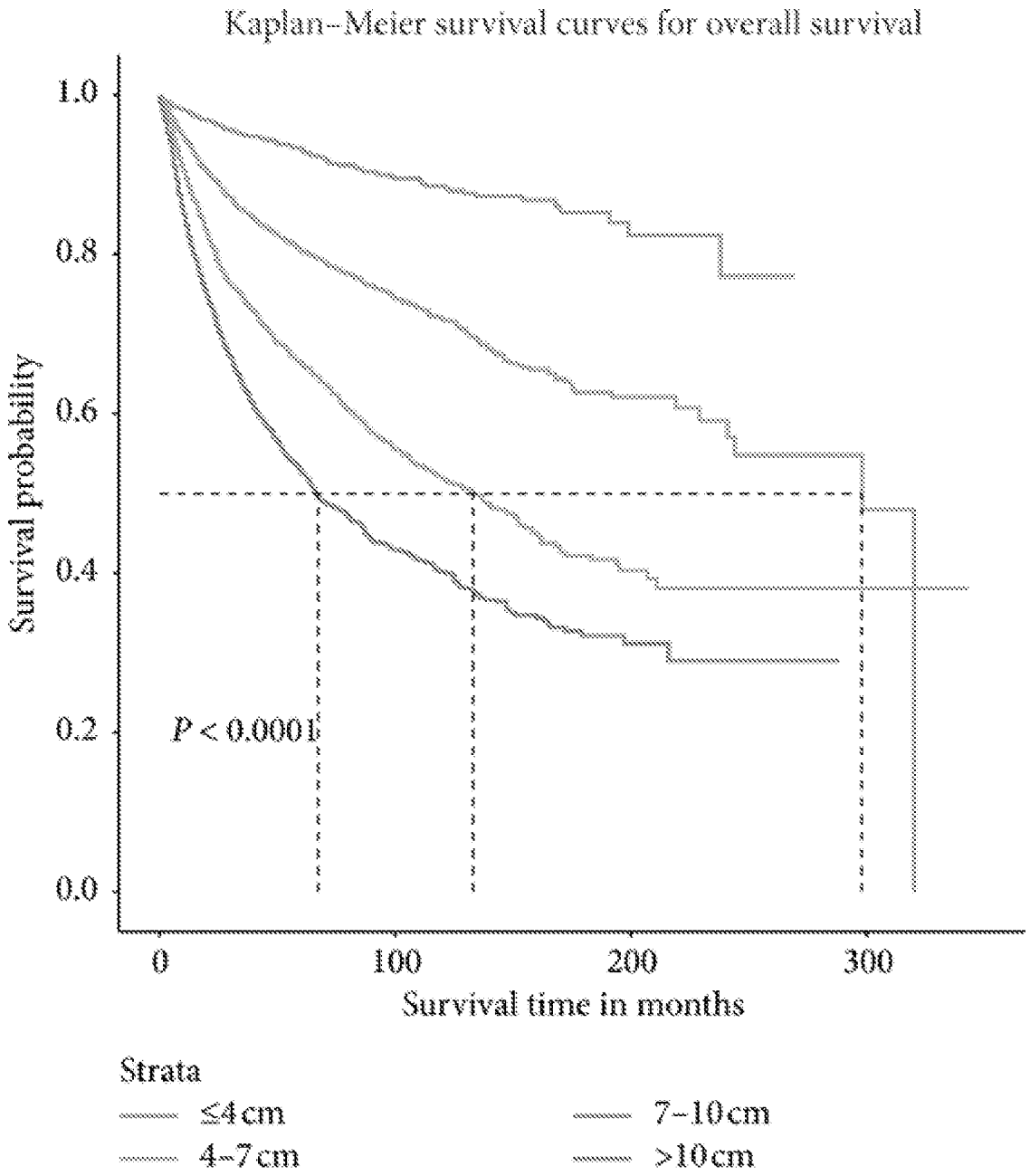

Kaplan–Meier survival curves for overall survival
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
P < 0.0001
0
100
200
300
Survival time in months
Strata
≤4cm
4–7cm
7–10cm
>10cm

FIG. 49

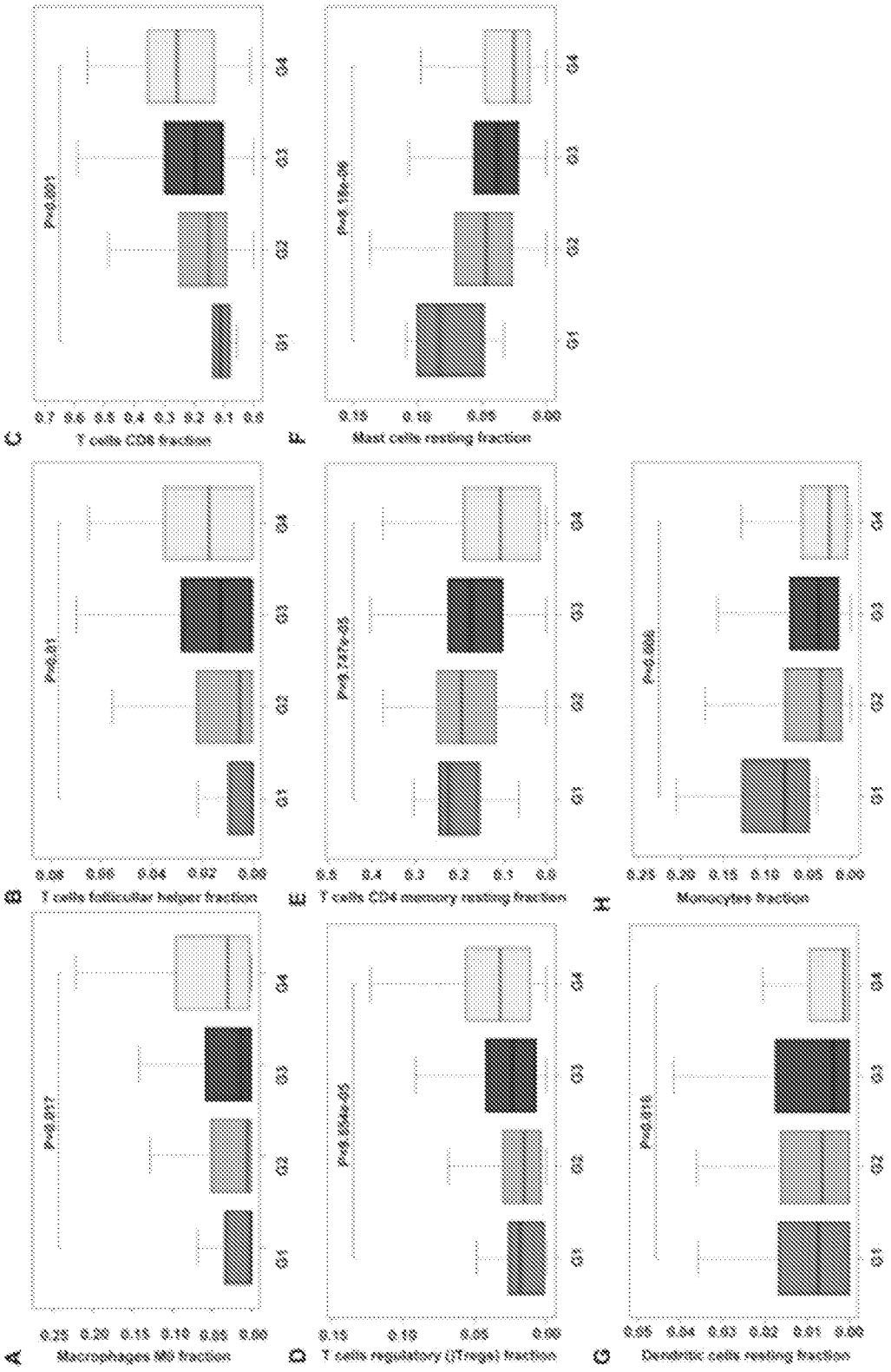

C
T cells CD8 fraction
P=0.0001
0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
F
Mast cells resting fraction
P=0.19e-06
0.15 0.10 0.05 0.00
B
T cells follicular helper fraction
P=0.01
0.08 0.06 0.04 0.02 0.00
E
T cells CD4 memory resting fraction
P=0.787e-05
0.5 0.4 0.3 0.2 0.1 0.0
H
Monocytes fraction
P=0.008
0.25 0.20 0.15 0.10 0.05 0.00
A
Macrophages M0 fraction
P=0.017
0.25 0.20 0.15 0.10 0.05 0.00
D
T cells regulatory (Tregs) fraction
P=5.93e-05
0.15 0.10 0.05 0.00
G
Dendritic cells resting fraction
P=0.016
0.05 0.04 0.03 0.02 0.01 0.00
G4
G3
G2
G1

FIG. 50

A.

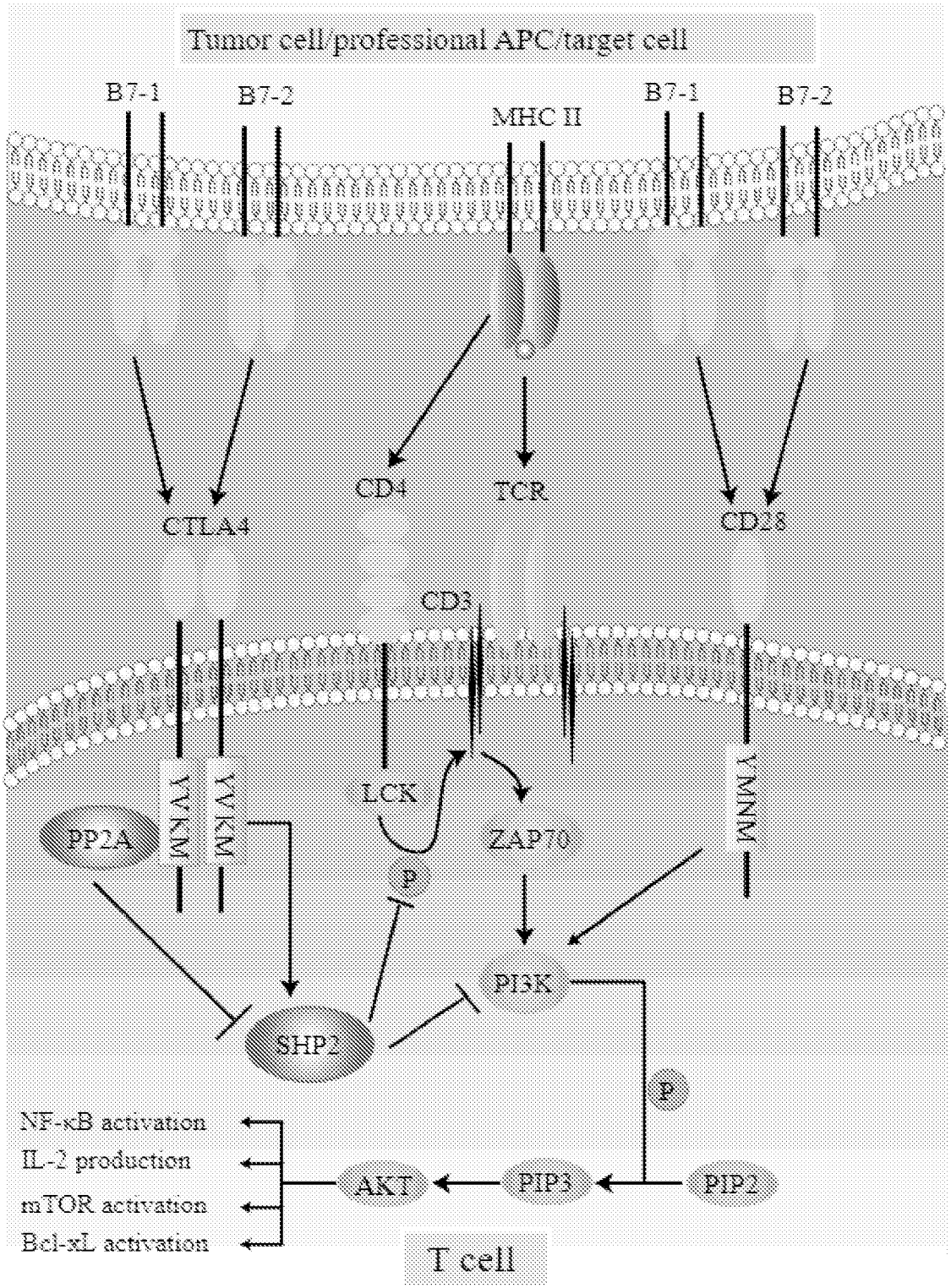

Tumor cell/professional APC/target cell
B7-1
B7-2
MHC II
B7-1
B7-2
CTLA4
CD4
TCR
CD28
CD3
YXXM
YXXM
LCK
ZAP70
YMNM
PP2A
P
PI3K
SHP2
P
NF-κB activation
IL-2 production
mTOR activation
Bcl-xL activation
AKT
PIP3
PIP2
T cell

FIG. 51

B.

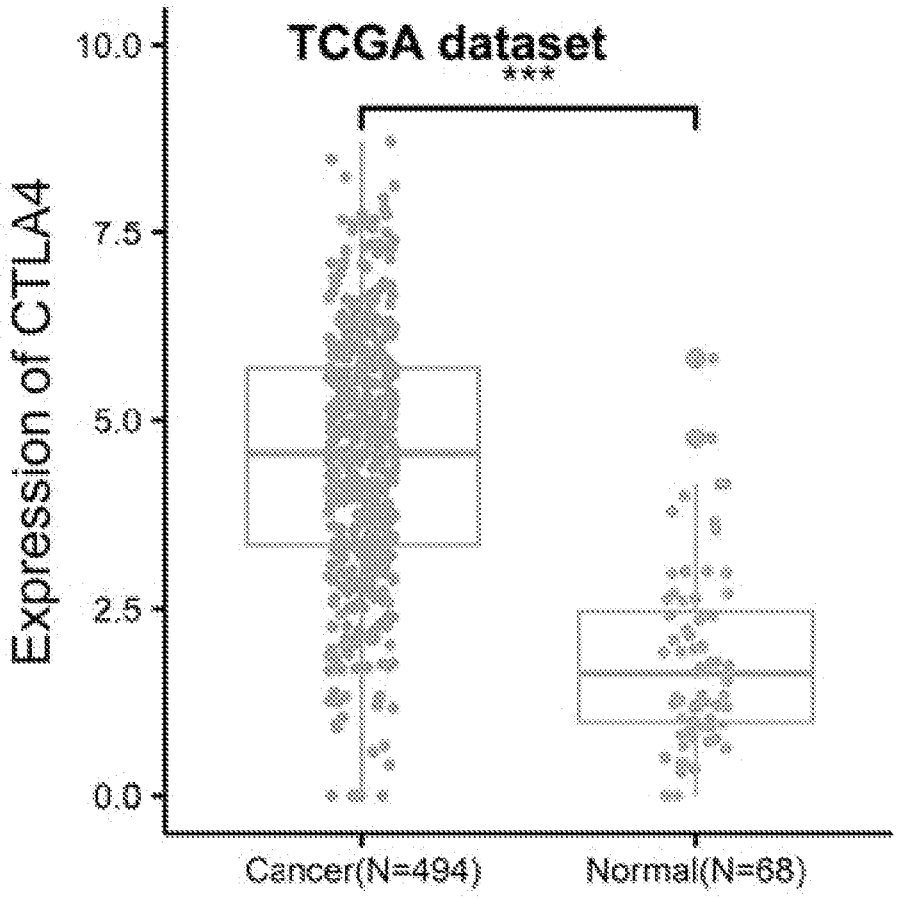

TCGA dataset
***
Expression of CTLA4
10.0
7.5
5.0
2.5
0.0
Cancer(N=494)
Normal(N=68)

FIG. 51 (cont)

C

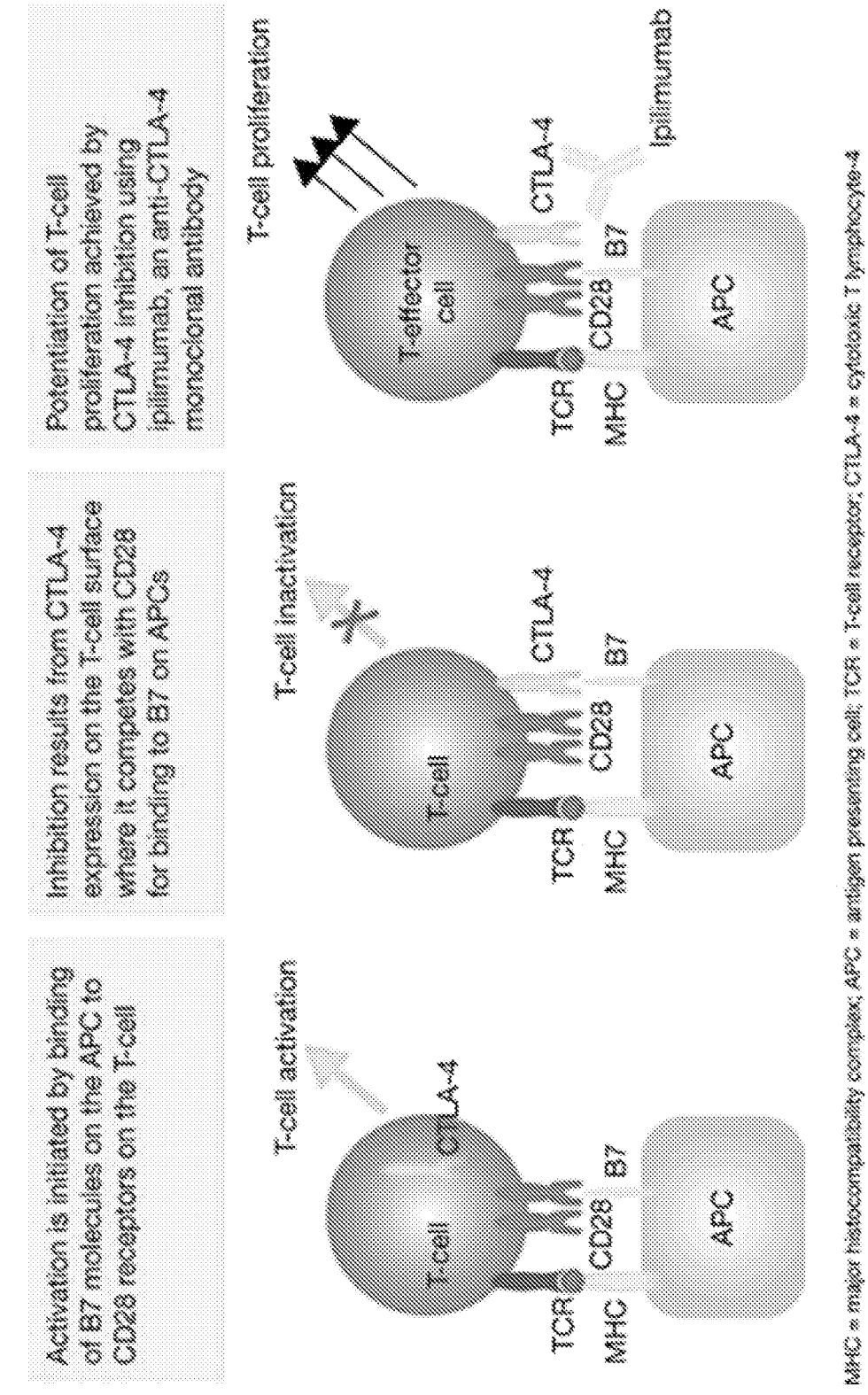

Activation is initiated by binding of B7 molecules on the APC to CD28 receptors on the T-cell
Inhibition results from CTLA-4 expression on the T-cell surface where it competes with CD28 for binding to B7 on APCs
Potentiation of T-cell proliferation achieved by CTLA-4 inhibition using ipilimumab, an anti-CTLA-4 monoclonal antibody
T-cell activation
T-cell inactivation
T-cell proliferation
T-cell
T-effector cell
CTLA-4
TCR
CD28
B7
MHC
APC
Ipilimumab
MHC = major histocompatibility complex; APC = antigen presenting cell; TCR = T-cell receptor; CTLA-4 = cytotoxic T lymphocyte-4

FIG. 51 (cont)

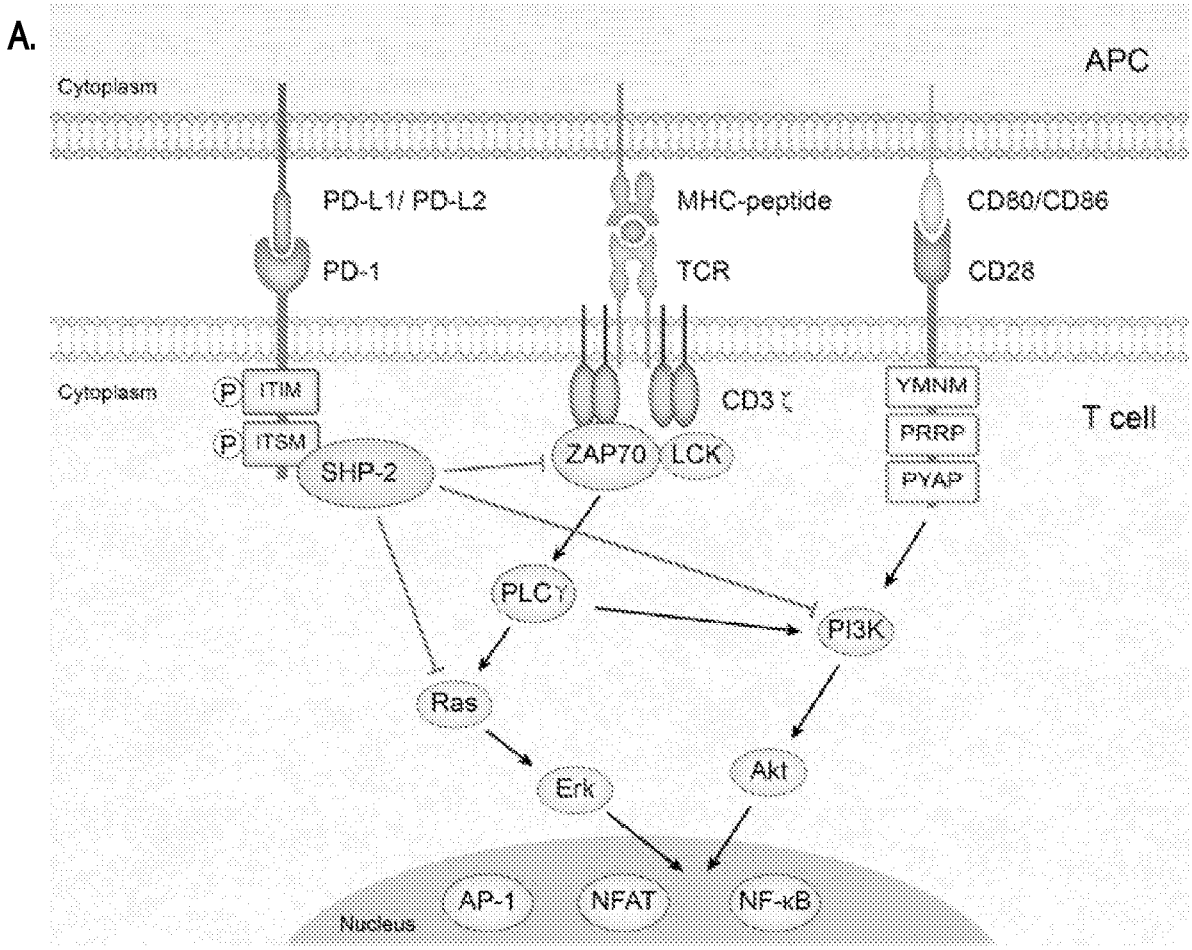
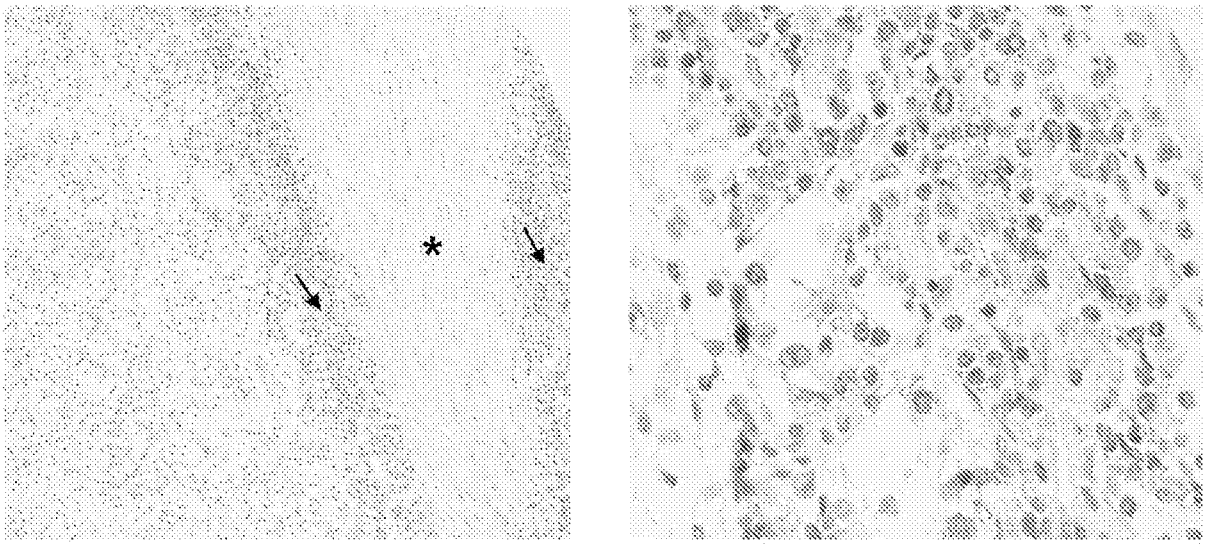

A.
APC
Cytoplasm
PD-L1/ PD-L2
PD-1
MHC-peptide
TCR
CD80/CD86
CD28
Cytoplasm
P ITIM
P ITSM
SHP-2
ZAP70
LCK
CD3 ζ
YMNM
PRRP
PYAP
T cell
PLCγ
PI3K
Ras
Erk
Akt
Nucleus
AP-1
NFAT
NF-κB

FIG. 52

B.



C.

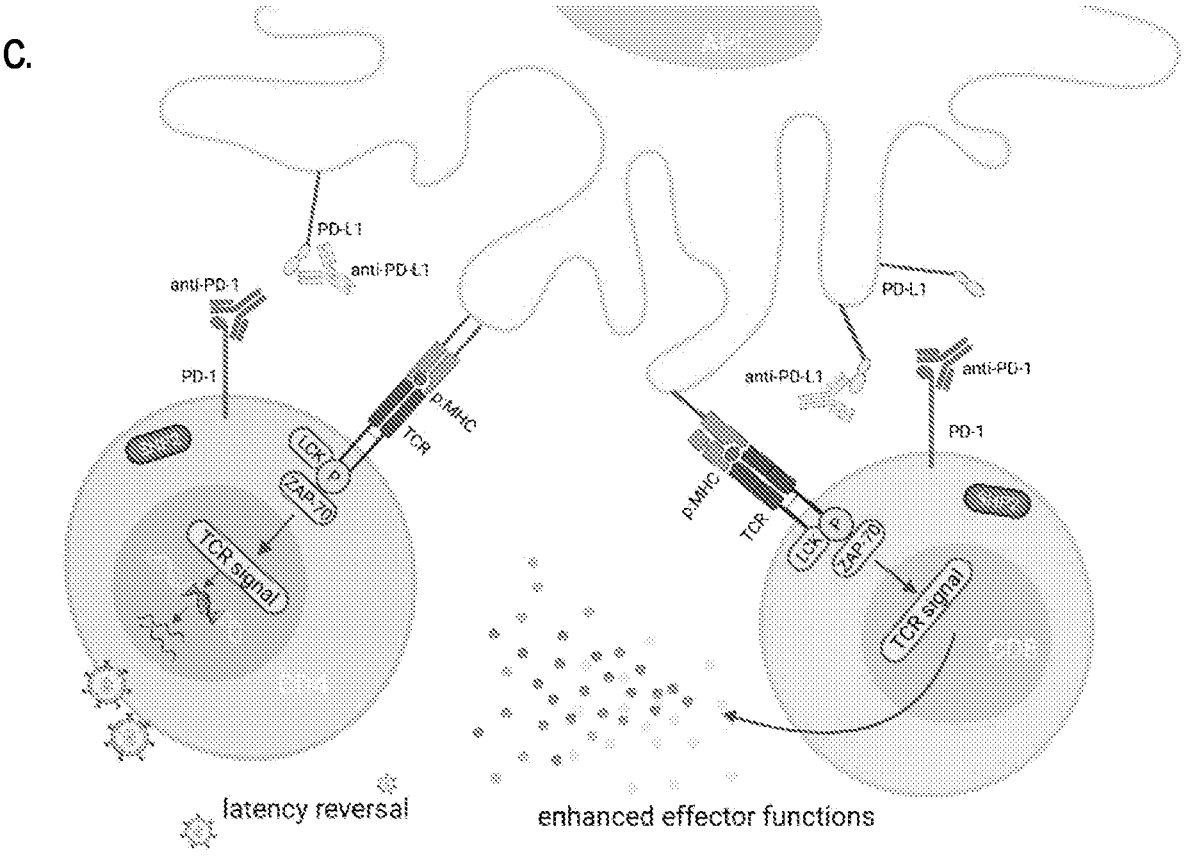


FIG. 52 (cont.)

A.

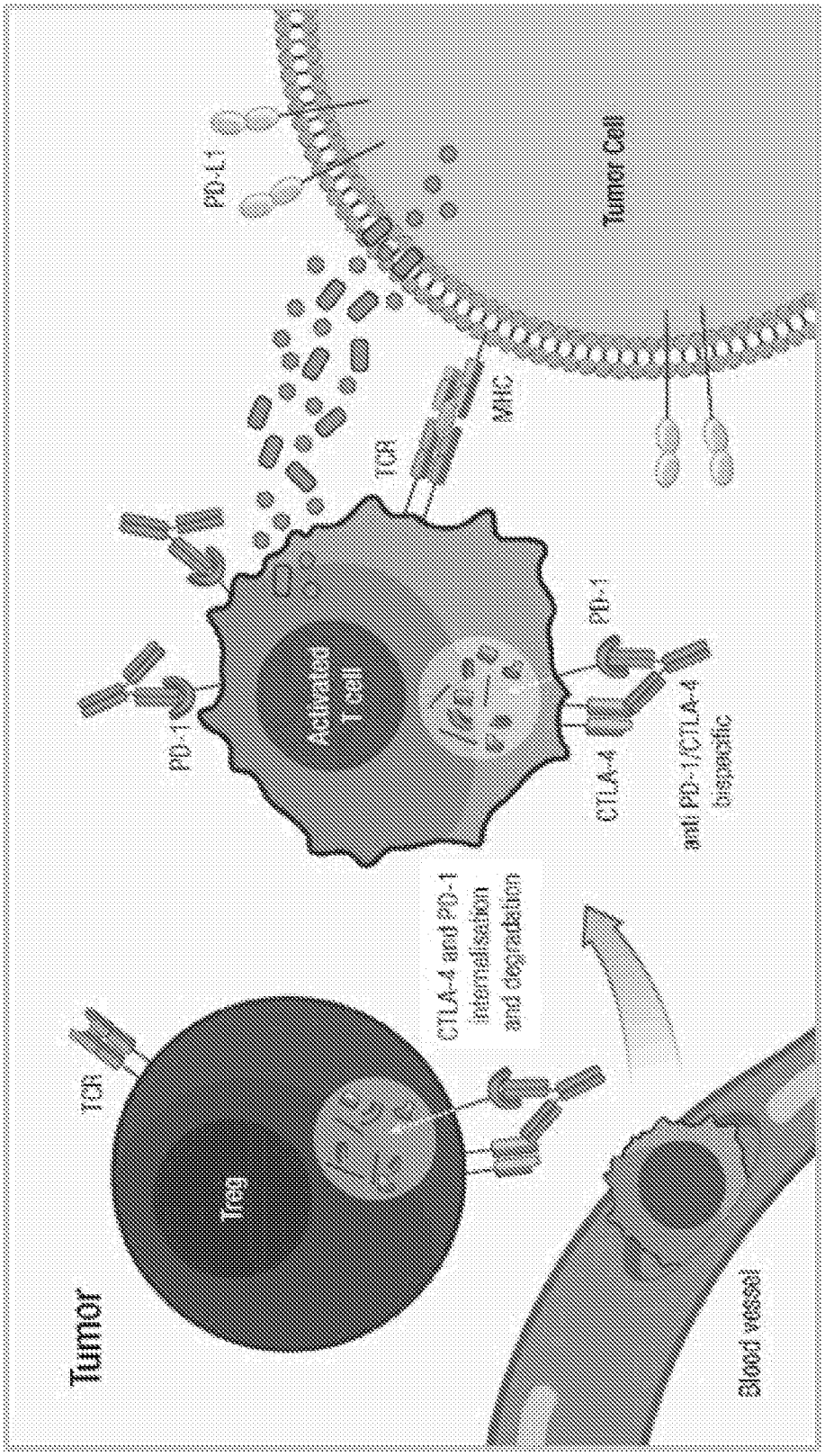

Tumor
Treg
TCR
CTLA-4 and PD-1 internalization and degradation
Blood vessel
anti PD-1/CTLA-4 bispecific
CTLA-4
PD-1
Activated T cell
PD-1
TCR
MHC
Tumor Cell
PD-L1

FIG. 53

B.

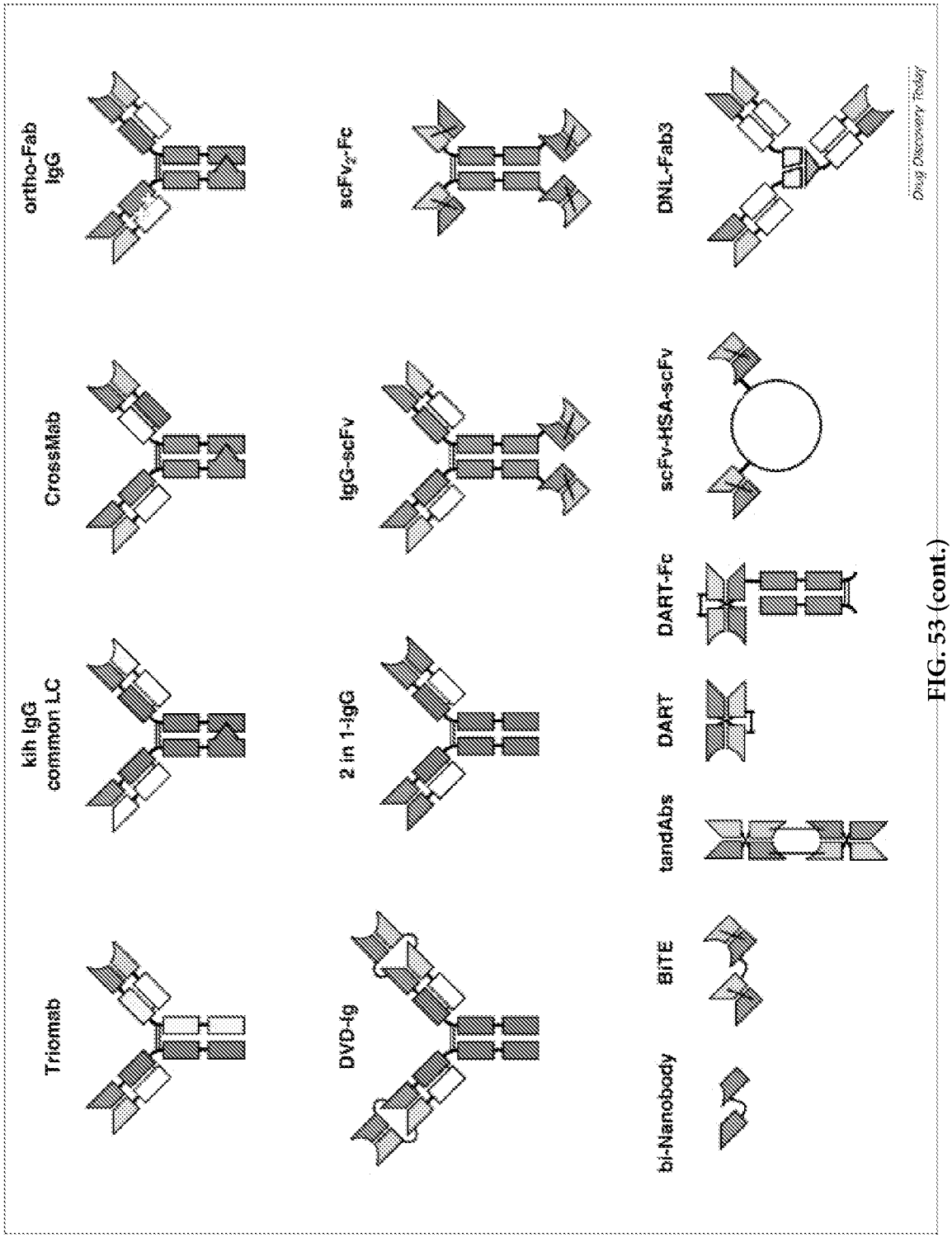

ortho-Fab IgG
CrossMab
kih IgG common LC
Triomab
scFv$_2$-Fc
IgG-scFv
2 in 1-IgG
DVD-Ig
DNL-Fab3
scFv-HSA-scFv
DART-Fc
DART
tandAbs
BiTE
bi-Nanobody
Drug Discovery Today

FIG. 53 (cont.)

Name	Format	Clinical Stage	Developed by
MGD2019	DART	Phase 1 (Unresectable metastatic solid tumors)	Macrogenomics
MEDI5752	Bivalent	Phase 1 in combination with chemotherapeutic drugs	Astrazeneca
AK104	Tetrameric	Phase 1 in combination with chemotherapeutic drugs	Akeso
KN049	Sc-Diabody-Fc	Phase 2	Alphamab

FIG. 54

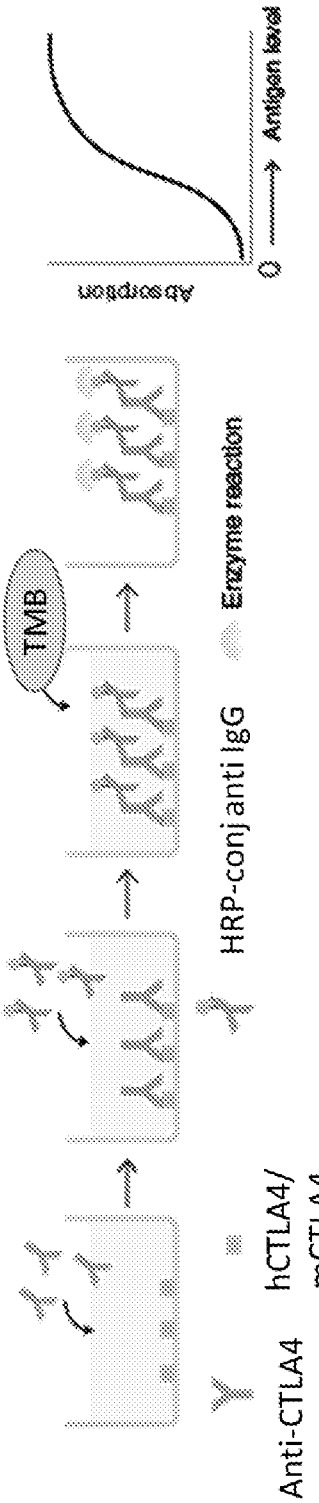

Absorption
0
Antigen level
TMB
HRP-conj anti IgG
Enzyme reaction
Anti-CTLA4
hCTLA4/
mCTLA4

FIG. 55

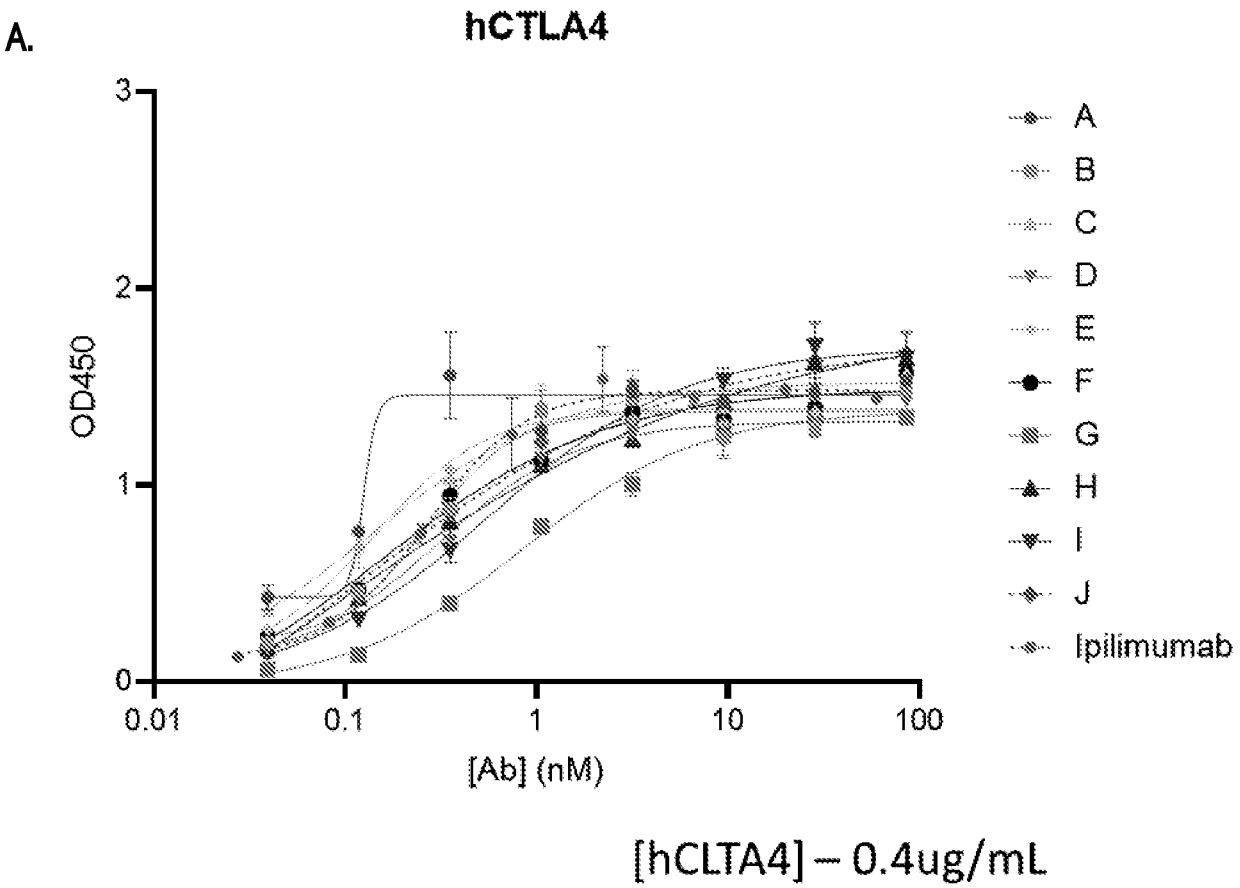

A.
hCTLA4
OD450
[Ab] (nM)
0.01
0.1
1
10
100
0
1
2
3
A
B
C
D
E
F
G
H
I
J
Ipilimumab
[hCLTA4] – 0.4ug/mL

FIG. 56

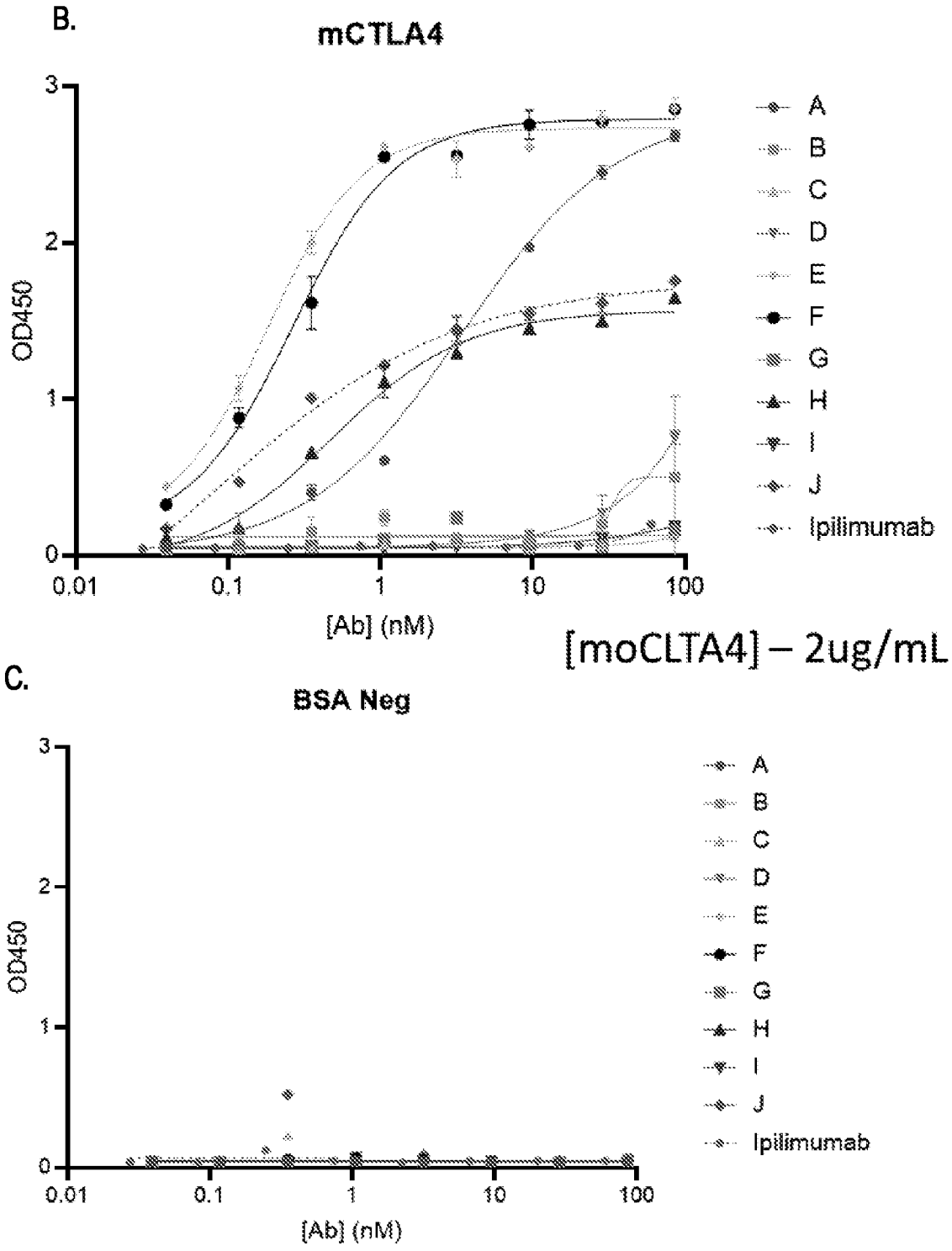

B.
mCTLA4
OD450
[Ab] (nM)
0.01
0.1
1
10
100
0
1
2
3
A
B
C
D
E
F
G
H
I
J
Ipilimumab
[moCLTA4] – 2ug/mL
C.
BSA Neg
OD450
[Ab] (nM)
Ipilimumab

FIG. 56 (cont.)

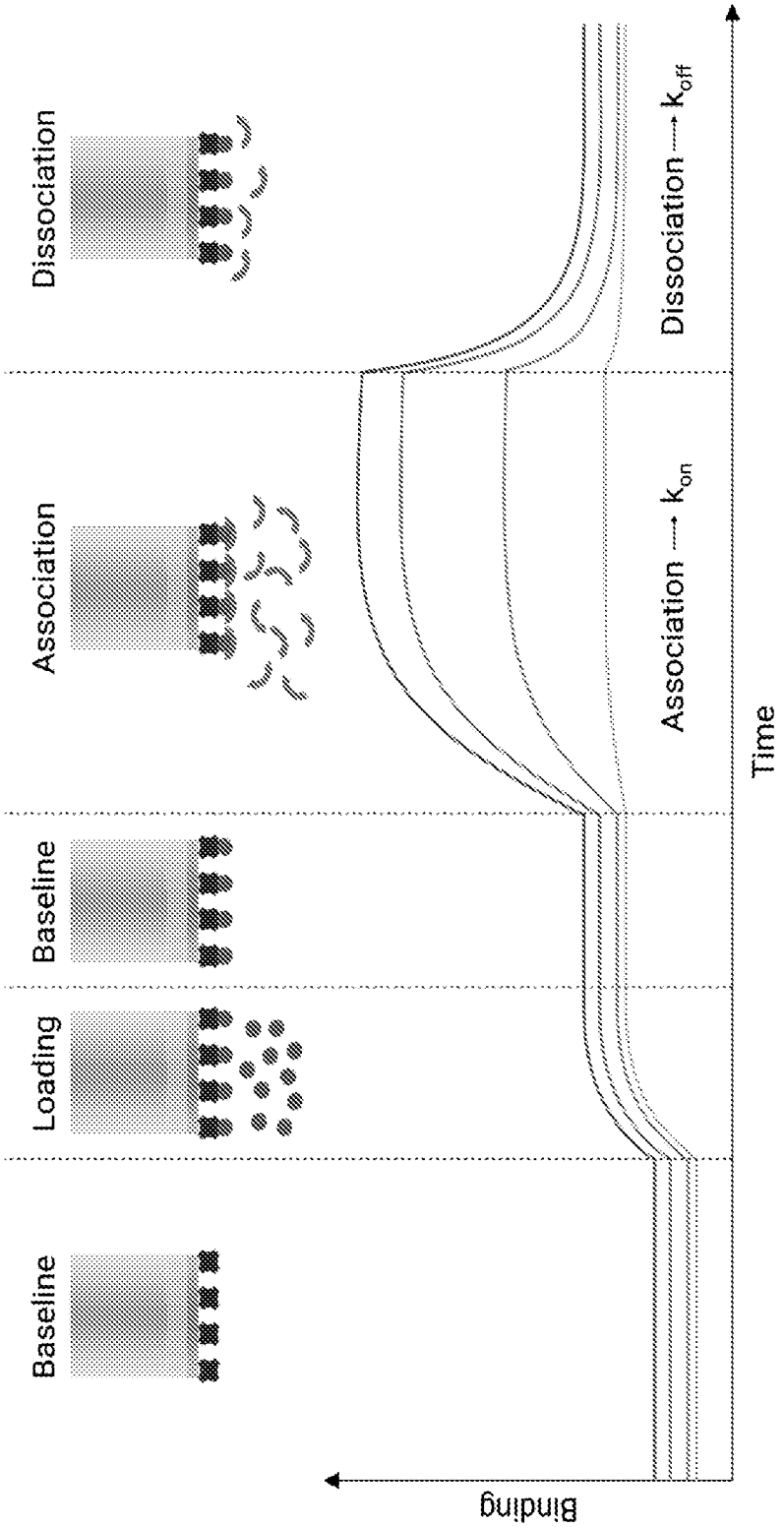

Baseline
Loading
Baseline
Association
Dissociation
Binding
Time
Association ⟶ k_{on}
Dissociation ⟶ k_{off}

FIG. 57

Ab	KD (M)	kon(1/Ms)	kdis(1/s)	Response (25nM)	Response (12.5 nM)
A	3.92E-10	6.29E+05	2.46E-04	0.76	0.43
F	1.25E-09	6.88E+05	8.60E-04	0.76	0.41
I	1.02E-09	1.09E+06	1.11E-03	0.71	0.45
C	1.26E-10	5.39E+05	6.79E-05	0.69	0.39
H	3.83E-10	5.02E+05	1.92E-04	0.64	0.35
E	1.31E-09	5.59E+05	7.32E-04	0.64	0.34
D	2.15E-10	4.75E+05	1.02E-04	0.63	0.34
B	1.98E-10	4.22E+05	8.35E-05	0.61	0.30
Ipilimumab	<1.0E-12	5.09E+05	<1.0E-07	0.60	0.33
J	3.56E-10	4.83E+05	1.72E-04	0.59	0.32
G	2.94E-10	5.41E+05	1.59E-04	0.45	0.24

FIG. 58

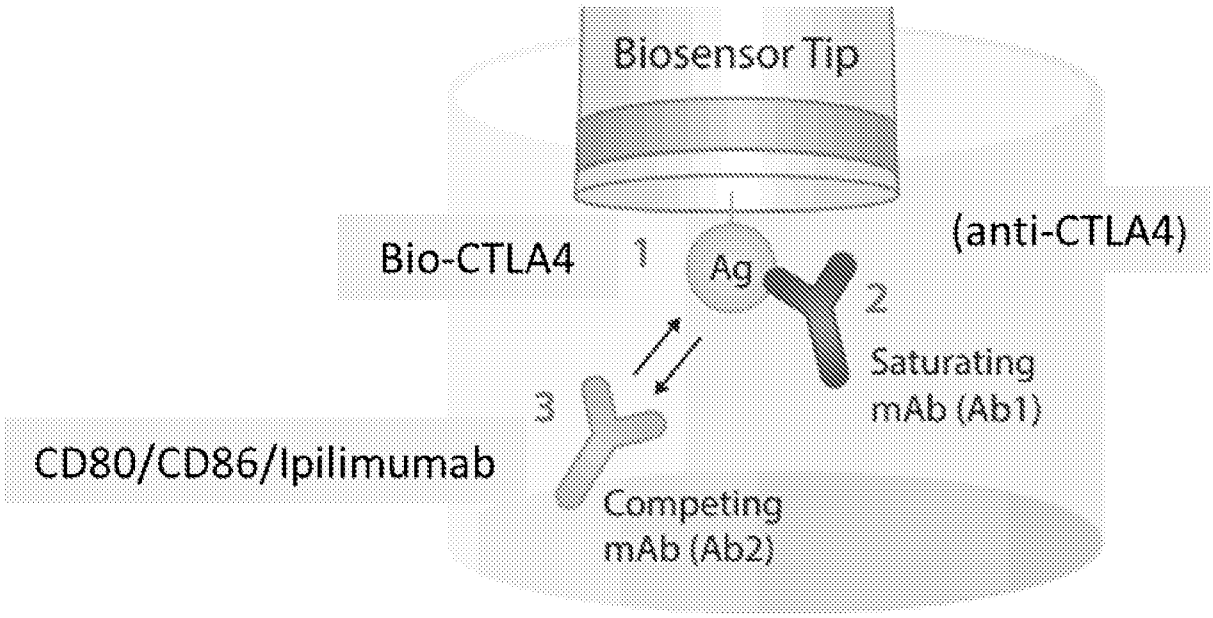
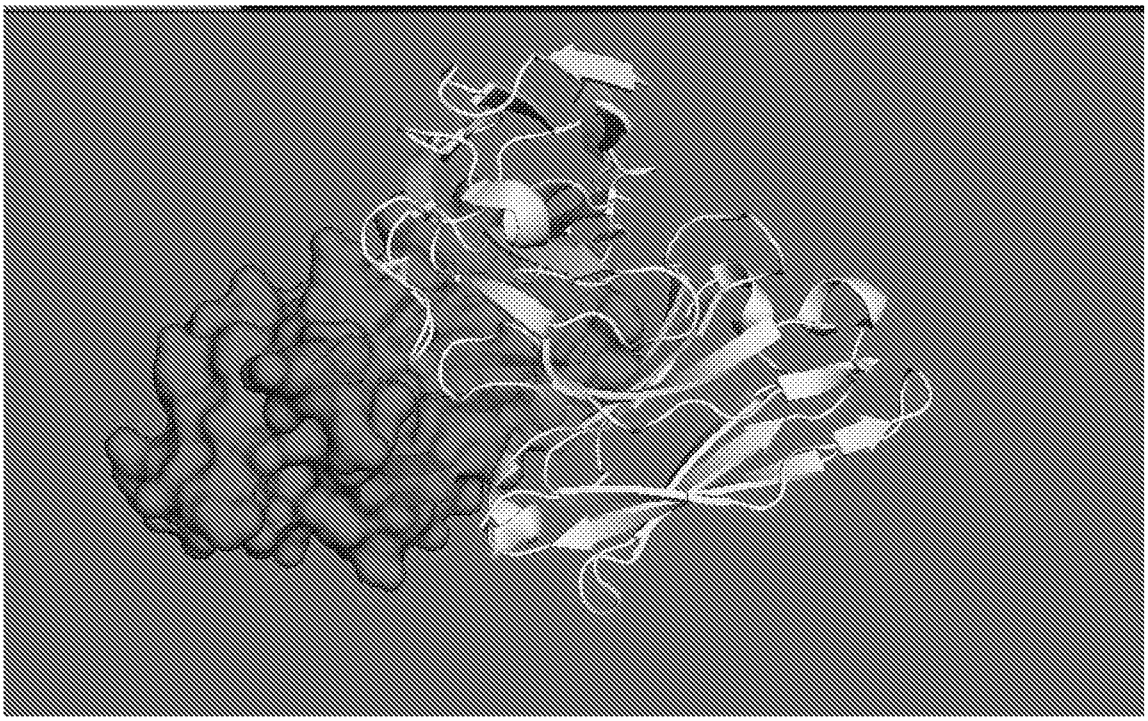

Biosensor Tip
Bio-CTLA4
1
Ag
(anti-CTLA4)
2
Saturating
mAb (Ab1)
3
CD80/CD86/Ipilimumab
Competing
mAb (Ab2)

FIG. 59

	Percentage blockade of binding		
Ab	CD80	Ipilimumab	CD86
A	79.6	83.1	100
B	83.1	82.5	100
H	86	86.9	100
J	89.3	86.6	100
E	88.3	93.6	100
F	85	94.4	100
G	83.85	76	100
I	88	85.6	100
D	85	83.6	100
C	80	86.7	100
Ipilimumab	95.6	99	100
Lab Contol	79	-1	100
PBST	0	0	0

FIG. 60

A.



B.

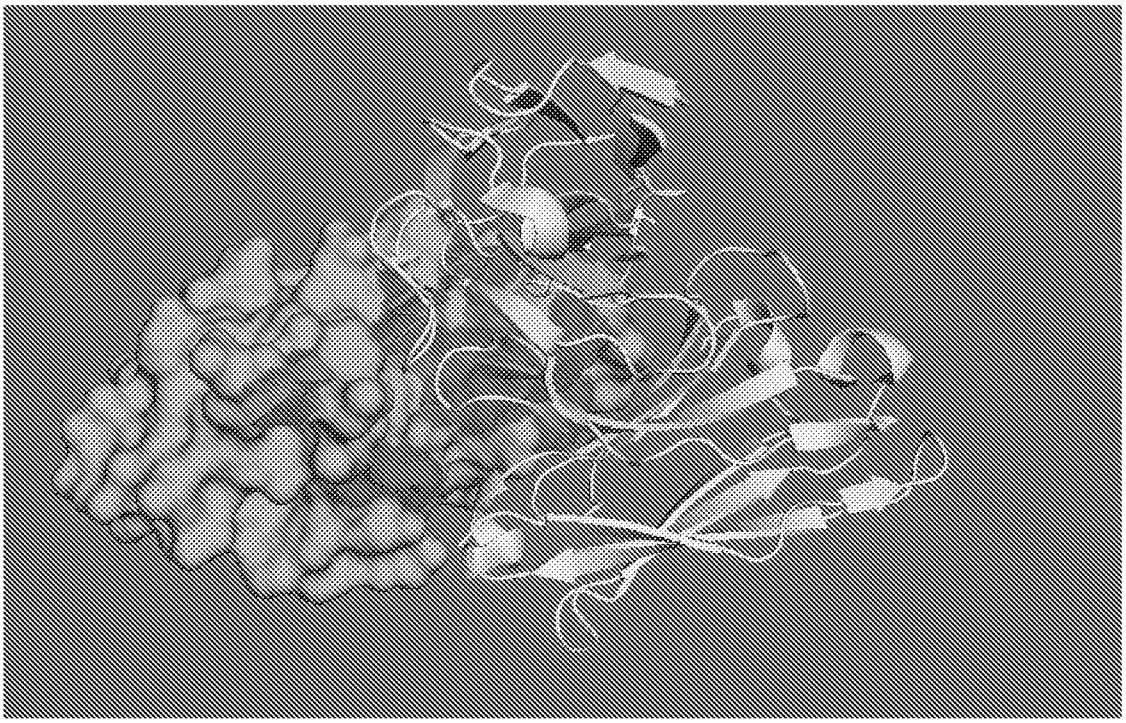
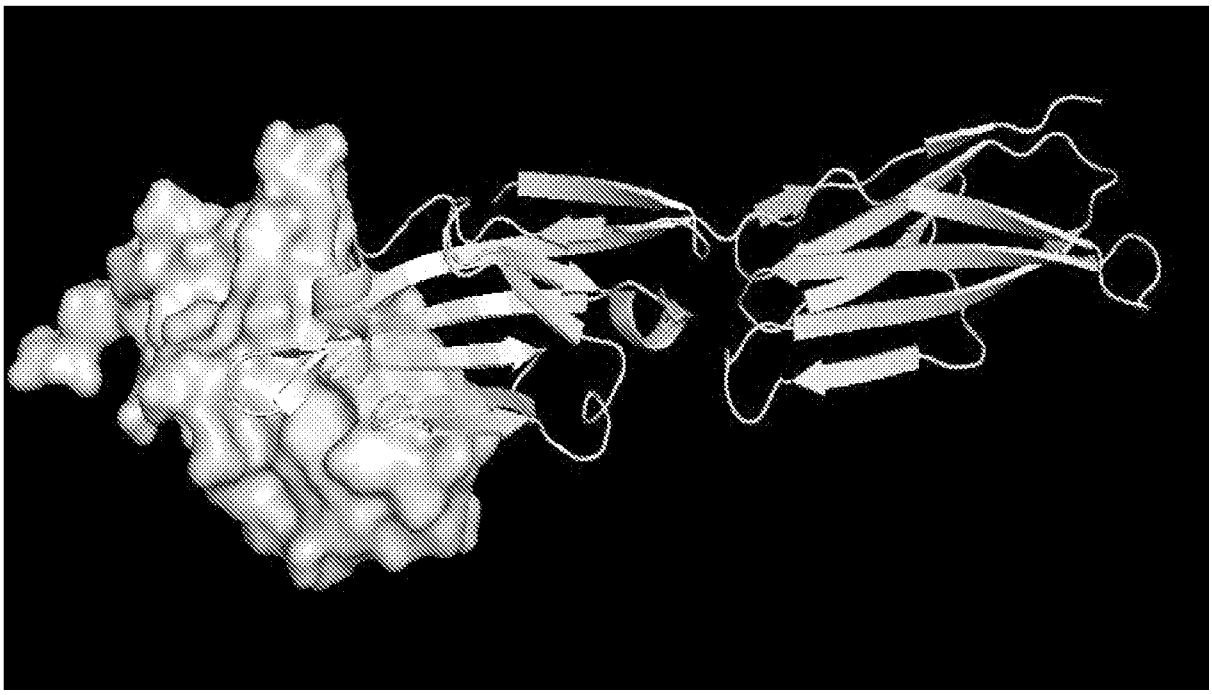


FIG. 61

A.



B.

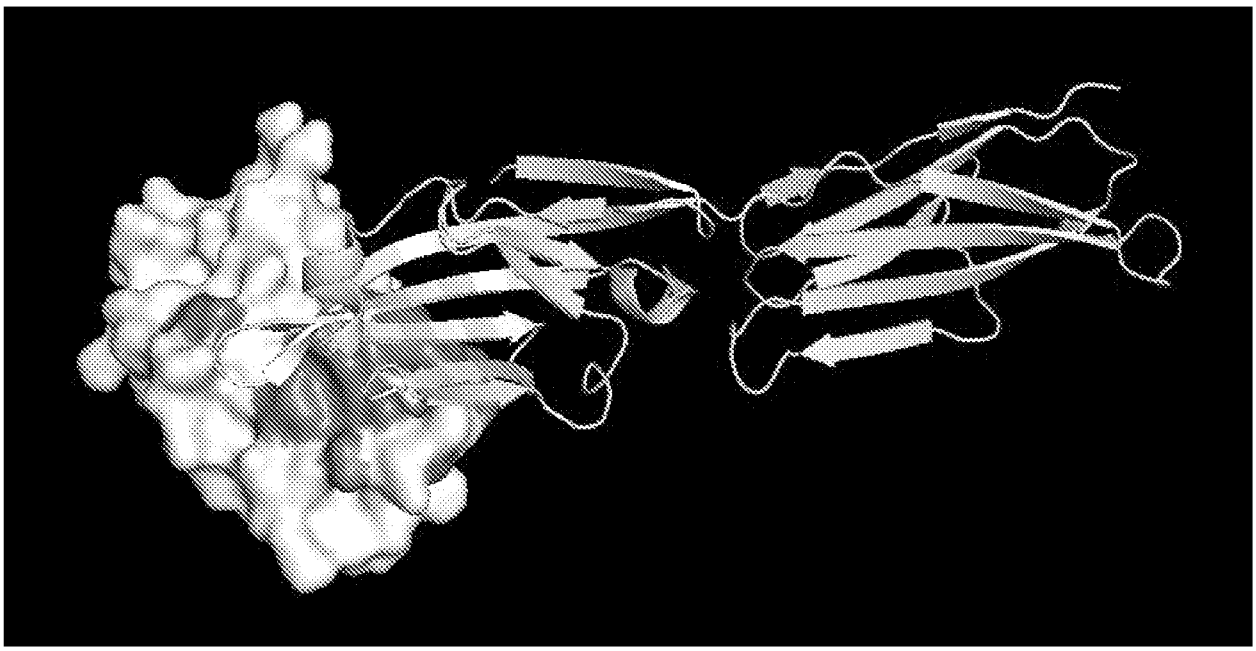


FIG. 62

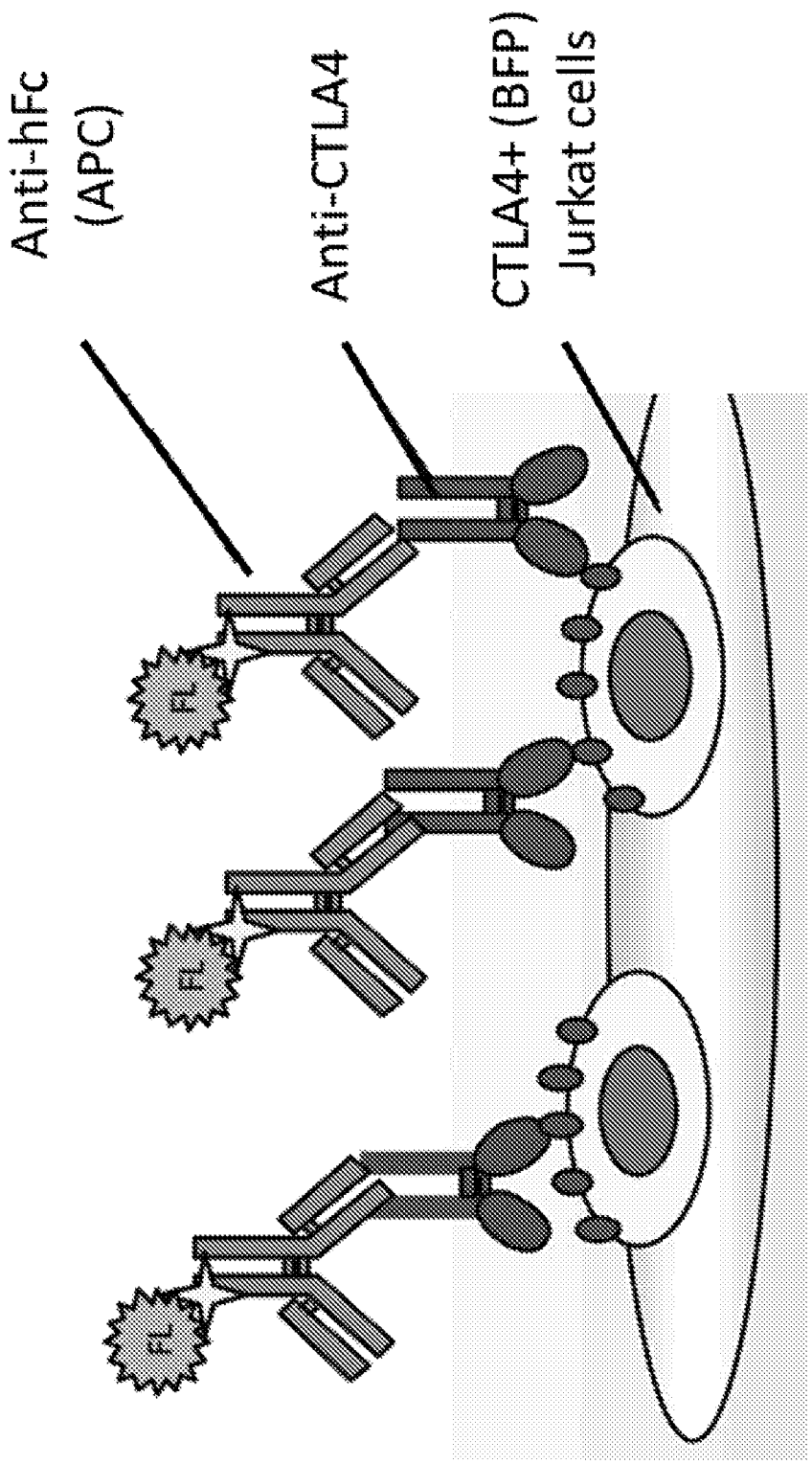


FIG. 63

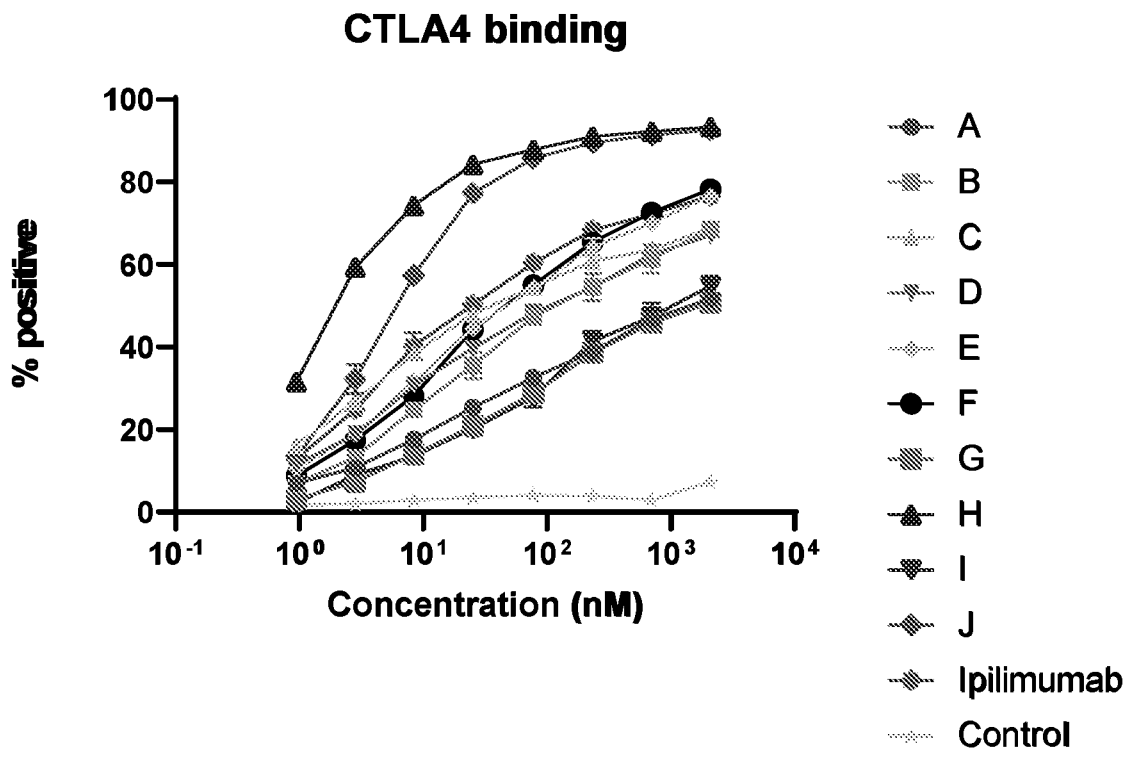

CTLA4 binding
% positive
100
80
60
40
20
0
10-1
100
101
102
103
104
Concentration (nM)
A
B
C
D
E
F
G
H
I
J
Ipilimumab
Control

FIG. 64

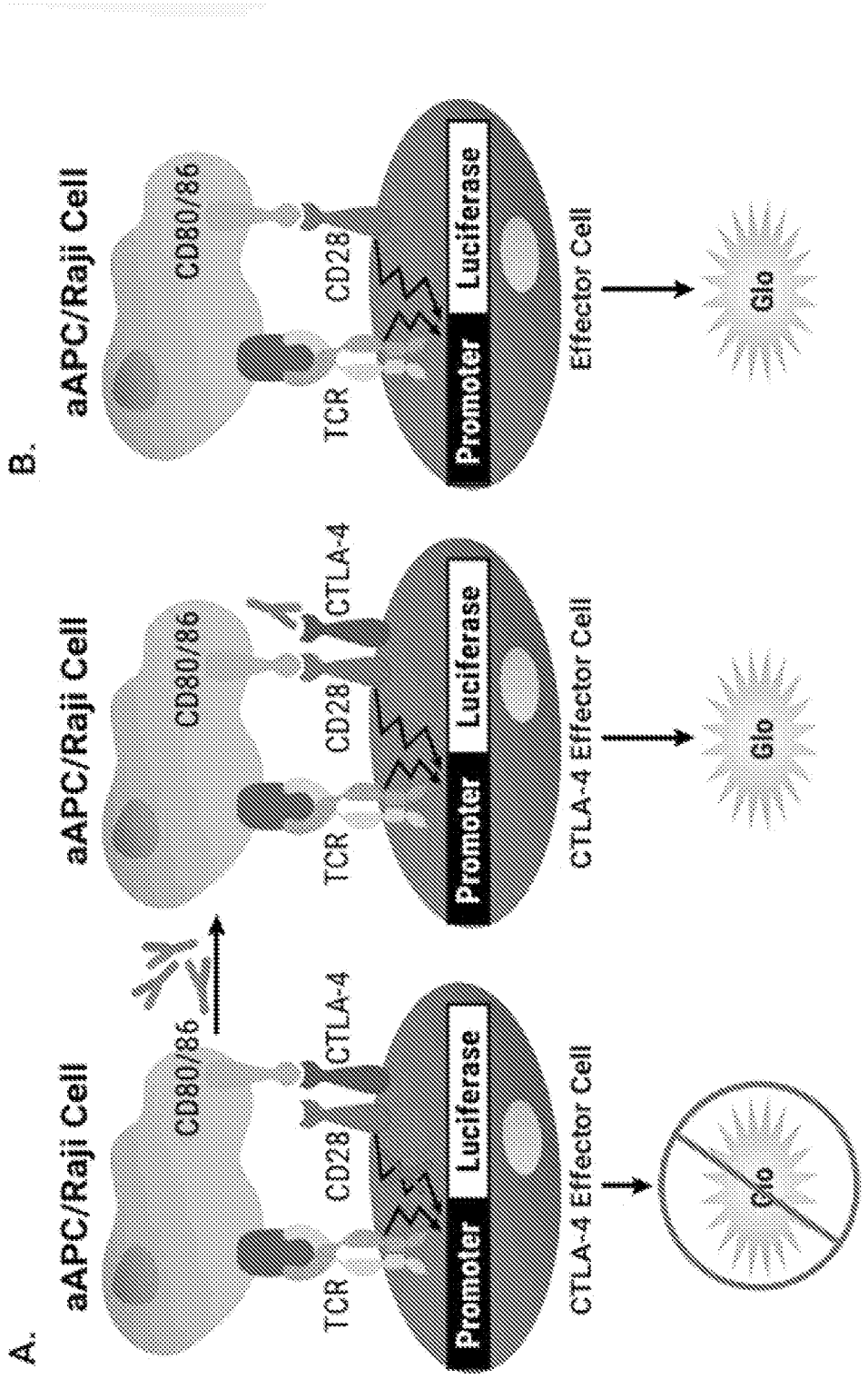

A.
aAPC/Raji Cell
CD80/86
CTLA-4
TCR
CD28
Promoter
Luciferase
CTLA-4 Effector Cell
Glo
B.
aAPC/Raji Cell
CD80/86
TCR
CD28
Promoter
Luciferase
Effector Cell
Glo

FIG. 65

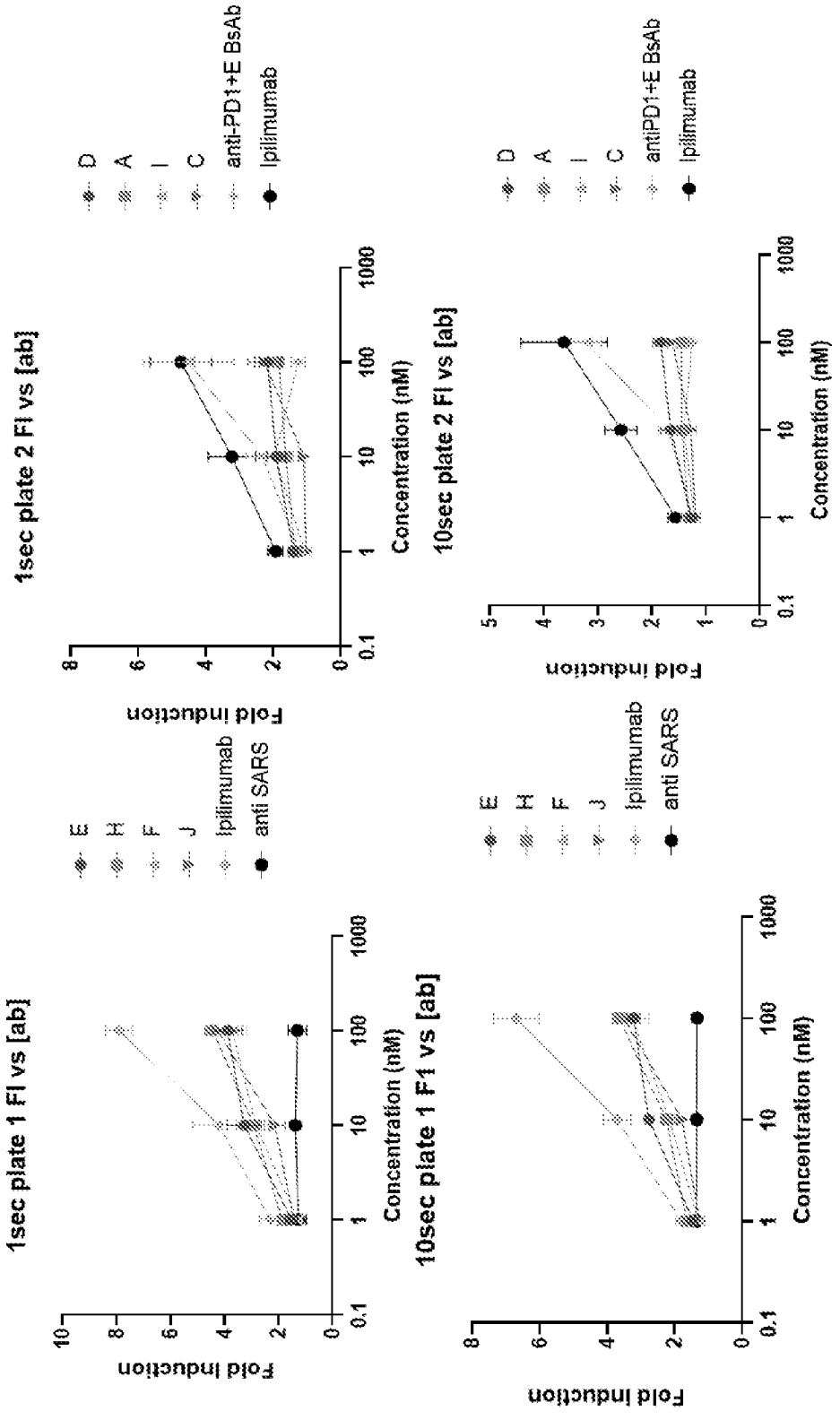

1sec plate 2 FI vs [ab]
Fold Induction
Concentration (nM)
D
A
I
C
anti-PD1+E BsAb
Ipilimumab
10sec plate 2 FI vs [ab]
Fold Induction
Concentration (nM)
D
A
I
C
antiPD1+E BsAb
Ipilimumab
1sec plate 1 FI vs [ab]
Fold Induction
Concentration (nM)
E
H
F
J
Ipilimumab
anti SARS
10sec plate 1 F1 vs [ab]
Fold Induction
Concentration (nM)
E
H
F
J
Ipilimumab
anti SARS

FIG. 66

Abs from soluble panning (VH over VL)

```
                                    FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT                FR3-IMGT                    CDR3-IMGT      FW4-IMGT
                                      (1-26)            (27-38)         (39-55)       (56-65)                  (66-104)
                                    ____________________ ___________ _____________ _____ ____________________________________ ____________________________
                                    1       10        20  30        40        50      60   70        80        90        100
                                    ........|.........|..... ...|..... .|.........|.... ....|.....  ....|.........|.........|.........|....
AM940220 Homsap IGHV3-49*04 F       EVQLVESGG.GLVQPGRSLRLSCTAS GFTF....GDYA MSWVRQAPGKGLEWVGF IRSKAYGGTT EYAASVK.GRFTISRDDSKSIAYLQMNSLKTEDTAVYYC TR
hCTLA4-Rd3b-T1-A3                   ?VQLV?SGG.GLVQPGRSLRLSC??S GFTF....GDYA MSWVRQAPGKGLEW?AF IR?KA??GG?T EYAASVK.GRFTISRDDSK??AYLQMNSLKTEDTAVYYC SNQRWLSSPL     WGQGTTVTVSS

                                    FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT                FR3-IMGT
                                      (1-26)            (27-38)         (39-55)       (56-65)                  (66-104)
                                    ____________________ ___________ _____________ _____ ____________________________________
                                    1       10        20  30        40        50      60   70        80        90        100
                                    ........|.........|..... ...|..... .|.........|.... ....|.....  ....|.........|.........|.........|....
Z73654 Homsap IGLV1-44*01 F         QSVLTQPPS.ASGTPGQRVTISCSGS SSNI....GSNT VNWYQQLPGTAPKLLIY SN.......N QRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC AAWDDSLNG
hCTLA4-Rd3b-T1-A3                   ??VLTQ?PS.ASGTPGQRVTISCSGS SSNI....GSNT VNWYQ?LPGTAPKLLIY SN.......N QRPSGVP.DRFSGSK..SGTSASLAISGL?SEDEADYYC AAWDDSLSGQV    FGGGTKLTVL

                                    FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT                FR3-IMGT
                                      (1-26)            (27-38)         (39-55)       (56-65)                  (66-104)
                                    ____________________ ___________ _____________ _____ ____________________________________
                                    1       10        20  30        40        50      60   70        80        90        100
                                    ........|.........|..... ...|..... .|.........|.... ....|.....  ....|.........|.........|.........|....
AB019439 Homsap IGHV3-21*01 F       EVQLVESGG.GLVKPGGSLRLSCAAS GFTF....SSYS MNWVRQAPGKGLEWVSS ISSS..SSYI YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AR
hCTLA4-T1-A6                        ?VQLV?SGG.GLV?PGGSLRLSCAAS GFTF....SSYS MNWVRQAPGKGLEWVSS ISSS..SSYI YYADSVK.GRFTISRDNAKNSLYLQMNSLR?EDTAVYYC ARLPYCSGGNCYDMDV WGQGTLVTVSS

                                    FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT                FR3-IMGT
                                      (1-26)            (27-38)         (39-55)       (56-65)                  (66-104)
                                    ____________________ ___________ _____________ _____ ____________________________________
                                    1       10        20  30        40        50      60   70        80        90        100
                                    ........|.........|..... ...|..... .|.........|.... ....|.....  ....|.........|.........|.........|....
Z73663 Homsap IGLV1-47*01 F         QSVLTQPPS.ASGTPGQRVTISCSGS SSNI....GSNY VYWYQQLPGTAPKLLIY RN.......N QRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYC AAWDDSLSG
hCTLA4-T1-A6                        QSVLTQPPS.ASGTPGQ?VTI?CSGS ?SNI....GSNY VYWYQQLPGTAPKLLIY RN.......N QRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYC AAWDDSLSGPV    FGGGTKLTVL

                                    FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT                FR3-IMGT
                                      (1-26)            (27-38)         (39-55)       (56-65)                  (66-104)
                                    ____________________ ___________ _____________ _____ ____________________________________
                                    1       10        20  30        40        50      60   70        80        90        100
                                    ........|.........|..... ...|..... .|.........|.... ....|.....  ....|.........|.........|.........|....
HM855666 Homsap IGHV3-7*03 F        EVQLVESGG.GLVQPGGSLRLSCAAS GFTF....SSYW MSWVRQAPGKGLEWVAN IKQD..GSEK YYVDSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC AR
hCTLA4-Rd3b-T1-A10                  ?VQLV?SGG.GLVQPGGSLRLSCAAS GF?F....??YW M?WVRQAPGKGLEWVAN IK?D..GSEK YYVDSVK.GRFT?SRDNAKNSLYLQMNSLRAEDTAVYYC ARGHFGMDV     WGPGTTVTVSS
```

FIG. 67

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                          FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT                FR3-IMGT
                          (1-26)            (27-38)         (39-55)       (56-65)                  (66-104)
                ________________________ ___________ _____________ _____ ____________________________________
                1       10        20     30          40        50    60    70        80        90        100
                .........|.........|..... ...|........ .|.........|..... ....|..... ....|.........|.........|.........|....
X56178 Homsap IGLV3-19*01 F     SSELTQDPA.VSVALGQTVRITCQGD SLR......SYY ASWYQQKPGQAPVLVIY GK.......N NRPSGIP.DRFSGSS..SGNTASLTITGAQAEDEADYYC NSRDSSGNH
hCTLA4-Rd3b-T1-A10              SSELTQDPA.VSVALGQTVRITCQGD SLR......%YY ASWYQQKPGQAP%%VI% GK.......% %RPSGIP.DRFSGS%..SGNTASLTIT%%QAEDEADYYC GSRDSSGTRVV     FGGGTKVTRP

                          FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT                FR3-IMGT
                          (1-26)            (27-38)         (39-55)       (56-65)                  (66-104)
                ________________________ ___________ _____________ _____ ____________________________________
                1       10        20     30          40        50    60    70        80        90        100
                .........|.........|..... ...|........ .|.........|..... ....|..... ....|.........|.........|.........|....
AC244456 Homsap IGHV3-30-3*01 F QVQLVESGG.GVVQPGRSLRLSCAAS GFTF....SSYA MHWVRQAPGKGLEWVAV IS                          YLQMNSLRAEDTAVYYC AR
hCTLA4-Rd3b-T2-C10              %VQLV%SGG.GVVQPGRSLRLSCAAS GFTF....SSYA MHWVRQAPGKGLEWVAV ISYD..GSNK YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARDFSSSFLLGGY   WGQGTLVTVSS

                          FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT                FR3-IMGT
                          (1-26)            (27-38)         (39-55)       (56-65)                  (66-104)
                ________________________ ___________ _____________ _____ ____________________________________
                1       10        20     30          40        50    60    70        80        90        100
                .........|.........|..... ...|........ .|.........|..... ....|..... ....|.........|.........|.........|....
AC279317 Homsap IGLV4-60*03 F   QPVLTQSSS.ASASLGSSVKLTCTLS SGHS.....SYI IAWHQQQPGKAPRYLMK LEGS...GSY NKGSGVP.DRFSGSS..SGADRYLTISNLQSEDEADYYC ETWDSNT
hCTLA4-Rd3b-T2-C10              %PVLTQSSS.ASASLGSSVKLTCTLS SGHS.....SYI IAWHQQQPGKAPRYLMK LEGS...GSY NKGSGVP.DRFSGSS..SGADRYLTISNLQSEDEADYYC ETWDSNLPSWV    FGGGTKLTVL
```

FIG. 67 CON'T

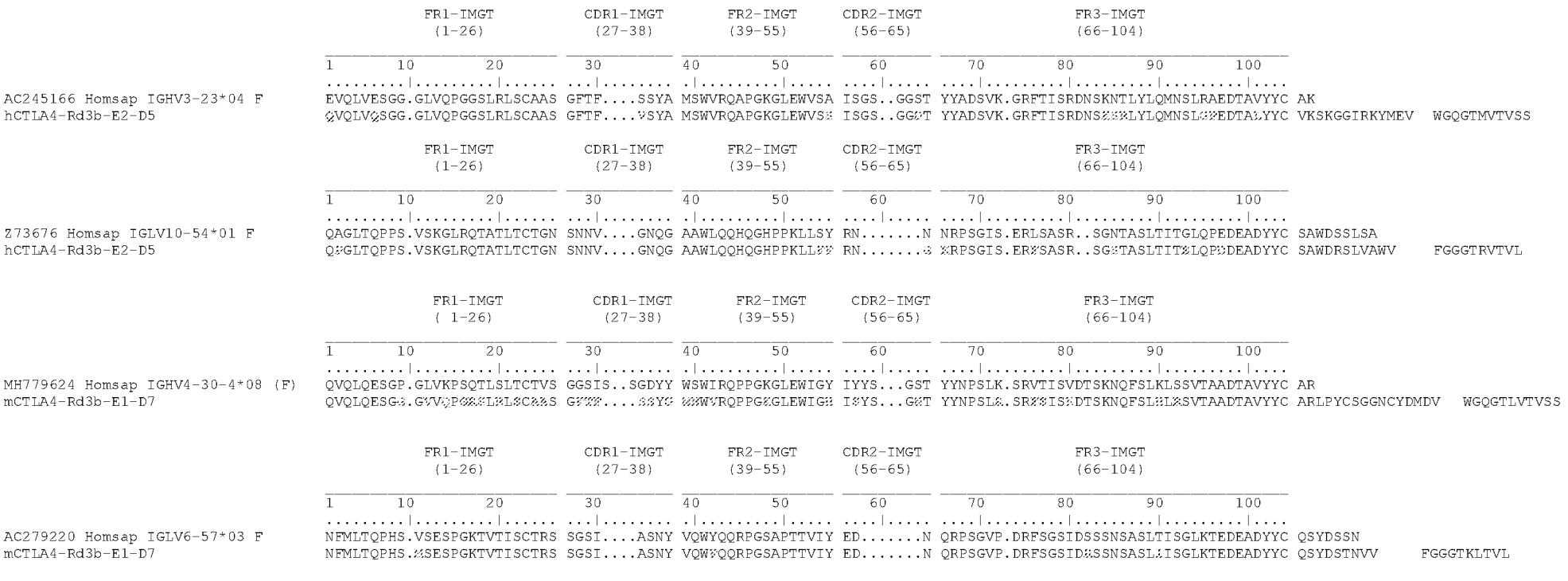
FR1-IMGT (1-26)
CDR1-IMGT (27-38)
FR2-IMGT (39-55)
CDR2-IMGT (56-65)
FR3-IMGT (66-104)
AC245166 Homsap IGHV3-23*04 F
EVQLVESGG.GLVQPGGSLRLSCAAS GFTF....SSYA MSWVRQAPGKGLEWVSA ISGS..GGST YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AK
hCTLA4-Rd3b-E2-D5
FR1-IMGT (1-26)
CDR1-IMGT (27-38)
FR2-IMGT (39-55)
CDR2-IMGT (56-65)
FR3-IMGT (66-104)
Z73676 Homsap IGLV10-54*01 F
QAGLTQPPS.VSKGLRQTATLTCTGN SNNV....GNQG AAWLQQHQGHPPKLLSY RN.......N NRPSGIS.ERLSASR..SGNTASLTITGLQPEDEADYYC SAWDSSLSA
hCTLA4-Rd3b-E2-D5
FR1-IMGT (1-26)
CDR1-IMGT (27-38)
FR2-IMGT (39-55)
CDR2-IMGT (56-65)
FR3-IMGT (66-104)
MH779624 Homsap IGHV4-30-4*08 (F)
QVQLQESGP.GLVKPSQTLSLTCTVS GGSIS..SGDYY WSWIRQPPGKGLEWIGY IYYS...GST YYNPSLK.SRVTISVDTSKNQFSLKLSSVTAADTAVYYC AR
mCTLA4-Rd3b-E1-D7
FR1-IMGT (1-26)
CDR1-IMGT (27-38)
FR2-IMGT (39-55)
CDR2-IMGT (56-65)
FR3-IMGT (66-104)
AC279220 Homsap IGLV6-57*03 F
NFMLTQPHS.VSESPGKTVTISCTRS SGSI....ASNY VQWYQQRPGSAPTTVIY ED.......N QRPSGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC QSYDSSN
mCTLA4-Rd3b-E1-D7

FIG. 67 CON'T

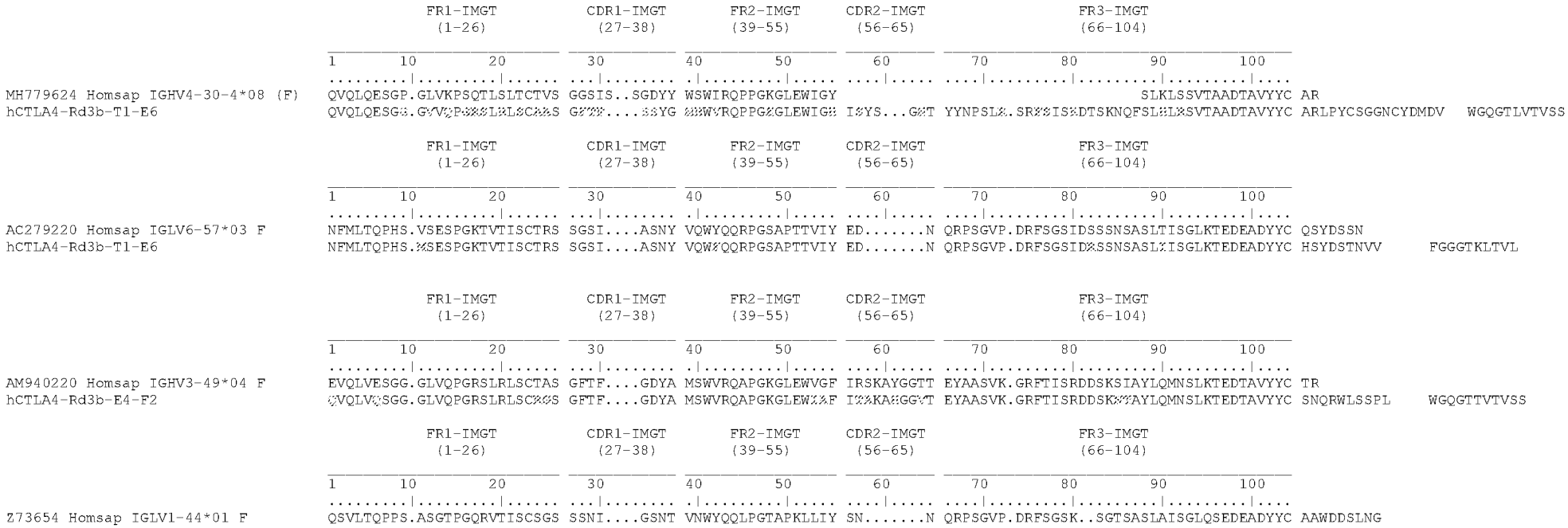
FR1-IMGT (1-26)
CDR1-IMGT (27-38)
FR2-IMGT (39-55)
CDR2-IMGT (56-65)
FR3-IMGT (66-104)
MH779624 Homsap IGHV4-30-4*08 (F) QVQLQESGP.GLVKPSQTLSLTCTVS GGSIS..SGDYY WSWIRQPPGKGLEWIGY SLKLSSVTAADTAVYYC AR
hCTLA4-Rd3b-T1-E6 QVQLQESG.G.V.P.....L.L.C...S G...Y....SYG ...W.RQPPG.GLEWIG. I.YS...G.T YYNPSL..SR..IS.DTSKNQFSL.L.SVTAADTAVYYC ARLPYCSGGNCYDMDV WGQGTLVTVSS
AC279220 Homsap IGLV6-57*03 F NFMLTQPHS.VSESPGKTVTISCTRS SGSI....ASNY VQWYQQRPGSAPTTVIY ED.....N QRPSGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC QSYDSSN
hCTLA4-Rd3b-T1-E6 NFMLTQPHS.XSESPGKTVTISCTRS SGSI....ASNY VQW.QQRPGSAPTTVIY ED.....N QRPSGVP.DRFSGSID.SSNSASL.ISGLKTEDEADYYC HSYDSTNVV FGGGTKLTVL
AM940220 Homsap IGHV3-49*04 F EVQLVESGG.GLVQPGRSLRLSCTAS GFTF....GDYA MSWVRQAPGKGLEWVGF IRSKAYGGTT EYAASVK.GRFTISRDDSKSIAYLQMNSLKTEDTAVYYC TR
hCTLA4-Rd3b-E4-F2 .VQLV.SGG.GLVQPGRSLRLSC.AS GFTF....GDYA MSWVRQAPGKGLEW.AF I..KA.GG.T EYAASVK.GRFTISRDDSK.YAYLQMNSLKTEDTAVYYC SNQRWLSSPL WGQGTTVTVSS
Z73654 Homsap IGLV1-44*01 F QSVLTQPPS.ASGTPGQRVTISCSGS SSNI....GSNT VNWYQQLPGTAPKLLIY SN.....N QRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC AAWDDSLNG

FIG. 67 CON'T

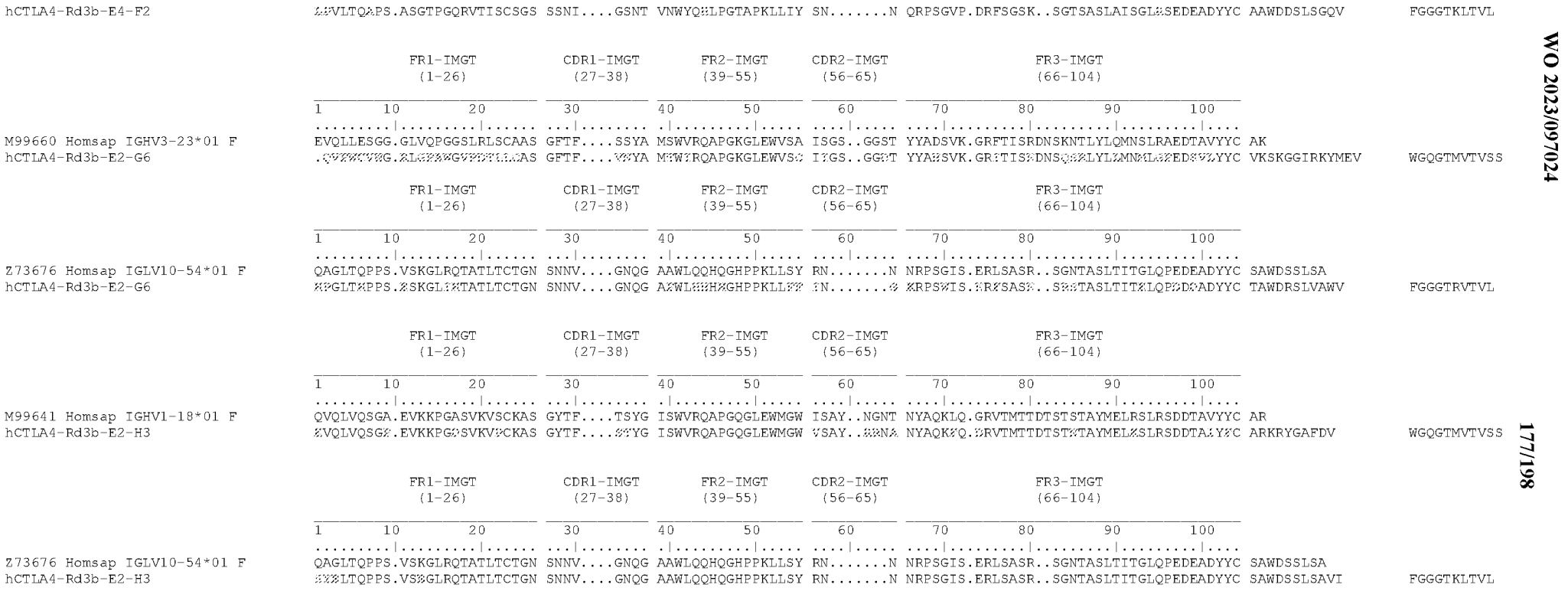
hCTLA4-Rd3b-E4-F2 EVLTQAPS.ASGTPGQRVTISCSGS SSNI....GSNT VNWYQHLPGTAPKLLIY SN.......N QRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC AAWDDSLSGQV FGGGTKLTVL
FR1-IMGT (1-26) CDR1-IMGT (27-38) FR2-IMGT (39-55) CDR2-IMGT (56-65) FR3-IMGT (66-104)
M99660 Homsap IGHV3-23*01 F EVQLLESGG.GLVQPGGSLRLSCAAS GFTF....SSYA MSWVRQAPGKGLEWVSA ISGS..GGST YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AK
hCTLA4-Rd3b-E2-G6 .QVQWQVWG.ALLKPSWGVVKPSETLSLTCAS GFTF....VSYA MTWIRQAPGKGLEWVSG I?GS..GG?T YYADSVK.GRITISRDNSQNTLYLQMNTLRAEDSAVYYC VKSKGGIRKYMEV WGQGTMVTVSS
FR1-IMGT (1-26) CDR1-IMGT (27-38) FR2-IMGT (39-55) CDR2-IMGT (56-65) FR3-IMGT (66-104)
Z73676 Homsap IGLV10-54*01 F QAGLTQPPS.VSKGLRQTATLTCTGN SNNV....GNQG AAWLQQHQGHPPKLLSY RN.......N NRPSGIS.ERLSASR..SGNTASLTITGLQPEDEADYYC SAWDSSLSA
hCTLA4-Rd3b-E2-G6 QPGLTQPPS.QSKGLRQTATLTCTGN SNNV....GNQG AQWLQQHQGHPPKLLPP INV.......S QRPSWIS.RRVSASR..SGNTASLTITGLQPDDQADYYC TAWDRSLVAWV FGGGTRVTVL
FR1-IMGT (1-26) CDR1-IMGT (27-38) FR2-IMGT (39-55) CDR2-IMGT (56-65) FR3-IMGT (66-104)
M99641 Homsap IGHV1-18*01 F QVQLVQSGA.EVKKPGASVKVSCKAS GYTF....TSYG ISWVRQAPGQGLEWMGW ISAY..NGNT NYAQKLQ.GRVTMTTDTSTSTAYMELRSLRSDDTAVYYC AR
hCTLA4-Rd3b-E2-H3 EVQLVQSGA.EVKKPGASVKVSCKAS GYTF....SYYG ISWVRQAPGQGLEWMGW VSAY..GGNA NYAQKFQ.GRVTMTTDTSTRTAYMELRSLRSDDTAIYYC ARKRYGAFDV WGQGTMVTVSS
FR1-IMGT (1-26) CDR1-IMGT (27-38) FR2-IMGT (39-55) CDR2-IMGT (56-65) FR3-IMGT (66-104)
Z73676 Homsap IGLV10-54*01 F QAGLTQPPS.VSKGLRQTATLTCTGN SNNV....GNQG AAWLQQHQGHPPKLLSY RN.......N NRPSGIS.ERLSASR..SGNTASLTITGLQPEDEADYYC SAWDSSLSA
hCTLA4-Rd3b-E2-H3 EVLTQPPS.VSAGLRQTATLTCTGN SNNV....GNQG AAWLQQHQGHPPKLLSY RN.......N NRPSGIS.ERLSASR..SGNTASLTITGLQPEDEADYYC SAWDSSLSAVI FGGGTKLTVL

FIG. 67 CON'T

Antibodies from PMPL (grouped by germline)
Anti-CTLA4 Vh:

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                                        FR1-IMGT      CDR1-IMGT     FR2-IMGT      CDR2-IMGT           FR3-IMGT                CDR3-IMGT     FW4-IMGT
                                        (1-26)        (27-38)       (39-55)       (56-65)             (66-104)
                                  ____________________ ___________ _____________ ___________ ____________________________________ ____________ ___________
                                  1       10        20  30        40        50        60        70        80        90        100
                                  .........|.........|.. ...|..... .|.........|.... ....|.... ....|.........|.........|.........|....

AC245166 Homsap IGHV3-23*04 F     EVQLVESGG.GLVQPGGSLRLSCAAS GFTF....SSYA MSWVRQAPGKGLEWVSA ISGS..GGST YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AK
CTLA4-PMPL-Rd2-E1-A8              QVQLVQSGG.GLVQPGGSLRLSCAAS GFTF....SSYV MSWVRQAPGKGLEWVSS ISGS..GGST DYADSVK.GRFPISRDNSKNTLYLEMNSLRAEDTAVYYC ARGGSAWSLDI   WGQGTTVTVSS
CTLA4-PMPL-Rd2-E1-B10             QVQLVQSGG.GLVQPGGSLRLSCAAS GFTF....SSYA MSWVRQAPGKGLEWVSA ISGS..GGST YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AREEGITGTGFDY WGQGTLVTVSS CTLA4pmpl-
Rd2-E2-A4: (1)          QVQLVQSGG.GLVQPGGSLRLSCAAS GFTF....SSYV MSWVRQAPGKGLEWVSS ISGS..GGST DYADSVK.GRFPISRDNSKNTLYLEMNSLRAEDTAVYYC ARGGSAWSLDI   WGQGTTVTVSS
```

```
                                        FR1-IMGT      CDR1-IMGT     FR2-IMGT      CDR2-IMGT           FR3-IMGT
                                        (1-26)        (27-38)       (39-55)       (56-65)             (66-104)
                                  ____________________ ___________ _____________ ___________ ____________________________________
                                  1       10        20  30        40        50        60        70        80        90        100
                                  .........|.........|.. ...|..... .|.........|.... ....|.... ....|.........|.........|.........|....
AC244456 Homsap IGHV3-30-3*01 F   QVQLVESGG.GVVQPGRSLRLSCAAS GFTF....SSYA MHWVRQAPGKGLEWVAV ISYD..GSNK YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AR
aCTLA4_T2-C10:                    EVQLVQSGG.GVVQPGRSLRLSCAAS GFTF....SSYA MHWVRQAPGKGLEWVAV ISYD..GSNK YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ARDFSSSFLLGGY WGQGTLVTVSS
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                                        FR1-IMGT      CDR1-IMGT     FR2-IMGT      CDR2-IMGT           FR3-IMGT
                                        (1-26)        (27-38)       (39-55)       (56-65)             (66-104)
                                  ____________________ ___________ _____________ ___________ ____________________________________
                                  1       10        20  30        40        50        60        70        80        90        100
                                  .........|.........|.. ...|..... .|.........|.... ....|.... ....|.........|.........|.........|....
X92217 Homsap IGHV3-13*01 F       EVQLVESGG.GLVQPGGSLRLSCAAS GFTF....SSYD MHWVRQATGKGLEWVSA IGTA...GDT YYPGSVK.GRFTISRENAKNSLYLQMNSLRAGDTAVYYC AR
CTLA4-PMPL-Rd2-E1-A10:            QVQLVQSGG.GLVQSGGSLRLSCAAS GFTF....SGYD MHWVRQAAGKGLEWVSN IGIR...GDT YYSDSVK.GRFIISRENAKSSLYLQMNSLRAGDTAVYYC VRDPSGHGMDV WGKGTTVTVSS
```

```
                                        FR1-IMGT      CDR1-IMGT     FR2-IMGT      CDR2-IMGT           FR3-IMGT
                                        (1-26)        (27-38)       (39-55)       (56-65)             (66-104)
                                  ____________________ ___________ _____________ ___________ ____________________________________
                                  1       10        20  30        40        50        60        70        80        90        100
                                  .........|.........|.. ...|..... .|.........|.... ....|.... ....|.........|.........|.........|....
X92206 Homsap IGHV3-72*01 F       EVQLVESGG.GLVQPGGSLRLSCAAS GFTF....SDHY MDWVRQAPGKGLEWVGR TRNKANSYTT EYAASVK.GRFTISRDDSKNSLYLQMNSLKTEDTAVYYC AR
CTLA4-PMPL-Rd2-E1-B11:            EVQLVQSGG.GLVQPGGSLRLSCAAS GFTF....SDHY MDWVRQAPGKGLEWVGR SRNKANSYTT EYAASVK.GRFTISRDESENSLYLQMNSLRAEDTAVYYC ARARGYMDV WGKGTTVTVSS
```

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                                        FR1-IMGT      CDR1-IMGT     FR2-IMGT      CDR2-IMGT           FR3-IMGT
                                        (1-26)        (27-38)       (39-55)       (56-65)             (66-104)
                                  ____________________ ___________ _____________ ___________ ____________________________________
                                  1       10        20  30        40        50        60        70        80        90        100
                                  .........|.........|.. ...|..... .|.........|.... ....|.... ....|.........|.........|.........|....
X92343 Homsap IGHV1-46*01 F       QVQLVQSGA.EVKKPGASVKVSCKAS GYTF....TSYY MHWVRQAPGQGLEWMGI INPS..GGST SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC AR
CTLA4-PMPL-Rd2-E1-A9              EVQLVQSGA.EVKKPGASVKVSCKAS GYTF....TSYY MHWVRQAPGQGLEWMGI INPS..GGST SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC ARELKRGDYYYYYGMDV WGQGTTVTVSS
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                                        FR1-IMGT      CDR1-IMGT     FR2-IMGT      CDR2-IMGT           FR3-IMGT
                                        (1-26)        (27-38)       (39-55)       (56-65)             (66-104)
                                  ____________________ ___________ _____________ ___________ ____________________________________ ____________ ___________
                                  1       10        20  30        40        50        60        70        80        90        100
                                  .........|.........|.. ...|..... .|.........|.... ....|.... ....|.........|.........|.........|....
M99641 Homsap IGHV1-18*01 F       QVQLVQSGA.EVKKPGASVKVSCKAS GYTF....TSYG ISWVRQAPGQGLEWMGW ISAY..NGNT NYAQKLQ.GRVTMTTDTSTSTAYMELRSLRSDDTAVYYC AR
CTLA4-PMPL-Rd2-E1-B6:             QVQLQQSGT.EVKKPGASVKVSCKAS GYIF....TSYG FTWVRQAPGQGLEWMGW ISSY..NGNT DYAQKFE.GRVTMTTDTSTTTAYMELRGLKSDDTAMYYC ARGPQMDV              WGQGTTVTVSS
CTLA4-PMPL-Rd2-E1-C12:            QVQLVQSGA.EVKKPGASVKVSCKAS GYIF....TSYG FTWVRQAPGQGLEWMGW ISSY..NGNT DYAQKFE.GRVTMTTDTSTTTAYMELRGLKSDDTAMYYC ARGPQMDV                WGQGTTVTVSS
CTLA4-PMPL-Rd2-E1-A12:            QVQLVQSGG.EVKKPGASVKVSCKAS GDTF....SRYG ITWVRQAPGQGLEWMGW MSTV..TGNT NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC ARGLCRDSSCLTPYYYYGMDV    WGKGTLVTVSS
CTLA4-PMPL-Rd2-E1-B12:            QVQLVQSGG.EVKKPGASVKVSCKAS GDTF....SRYG ITWVRQAPGQGLEWMGW MSAY..NGNT NYAQKLQ.GRVTMTTDTSTSTAYMELRSLRSDDTAVYYC ARGLCRDSSCLTPYYYYGMDV    WGKGTLVTVSS
CTLA4pmpl-Rd2-E2-G5:  (1)         EVQLVESGA.EVRKPGESLTISCKAS GYTF....TSYG ISWVRQAPGQGLEWMGW ISAY..NGNT NYAQKLQ.GRVTMTTDTSTSTAYMELRSLRSDDTAVYYC ATDLWPIYCSGGSCYETSYYGMDV WGQGTLVTVSS
CTLA4pmpl-Rd2-E2-D10: (3)         QVQLVQSGG.EVKKPGASVKVSCKAS GDTF....SRYG ITWVRQAPGQGLEWMGW MSTV..TGNT NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC ARGLCRDSSCLTPYYYYGMDV    WGKGTLVTVSS
CTLA4pmpl-Rd2-E2-H10: (1)         QVQLVQSGG.EVKKPGASVKVSCKAS GDTF....SRYG ITWVRQAPGQGLEWMGW MSTV..TGNT NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC ARGLCRDSSCLTPYYYYGMDV    WGKGTLVTVSS
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FIG. 67 CON'T

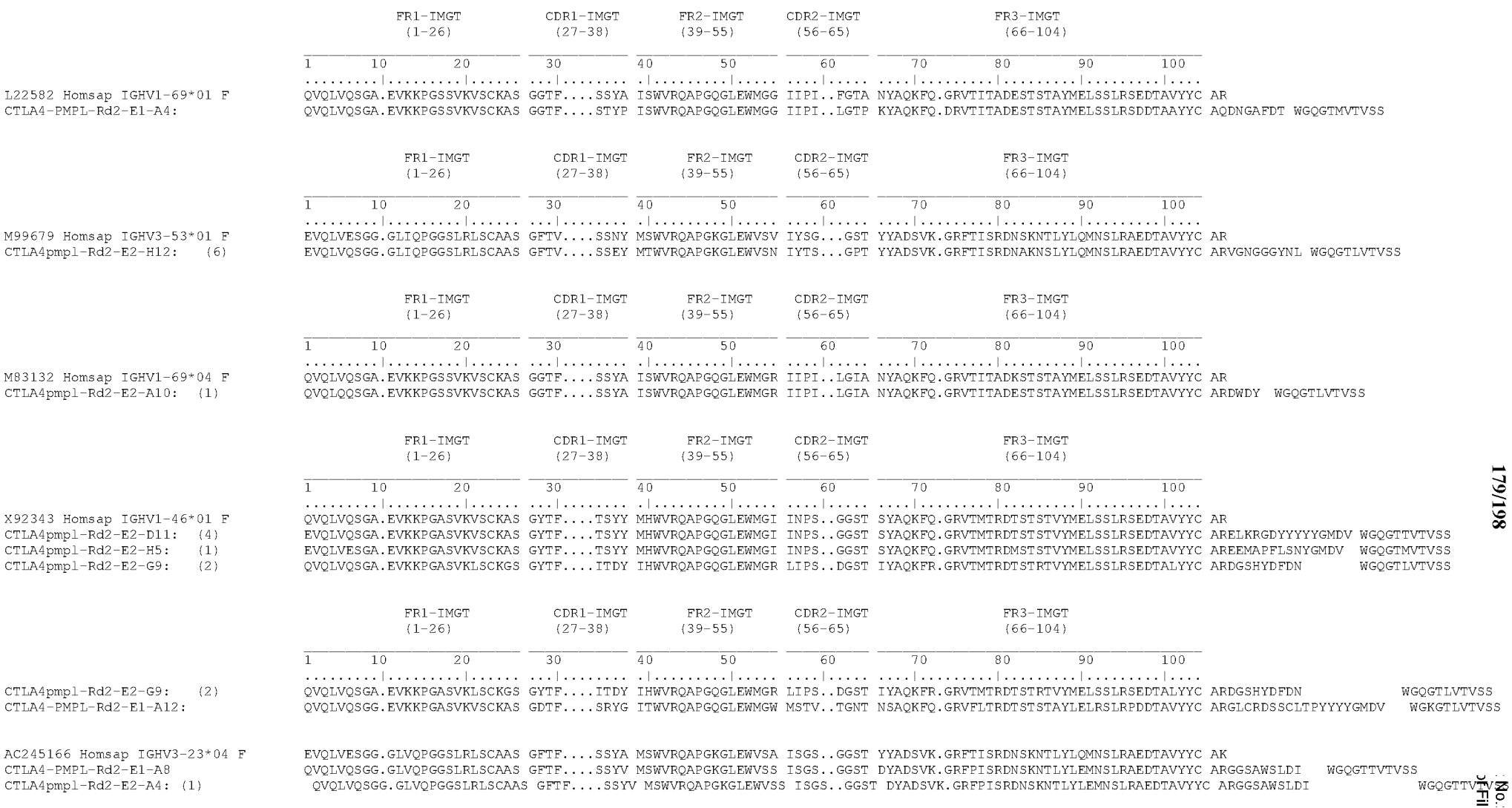
FR1-IMGT (1-26)
CDR1-IMGT (27-38)
FR2-IMGT (39-55)
CDR2-IMGT (56-65)
FR3-IMGT (66-104)
L22582 Homsap IGHV1-69*01 F QVQLVQSGA.EVKKPGSSVKVSCKAS GGTF....SSYA ISWVRQAPGQGLEWMGG IIPI..FGTA NYAQKFQ.GRVTITADESTSTAYMELSSLRSEDTAVYYC AR
CTLA4-PMPL-Rd2-E1-A4: QVQLVQSGA.EVKKPGSSVKVSCKAS GGTF....STYP ISWVRQAPGQGLEWMGG IIPI..LGTP KYAQKFQ.DRVTITADESTSTAYMELSSLRSDDTAAYYC AQDNGAFDT WGQGTMVTVSS
M99679 Homsap IGHV3-53*01 F EVQLVESGG.GLIQPGGSLRLSCAAS GFTV....SSNY MSWVRQAPGKGLEWVSV IYSG...GST YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AR
CTLA4pmpl-Rd2-E2-H12: (6) EVQLVQSGG.GLIQPGGSLRLSCAAS GFTV....SSEY MTWVRQAPGKGLEWVSN IYTS...GPT YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC ARVGNGGGYNL WGQGTLVTVSS
M83132 Homsap IGHV1-69*04 F QVQLVQSGA.EVKKPGSSVKVSCKAS GGTF....SSYA ISWVRQAPGQGLEWMGR IIPI..LGIA NYAQKFQ.GRVTITADESTSTAYMELSSLRSEDTAVYYC AR
CTLA4pmpl-Rd2-E2-A10: (1) QVQLQQSGA.EVKKPGSSVKVSCKAS GGTF....SSYA ISWVRQAPGQGLEWMGR IIPI..LGIA NYAQKFQ.GRVTITADESTSTAYMELSSLRSEDTAVYYC ARDWDY WGQGTLVTVSS
X92343 Homsap IGHV1-46*01 F QVQLVQSGA.EVKKPGASVKVSCKAS GYTF....TSYY MHWVRQAPGQGLEWMGI INPS..GGST SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC AR
CTLA4pmpl-Rd2-E2-D11: (4) EVQLVQSGA.EVKKPGASVKVSCKAS GYTF....TSYY MHWVRQAPGQGLEWMGI INPS..GGST SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC ARELKRGDYYYYYGMDV WGQGTTVTVSS
CTLA4pmpl-Rd2-E2-H5: (1) EVQLVESGA.EVKKPGASVKVSCKAS GYTF....TSYY MHWVRQAPGQGLEWMGI INPS..GGST SYAQKFQ.GRVTMTRDMSTSTVYMELSSLRSEDTAVYYC AREEMAPFLSNYGMDV WGQGTMVTVSS
CTLA4pmpl-Rd2-E2-G9: (2) QVQLVQSGA.EVKKPGASVKLSCKGS GYTF....ITDY IHWVRQAPGQGLEWMGR LIPS..DGST IYAQKFR.GRVTMTRDTSTRTVYMELSSLRSEDTALYYC ARDGSHYDFDN WGQGTLVTVSS
CTLA4pmpl-Rd2-E2-G9: (2) QVQLVQSGA.EVKKPGASVKLSCKGS GYTF....ITDY IHWVRQAPGQGLEWMGR LIPS..DGST IYAQKFR.GRVTMTRDTSTRTVYMELSSLRSEDTALYYC ARDGSHYDFDN WGQGTLVTVSS
CTLA4-PMPL-Rd2-E1-A12: QVQLVQSGG.EVKKPGASVKVSCKAS GDTF....SRYG ITWVRQAPGQGLEWMGW MSTV..TGNT NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC ARGLCRDSSCLTPYYYYGMDV WGKGTLVTVSS
AC245166 Homsap IGHV3-23*04 F EVQLVESGG.GLVQPGGSLRLSCAAS GFTF....SSYA MSWVRQAPGKGLEWVSA ISGS..GGST YYADSVK.GRFTISRDNSKNTLYLQMNSLRAEDTAVYYC AK
CTLA4-PMPL-Rd2-E1-A8 QVQLVQSGG.GLVQPGGSLRLSCAAS GFTF....SSYV MSWVRQAPGKGLEWVSS ISGS..GGST DYADSVK.GRFPISRDNSKNTLYLEMNSLRAEDTAVYYC ARGGSAWSLDI WGQGTTVTVSS
CTLA4pmpl-Rd2-E2-A4: (1) QVQLVQSGG.GLVQPGGSLRLSCAAS GFTF....SSYV MSWVRQAPGKGLEWVSS ISGS..GGST DYADSVK.GRFPISRDNSKNTLYLEMNSLRAEDTAVYYC ARGGSAWSLDI WGQGTTVTVSS

FIG. 67 CON'T

Anti CTLA-4 Vl:

	FR1-IMGT (1-26)	CDR1-IMGT (27-38)	FR2-IMGT (39-55)	CDR2-IMGT (56-65)	FR3-IMGT (66-104)	
X17263 Homsap IGKV1D-12*01 F	DIQMTQSPSSVSASVGDRVTITCRAS	QGI.....SSW	LAWYQQKPGKAPKLLIY	AA.....S	SLQSGVP.SRFSGSG..SGTDFTLTISSLQPEDFATYYC	QQANSFP
CTLA4-PMPL-Rd2-E1-A8:	DIQMTQSPSSVSASIGDRVTITCRAS	QDI.....SNS	LAWYQQKPGKAPKLLIY	GA.....S	NLRSGVP.SRFSGGG..SGTYFTLTISSLQPEDFATYYC	QQGNSFPIT FGQGTRLEIK

	FR1-IMGT (1-26)	CDR1-IMGT (27-38)	FR2-IMGT (39-55)	CDR2-IMGT (56-65)	FR3-IMGT (66-104)	
Z73650 Homsap IGLV8-61*01 F	QTVVTQEPS.FSVSPGGTVTLTCGLS	SGSVS...TSYY	PSWYQQTPGQAPRTLIY	ST.....N	TRSSGVP.DRFSGSI..LGNKAALTITGAQADDESDYYC	VLYMGSGI
CTLA4-PMPL-E1-Rd2-B10:	QTVVTQEPS.FSVSPGGTVTLTCGLS	SGSVS...TSYY	PSWYQQTPGQAPRTLIY	TT.....N	TRSSGVP.DRFSGSI..LGNKAALTITGAQADDESDYYC	VLYMGSGIWV FGGGTKLTVL

	FR1-IMGT (1-26)	CDR1-IMGT (27-38)	FR2-IMGT (39-55)	CDR2-IMGT (56-65)	FR3-IMGT (66-104)	
AC279317 Homsap IGLV4-60*03 F	QPVLTQSSS.ASASLGSSVKLTCTLS	SGHS.....SYI	IAWHQQQPGKAPRYLMK	LEGS...GSY	NKGSGVP.DRFSGSS..SGADRYLTISNLQSEDEADYYC	ETWDSNT
aCTLA4_T2-C10:	LPVLTQSSS.ASASLGSSVKLTCTLS	SGHS.....SYI	IAWHQQQPGKAPRYLMK	LEGS...GSY	NKGSGVP.DRFSGSS..SGADRYLTISNLQSEDEADYYC	ETWDSNLPSWV FGGGTKLTVL

	FR1-IMGT (1-26)	CDR1-IMGT (27-38)	FR2-IMGT (39-55)	CDR2-IMGT (56-65)	FR3-IMGT (66-104)	
D87007 Homsap IGLV3-21*02 F	SYVLTQPPS.VSVAPGQTARITCGGN	NIG.....SKS	VHWYQQKPGQAPVLVVY	DD.....S	DRPSGIP.ERFSGSN..SGNTATLTISRVEAGDEADYYC	QVWDSSSDH
CTLA4-PMPL-Rd2-E1-A10:	QPVLTQPPS.VSVAPGQTARITCGGN	NIG.....SKS	VHWYQQKPGQAPVLVVY	DD.....S	DRPSGIP.ERFSGSN..SGNTATLTISRVEAGDEADYYC	QVWANSTVV FGGGTKVTVL

FIG. 67 CON'T

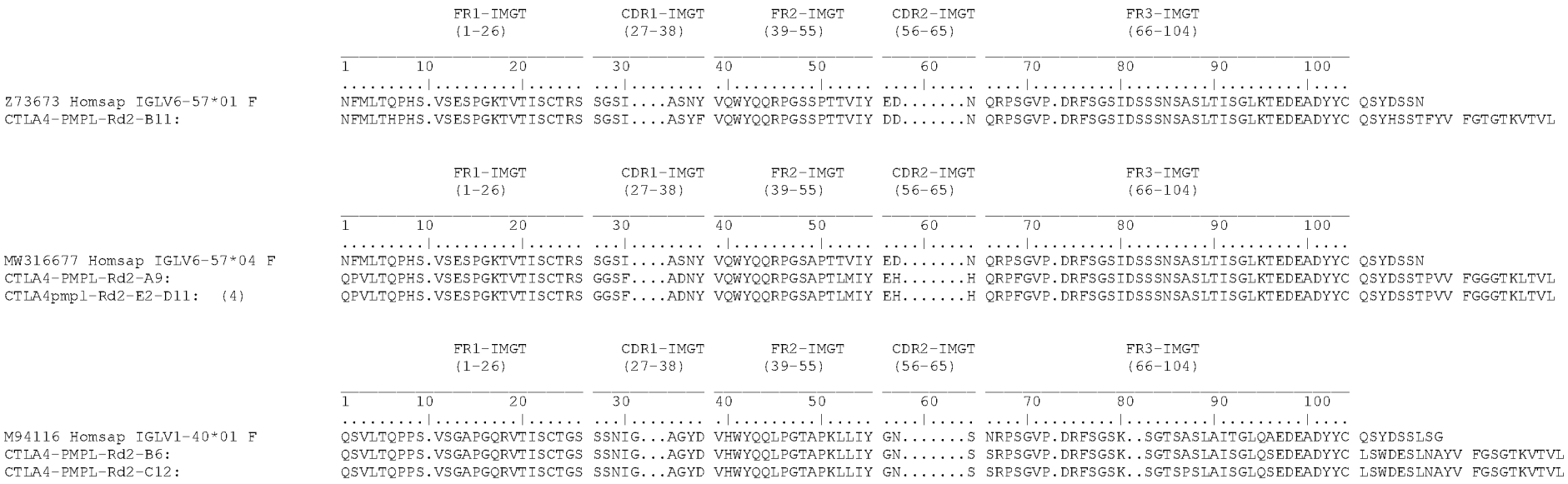
FR1-IMGT (1-26)
CDR1-IMGT (27-38)
FR2-IMGT (39-55)
CDR2-IMGT (56-65)
FR3-IMGT (66-104)
Z73673 Homsap IGLV6-57*01 F NFMLTQPHS.VSESPGKTVTISCTRS SGSI....ASNY VQWYQQRPGSSPTTVIY ED.....N QRPSGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC QSYDSSN
CTLA4-PMPL-Rd2-B11: NFMLTHPHS.VSESPGKTVTISCTRS SGSI....ASYF VQWYQQRPGSSPTTVIY DD.....N QRPSGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC QSYHSSTFYV FGTGTKVTVL
MW316677 Homsap IGLV6-57*04 F NFMLTQPHS.VSESPGKTVTISCTRS SGSI....ASNY VQWYQQRPGSAPTTVIY ED.....N QRPSGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC QSYDSSN
CTLA4-PMPL-Rd2-A9: QPVLTQPHS.VSESPGKTVTISCTRS GGSF....ADNY VQWYQQRPGSAPTLMIY EH.....H QRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC QSYDSSTPVV FGGGTKLTVL
CTLA4pmpl-Rd2-E2-D11: (4) QPVLTQPHS.VSESPGKTVTISCTRS GGSF....ADNY VQWYQQRPGSAPTLMIY EH.....H QRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC QSYDSSTPVV FGGGTKLTVL
M94116 Homsap IGLV1-40*01 F QSVLTQPPS.VSGAPGQRVTISCTGS SSNIG...AGYD VHWYQQLPGTAPKLLIY GN.....S NRPSGVP.DRFSGSK..SGTSASLAITGLQAEDEADYYC QSYDSSLSG
CTLA4-PMPL-Rd2-B6: QSVLTQPPS.VSGAPGQRVTISCTGS SSNIG...AGYD VHWYQQLPGTAPKLLIY GN.....S SRPSGVP.DRFSGSK..SGTSASLAISGLQSEDEADYYC LSWDESLNAYV FGSGTKVTVL
CTLA4-PMPL-Rd2-C12: QSVLTQPPS.VSGAPGQRVTISCTGS SSNIG...AGYD VHWYQQLPGTAPKLLIY GN.....S SRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYC LSWDESLNAYV FGSGTKVTVL

FIG. 67 CON'T

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                          FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT              FR3-IMGT
                            (1-26)            (27-38)         (39-55)       (56-65)                (66-104)

                          1       10        20          30        40        50          60        70        80        90        100
                          ........|.........|..... ...|........ .|.........|..... ....|..... ....|.........|.........|.........|....
AC279423 Homsap IGLV2-11*01 F QSALTQPRS.VSGSPGQSVTISCTGT SSDVG...GYNY VSWYQQHPGKAPKLMIY DV.......S KRPSGVP.DRFSGSK..SGNTASLTISGLQAEDEADYYC CSYAGSYTF
CTLA4-PMPL-Rd2-E1-A4:     QSALTQPRS.VSGSPGQSVTISCTGT SSDVG...GSDY VSWYQQHPGKAPKLIIY EV.......S KRPSGVS.DRFSGSK..SGNTASLRISGLQAQDEADYYC CSYAGSSTFV FGSGTEVTVL
CTLA4pmpl-Rd2-E2-G9: (2)  QPVLTQPRS.VSGSPGQSVTISCTGT SSDVG...GYNY VSWYQQHPGKAPKLIIY EV.......N KRPSGVP.DRFSGSK..SGNTASLTVSGLQAEDEADYYC SSYSSSSTLV FGGGTKLTVL

                          FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT              FR3-IMGT
                            (1-26)            (27-38)         (39-55)       (56-65)                (66-104)

                          1       10        20          30        40        50          60        70        80        90        100
                          ........|.........|..... ...|........ .|.........|..... ....|..... ....|.........|.........|.........|....
MW316675 Homsap IGLV7-46*04 F QAVVTQEPS.LTVSPGGTVTLTCGSS TGAVT...SGHY PYWFQQKPGQAPRTLIY DT.......S NKHSWTP.ARFSGSL..LGGKAALTLSGAQPEDEAEYYC LLSYSGAR
CTLA4-PMPL-Rd2-E1-A12:    QTVVTQEPS.LTVSPGGTVTLTCGSS TGAVT...TGHY PYWFQQKPGQAPTTLIY DA.......T HKHSWTP.ARFSGSV..LGGKAALTLSGAQPEDEADYYC LLSYSGARV FGGGTKLTVL
CTLA4-PMPL-Rd2-E1-B12:    QTVVTQEPS.LTVSPGGTVTLTCGSS TGAVT...TGHY PYWFQQKPGQAPTTLIY DA.......T HKHSWTP.ARFSGSV..LGGKAALTLSGAQPEDEADYYC LLSYSGARV FGGGTKLTVL

                          FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT              FR3-IMGT
                            (1-26)            (27-38)         (39-55)       (56-65)                (66-104)

                          1       10        20          30        40        50          60        70        80        90        100
                          ........|.........|..... ...|........ .|.........|..... ....|..... ....|.........|.........|.........|....
Z73664 Homsap IGLV2-14*01 F QSALTQPAS.VSGSPGQSITISCTGT SSDVG...GYNY VSWYQQHPGKAPKLMIY EV.......S NRPSGVS.NRFSGSK..SGNTASLTISGLQAEDEADYYC SSYTSSSTL
CTLA4pmpl-Rd2-E2-H12:  (6) QSALTQPAS.VSGSPGQSITISCTGT SGDVG...AHDY VSWYQQHPGKAPKLMIY EG.......S KRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYC SSFAGTNYV FGTGTKVAVL
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FIG. 67 CON'T

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                                FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT              FR3-IMGT
                                  (1-26)            (27-38)         (39-55)       (56-65)                (66-104)

                                ____________________ _________ _____________ _____ ____________________________________
                                1       10        20   30      40        50    60    70        80        90        100
                                ........|.........|..... ...|..... .|........|.... ....|.... ....|.........|.........|....
M94116 Homsap IGLV1-40*01 F     QSVLTQPPS.VSGAPGQRVTISCTGS SSNIG...AGYD VHWYQQLPGTAPKLLIY GN.......S NRPSGVP.DRFSGSK..SGTSASLAITGLQAEDEADYYC QSYDSSLSG
CTLA4pmpl-Rd2-E2-A4: (1)        IQMTQSPSS.VSASIGDRVTITCRAS QDI......SNS LAWYQQKPGKAPKLLIY GA.......S NLRSGVP.SRFSGGG..SGTYFTLTISSLQPEDFATYYC QQGNSFPIT
CTLA4pmpl-Rd2-E2-H2: (12)       QSVLTQPPS.VSGAPGQRVTISCTGS SSNIG...AGYD VHWYQQLPGTAPKLLIY GN.......S SRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYC LSWDESLNAYV FGSGTKVTVL

                                FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT              FR3-IMGT
                                  (1-26)            (27-38)         (39-55)       (56-65)                (66-104)

                                ____________________ _________ _____________ _____ ____________________________________
                                1       10        20   30      40        50    60    70        80        90        100
                                ........|.........|..... ...|..... .|........|.... ....|.... ....|.........|.........|....
D87016 Homsap IGLV1-47*02 F     QSVLTQPPS.ASGTPGQRVTISCSGS SSNI....GSNY VYWYQQLPGTAPKLLIY SN.......N QRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYC AAWDDSLSG
CTLA4pmpl-Rd2-E2-G5:   (1)      QPGLTQPPS.ASGTPGQRVTLSCSGS SSNI....GSNY VFWYQQLPGTAPKLLIY SN.......N QRPSGVP.DRFSASK..SGTSASLAISGLRSEDEADYYC AAWDDSLSGWV FGGGTKLTVL

                                FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT              FR3-IMGT
                                  (1-26)            (27-38)         (39-55)       (56-65)                (66-104)

                                ____________________ _________ _____________ _____ ____________________________________
                                1       10        20   30      40        50    60    70        80        90        100
                                ........|.........|..... ...|..... .|........|.... ....|.... ....|.........|.........|....
KM455556 Homsap IGLV6-57*02 F   NFMLTQPHS.VSESPGKTVTISCTGS SGSI....ASNY VQWYQQRPGSAPTTVIY ED.......N QRPSGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC QSYDSSN
CTLA4pmpl-Rd2-E2-H5:    (1)     NFMLTHPHS.VSESPGKTVTISCTGS SDSL....ASNY VQWYQQRPGSAPTTVIY EN.......N QRPSGVP.DRFSGSIDGSSNSASLTISALETEDEADYYC QSYDGTPV FGTGTKLTVL

                                FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT              FR3-IMGT
                                  (1-26)            (27-38)         (39-55)       (56-65)                (66-104)

                                ____________________ _________ _____________ _____ ____________________________________
                                1       10        20   30      40        50    60    70        80        90        100
                                ........|.........|..... ...|..... .|........|.... ....|.... ....|.........|.........|....
Z73674 Homsap IGLV7-46*01 F     QAVVTQEPS.LTVSPGGTVTLTCGSS TGAVT...SGHY PYWFQQKPGQAPRTLIY DT.......S NKHSWTP.ARFSGSL..LGGKAALTLSGAQPEDEAEYYC LLSYSGAR
CTLA4pmpl-Rd2-E2-D10:  (3)      QTVVTQEPS.LTVSPGGTVTLTCGSS TGAVT...SGHY PYWFQQKPGQAPRTLIY DT.......T NRHSWTP.ARFSGSL..LGAKAALTLSGVQPEDEADYYC LLSYSGDRV FGGETKLTVL
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FIG. 67 CON'T

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                                FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT              FR3-IMGT
                                  (1-26)            (27-38)         (39-55)       (56-65)                (66-104)
                   ____________________________ _____________ _______________ _____________ ____________________________________
                   1        10        20        30          40        50        60        70        80        90        100
                   .........|.........|..... ...|........ .|.........|..... ....|..... ....|.........|.........|.........|....
MW316675 Homsap IGLV7-46*04 F QAVVTQEPS.LTVSPGGTVTLTCGSS TGAVT...SGHY PYWFQQKPGQAPRTLIY DT.......S NKHSWTP.ARFSGSL..LGGKAALTLSGAQPEDEAEYYC LLSYSGAR
CTLA4pmpl-Rd2-E2-H10: (1)  QTVVTQEPS.LTVSPGGTVTLTCGSS TGAVT...TGHY PYWFQQKPGQAPTTLIY DA.......T HKHSWTP.ARFSGSV..LGGKAALTLSGAQPEDEADYYC LLSYSGARV FGGGTKLTVL

                                FR1-IMGT          CDR1-IMGT       FR2-IMGT      CDR2-IMGT              FR3-IMGT
                                  (1-26)            (27-38)         (39-55)       (56-65)                (66-104)
                   ____________________________ _____________ _______________ _____________ ____________________________________
                   1        10        20        30          40        50        60        70        80        90        100
                   .........|.........|..... ...|........ .|.........|..... ....|..... ....|.........|.........|.........|....
Z73650 Homsap IGLV8-61*01 F QTVVTQEPS.FSVSPGGTVTLTCGLS SGSVS...TSYY PSWYQQTPGQAPRTLIY ST.......N TRSSGVP.DRFSGSI..LGNKAALTITGAQADDESDYYC VLYMGSGI
CTLA4pmpl-Rd2-E2-A10:    (1)  QTVVTQEPS.FSVAPGGTVTLTCALS SGSVS...SNYH PSWFQQTPGQAPRTLIY NT.......D IRSHGVP.DRFSGSL..LGNKAALTITGAQPNDESEYYC ALYMGSGISI FGGGTKVTVL
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FIG. 67 CON'T

	Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele
aa)	hCTLA4-Rd3b-T1-E6		Homsap IGHV4-30-4*08 (F)	Homsap IGHJ6*02 F	Homsap IGHD2-15*01 F
bb)	hCTLA4-Rd3b-E4-F2		Homsap IGHV3-49*04 F	Homsap IGHJ3*01 F, or Homsap IGHJ3*02 F or Homsap IGHJ6*02 F or Homsap IGHJ6*03 F	Homsap IGHD5-18*01 F
cc)	hCTLA4-Rd3b-T1-A3		Homsap IGHV3-49*04 F	Homsap IGHJ3*01 F, or Homsap IGHJ3*02 F or Homsap IGHJ6*02 F or Homsap IGHJ6*03 F	Homsap IGHD5-18*01 F
dd)	hCTLA4-T1-A6		Homsap IGHV3-21*01 F	Homsap IGHJ4*01 F, or Homsap IGHJ4*03 F	Homsap IGHD1-26*01 F
ee)	hCTLA4-Rd3b-T1-A10		Homsap IGHV3-7*03 F	Homsap IGHJ6*02 F	Homsap IGHD2-21*01 F
ff)	hCTLA4-Rd3b-E2-D5		Homsap IGHV3-23*04 F	Homsap IGHJ3*01 F	Homsap IGHD4-23*01 ORF
gg)	hCTLA4-Rd3b-E2-G6		Homsap IGHV3-23*01 F, or Homsap IGHV3-23D*01 F	Homsap IGHJ3*01 F	Homsap IGHD4-23*01 ORF
hh)	hCTLA4-Rd3b-E2-H3		Homsap IGHV1-18*01 F	Homsap IGHJ3*01 F	Homsap IGHD4-17*01 F
ii)	CTLA4pmpl-Rd2-E2-H12	productive	Homsap IGHV3-53*01 F, or Homsap IGHV3-53*03 F	Homsap IGHJ1*01 F	Homsap IGHD5-24*01 ORF
jj)	CTLA4pmpl-Rd2-E2-H2	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*02 F, or Homsap IGHJ6*03 F	Homsap IGHD1-14*01 ORF
kk)	CTLA4pmpl-Rd2-E2-D10	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*04 F	Homsap IGHD2-15*01 F
ll)	CTLA4pmpl-Rd2-E2-D11	productive	Homsap IGHV1-46*01 F, or Homsap IGHV1-46*03 F	Homsap IGHJ6*02 F	Homsap IGHD1-1*01 F

FIG. 68

	V-D-J-REGION	V-J-REGION	V-REGION
aa)	QVQLQESGG.GVVQPGRSLRLSCAASGFTF....SSYGMHWVRQPPGEGLEWIGHISYS...GNTYYNPSLR.SRFSISKDTSKNQFSLHLRS VTAADTAVYYCARLPYCSGGNCYDMDVWGQGTLVTVSS		QVQLQESGG.GVVQPGRSLRLSCAASGFTF....SSYGMHWVRQPPGEGLEWIGHISYS...G LRSVTAADTAVYYCAR
bb)	QVQLVQSGG.GLVQPGRSLRLSCRGSGFTF....GDYAMSWVRQAPGKGLEWIAFITAKAHGGVTEYAASVK.GRFTISRDDSKNTAYLQM NSLKTEDTAVYYCSNQRWLSSPLWGQGTTVTVSS		QVQLVQSGG.GLVQPGRSLRLSCRGSGFTF....GDYAMSWVRQAPGKGLEWIAFITAKAH LQMNSLKTEDTAVYYCS
cc)	QVQLVQSGG.GLVQPGRSLRLSCRGSGFTF....GDYAMSWVRQAPGKGLEWIAFIRAKAHGGVTEYAASVK.GRFTISRDDSKNTAYLQM NSLKTEDTAVYYCSNQRWLSSPLWGQGTTVTVSS		QVQLVQSGG.GLVQPGRSLRLSCRGSGFTF....GDYAMSWVRQAPGKGLEWIAFIRAKAH LQMNSLKTEDTAVYYCS
dd)	QVQLVQSGG.GLVQPGGSLRLSCAASGFTF....SSYSMNWVRQAPGKGLEWVSSISSS..SSYIYYADSVK.GRFTISRDNAKNSLYLQMNS LRDEDTAVYYCARGVGGTMKMDVWGQGTLVTVSS		QVQLVQSGG.GLVQPGGSLRLSCAASGFTF....SSYSMNWVRQAPGKGLEWVSSISSS..S QMNSLRDEDTAVYYCAR
ee)	QVQLVQSGG.GLVQPGGSLRLSCAASGFGF....KNYWMTWVRQAPGKGLEWVANIKKD..GSEKYYVDSVK.GRFTSSRDNAKNSLYLQM NSLRAEDTAVYYCARGHFGMDVWGPGTTVTVSS		QVQLVQSGG.GLVQPGGSLRLSCAASGFGF....KNYWMTWVRQAPGKGLEWVANIKKD..G YLQMNSLRAEDTAVYYCA
ff)	QVQLVQSGG.GLVQPGGSLRLSCAASGFTF....VSYAMSWVRQAPGKGLEWVSSISGS..GGDTYYADSVK.GRFTISRDNSESRLYLQMN SLGPEDTALYYCVKSKGGIRKYMEVWGQGTMVTVSS		QVQLVQSGG.GLVQPGGSLRLSCAASGFTF....VSYAMSWVRQAPGKGLEWVSSISGS..G QMNSLGPEDTALYYCV
gg)	.QVPWCVWG.RLGPAWGVPDTLLCASGFTF....VNYAMTWIRQAPGKGLEWVSCIIGS..GGDTYYAHSVK.GRITISKDNSQSRLYLLMNML GPEDSVLYYCVKSKGGIRKYMEVWGQGTMVTVSS		.QVPWCVWG.RLGPAWGVPDTLLCASGFTF....VNYAMTWIRQAPGKGLEWVSCIIGS..GG MNMLGPEDSVLYYCV
hh)	EVQLVQSGP.EVKKPGDSVKVPCKASGYTF....STYGISWVRQAPGQGLEWMGWVSAY..RRNANYAQKFQ.DRVTMTTDTSTNTAYMEL KSLRSDDTAIYFCARKRYGAFDVWGQGTMVTVSS		EVQLVQSGP.EVKKPGDSVKVPCKASGYTF....STYGISWVRQAPGQGLEWMGWVSAY..F YMELKSLRSDDTAIYFCAR
ii)	EVQLVQSGG.GLIQPGGSLRLSCAASGFTV....SSEYMTWVRQAPGKGLEWVSNIYTS...GPTYYADSVK.GRFTISRDNAKNSLYLQMNSL RAEDTAVYYCARVGNGGGYNLWGQGTLVTVSS		EVQLVQSGG.GLIQPGGSLRLSCAASGFTV....SSEYMTWVRQAPGKGLEWVSNIYTS...GF MNSLRAEDTAVYYCAR
jj)	QVQLQQSGT.EVKKPGASVKVSCKASGYIF....TSYGFTWVRQAPGQGLEWMGWISSY..NGNTDYAQKFE.GRVTMTTDTSTTTAYMELR GLKSDDTAMYYCARGPQMDVWGQGTTVTVSS		QVQLQQSGT.EVKKPGASVKVSCKASGYIF....TSYGFTWVRQAPGQGLEWMGWISSY..N MELRGLKSDDTAMYYCAR
kk)	QVQLVQSGG.EVKKPGASVKVSCKASGDTF....SRYGITWVRQAPGQGLEWMGWMSTV..TGNTNSAQKFQ.GRVFLTRDTSTSTAYLEL RSLRPDDTAVYYCARGLCRDSSCLTPYYYYGMDVWGKGTLVTVSS		QVQLVQSGG.EVKKPGASVKVSCKASGDTF....SRYGITWVRQAPGQGLEWMGWMSTV..' YLELRSLRPDDTAVYYCAR
ll)	EVQLVQSGA.EVKKPGASVKVSCKASGYTF....TSYYMHWVRQAPGQGLEWMGIINPS..GGSTSYAQKFQ.GRVTMTRDTSTSTVYMELS SLRSEDTAVYYCARELKRGDYYYYYGMDVWGQGTTVTVSS		EVQLVQSGA.EVKKPGASVKVSCKASGYTF....TSYYMHWVRQAPGQGLEWMGIINPS..G MELSSLRSEDTAVYYCAR

FIG. 68 CON'T

	FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
aa)	QVQLQESGG.GVVQPGRSLRLSCAAS	GFTF....SSYG	MHWVRQPPGEGLEWIGH	ISYS...GNTKNQFSLHLRSVTAADTAVYYC	YYNPSLR.SRFSISKDTS	ARLPYCSGGNCYDMDV	CARLPYCSGGNCYDMDVW	CYDMDVWGQGTLVTVSS	WGQGTLVTVSS
bb)	QVQLVQSGG.GLVQPGRSLRLSCRGS	GFTF....GDYA	MSWVRQAPGKGLEWIAF	ITAKAHGGVT	EYAASVK.GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC	SNQRWLSSPL	CSNQRWLSSPLW	WGQGTTVTVSS	WGQGTTVTVSS
cc)	QVQLVQSGG.GLVQPGRSLRLSCRGS	GFTF....GDYA	MSWVRQAPGKGLEWIAF	IRAKAHGGVT	EYAASVK.GRFTISRDDSKNTAYLQMNSLKTEDTAVYYC	SNQRWLSSPL	CSNQRWLSSPLW	WGQGTTVTVSS	WGQGTTVTVSS
dd)	QVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF....SSYS	MNWVRQAPGKGLEWVSS	ISSS..SSYI	YYADSVK.GRFTISRDNAKNSLYLQMNSLRDEDTAVYYC	ARGVGGTMKMDV	CARGVGGTMKMDVW	DVWGQGTLVTVSS	WGQGTLVTVSS
ee)	QVQLVQSGG.GLVQPGGSLRLSCAAS	GFGF....KNYW	MTWVRQAPGKGLEWVAN	IKKD..GSEK	YYVDSVK.GRFTSSRDNAKNSLYLQMNSLRAEDTAVYYC	ARGHFGMDV	CARGHFGMDVW	GMDVWGPGTTVTVSS	WGPGTTVTVSS
ff)	QVQLVQSGG.GLVQPGGSLRLSCAAS	GFTF....VSYA	MSWVRQAPGKGLEWVSS	ISGS..GGDT	YYADSVK.GRFTISRDNSESRLYLQMNSLGPEDTALYYC	VKSKGGIRKYMEV	CVKSKGGIRKYMEVW	EVWGQGTMVTVSS	WGQGTMVTVSS
gg)	.QVPWCVWG.RLGPAWGVPDTLLCAS	GFTF....VNYA	MTWIRQAPGKGLEWVSC	IIGS..GGDT	YYAHSVK.GRITISKDNSQSRLYLLMNMLGPEDSVLYYC	VKSKGGIRKYMEV	CVKSKGGIRKYMEVW	EVWGQGTMVTVSS	WGQGTMVTVSS
hh)	EVQLVQSGP.EVKKPGDSVKVPCKAS	GYTF....STYG	ISWVRQAPGQGLEWMGW	VSAY..RRNA	NYAQKFQ.DRVTMTTDTSTNTAYMELKSLRSDDTAIYFC	ARKRYGAFDV	CARKRYGAFDVW	AFDVWGQGTMVTVSS	WGQGTMVTVSS
ii)	EVQLVQSGG.GLIQPGGSLRLSCAAS	GFTV....SSEY	MTWVRQAPGKGLEWVSN	IYTS...GPT	YYADSVK.GRFTISRDNAKNSLYLQMNSLRAEDTAVYYC	ARVGNGGGYNL	CARVGNGGGYNLW	WGQGTLVTVSS	WGQGTLVTVSS
jj)	QVQLQQSGT.EVKKPGASVKVSCKAS	GYIF....TSYG	FTWVRQAPGQGLEWMGW	ISSY..NGNT	DYAQKFE.GRVTMTTDTSTTTAYMELRGLKSDDTAMYYC	ARGPQMDV	CARGPQMDVW	MDVWGQGTTVTVSS	WGQGTTVTVSS
kk)	QVQLVQSGG.EVKKPGASVKVSCKAS	GDTF....SRYG	ITWVRQAPGQGLEWMGW	MSTV..TGNT	NSAQKFQ.GRVFLTRDTSTSTAYLELRSLRPDDTAVYYC	ARGLCRDSSCLTPYYYYGMDV	CARGLCRDSSCLTPYYYYGMDVW	YYYYGMDVWGKGTLVTVSS	WGKGTLVTVSS
ll)	EVQLVQSGA.EVKKPGASVKVSCKAS	GYTF....TSYY	MHWVRQAPGQGLEWMGI	INPS..GGST	SYAQKFQ.GRVTMTRDTSTSTVYMELSSLRSEDTAVYYC	ARELKRGDYYYYYGMDV	CARELKRGDYYYYYGMDVW	YYYYYGMDVWGQGTTVTVSS	WGQGTTVTVSS

FIG. 68 CON'T

	Sequence ID	V-GENE and allele	J-GENE and allele
aa)	hCTLA4-Rd3b-T1-E6	Homsap IGLV6-57*03 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F
bb)	hCTLA4-Rd3b-E4-F2	Homsap IGLV1-44*01 F	Homsap IGLJ3*02 F
cc)	hCTLA4-Rd3b-T1-A3	Homsap IGLV1-44*01 F	Homsap IGLJ3*02 F
dd)	hCTLA4-T1-A6	Homsap IGLV1-47*01 F	Homsap IGLJ3*02 F
ee)	hCTLA4-Rd3b-T1-A10	Homsap IGLV3-19*01 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F
ff)	hCTLA4-Rd3b-E2-D5	Homsap IGLV10-54*01 F	Homsap IGLJ3*02 F
gg)	hCTLA4-Rd3b-E2-G6	Homsap IGLV10-54*01 F	Homsap IGLJ3*02 F
hh)	hCTLA4-Rd3b-E2-H3	Homsap IGLV10-54*01 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F
ii)			
jj)			
kk)			
ll)			

FIG. 68 CON'T

	D-GENE and allele	V-D-J-REGION	V-J-REGION	V-REGION
aa)			NFMLTQPHS.MSESPGKTVTISCTRSSGSI....ASNYVQWFQQRPGSAPTTVIYED.....NQRPSGVP.DRFSGSIDRSSNSASLIISGLKTEDEADYYCHSYDSTNVVFGGGTKLTVL	NFMLTQPHS.MSESPGKTVTISCTRSSGSI....ASNYVQWFQQRPGSAPTTVIYED.....NQRPSGVP.DRFSGSIDRSSNSASLIISGLKTEDEADYYCHSYDSTN
bb)			LPVLTQAPS.ASGTPGQRVTISCSGSSSNI....GSNTVNWYQHLPGTAPKLLIYSN.....NQRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYCAAWDDSLSGQVFGGGTKLTVL	LPVLTQAPS.ASGTPGQRVTISCSGSSSNI....GSNTVNWYQHLPGTAPKLLIYSN.....NQRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYCAAWDDSLSG
cc)			LPVLTQAPS.ASGTPGQRVTISCSGSSSNI....GSNTVNWYQHLPGTAPKLLIYSN.....NQRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYCAAWDDSLSGQVFGGGTKLTVL	LPVLTQAPS.ASGTPGQRVTISCSGSSSNI....GSNTVNWYQHLPGTAPKLLIYSN.....NQRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYCAAWDDSLSG
dd)			QSVLTQPPS.ASGTPGQTVTITCSGSDSNI....GSNYVYWYQQLPGTAPKLLIYRN.....NQRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYCAAWDDSLSGPVFGGGTKLTVL	QSVLTQPPS.ASGTPGQTVTITCSGSDSNI....GSNYVYWYQQLPGTAPKLLIYRN.....NQRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYCAAWDDSLSG
ee)			SSELTQDPA.VSVALGQTVRITCQGDSLR.....RYYASWYQQKPGQAPLVVIFGK.....DKRPSGIP.DRFSGSR..SGNTASLTITATQAEDEADYYCGSRDSSGTRVVFGGGTKVTRP	SSELTQDPA.VSVALGQTVRITCQGDSLR.....RYYASWYQQKPGQAPLVVIFGK.....DKRPSGIP.DRFSGSR..SGNTASLTITATQAEDEADYYCGSRDSSGT
ff)			QPGLTQPPS.VSKGLRQTATLTCTGNSNNV....GNQGAAWLQQHQGHPPKLLFFRN.....GKRPSGIS.ERFSASR..SGSTASLTITELQPDDEADYYCSAWDRSLVAWVFGGGTRVTVL	QPGLTQPPS.VSKGLRQTATLTCTGNSNNV....GNQGAAWLQQHQGHPPKLLFFRN.....GKRPSGIS.ERFSASR..SGSTASLTITELQPDDEADYYCSAWDRSLVA
gg)			HPGLTHPPS.ESKGLIHTATLTCTGNSNNV....GNQGAPWLHHHHGHPPKLLFFIN.....GKRPSWIS.KRFSASK..SRSTASLTITELQPDDDADYYCTAWDRSLVAWVFGGGTRVTVL	HPGLTHPPS.ESKGLIHTATLTCTGNSNNV....GNQGAPWLHHHHGHPPKLLFFIN.....GKRPSWIS.KRFSASK..SRSTASLTITELQPDDDADYYCTAWDRSLVA
hh)			SYELTQPPS.VSEGLRQTATLTCTGNSNNV....GNQGAAWLQQHQGHPPKLLSYRN.....NNRPSGIS.ERLSASR..SGNTASLTITGLQPEDEADYYCSAWDSSLSAVIFGGGTKLTVL	SYELTQPPS.VSEGLRQTATLTCTGNSNNV....GNQGAAWLQQHQGHPPKLLSYRN.....NNRPSGIS.ERLSASR..SGNTASLTITGLQPEDEADYYCSAWDSSLSA
ii)			QSALTQPAS.VSGSPGQSITISCTGTSGDVG...AHDYVSWYQQHPGKAPKLMIYEG.....SKRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYCSSFAGTNNYVFGTGTKVAVL	QSALTQPAS.VSGSPGQSITISCTGTSGDVG...AHDYVSWYQQHPGKAPKLMIYEG.....SKRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYCSSFAGTN
jj)			QSVLTQPPS.VSGAPGQRVTISCTGSSSNIG...AGYDVHWYQQLPGTAPKLLIYGN.....SSRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYCLSWDESLNAYVFGSGTKVTVL	QSVLTQPPS.VSGAPGQRVTISCTGSSSNIG...AGYDVHWYQQLPGTAPKLLIYGN.....SSRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYCLSW
kk)			QTVVTQEPS.LTVSPGGTVTLTCGSSTGAVT...SGHYPYWFQQKPGQAPRTLIYDT.....TNRHSWTP.ARFSGSL..LGAKAALTLSGVQPEDEADYYCLLSYSGDRVFGGETKLTVL	QTVVTQEPS.LTVSPGGTVTLTCGSSTGAVT...SGHYPYWFQQKPGQAPRTLIYDT.....TNRHSWTP.ARFSGSL..LGAKAALTLSGVQPEDEADYYCLLSYSGD
ll)			QPVLTQPHS.VSESPGKTVTISCTRSGGSF....ADNYVQWYQQRPGSAPTLMIYEH.....HQRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSSTPVVFGGGTKLTVL	QPVLTQPHS.VSESPGKTVTISCTRSGGSF....ADNYVQWYQQRPGSAPTLMIYEH.....HQRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYCQSYDSST

FIG. 68 CON'T

	FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
aa)	NFMLTQPHS.MSESPGKTVTISCTRS	SGSI....ASNY	VQWFQQRPGSAPTTVIY	ED.....N	QRPSGVP.DRFSGSIDRSSNSASLIISGLKTEDEADYYC	HSYDSTNVV	CHSYDSTNVVF	VVFGGGTKLTVL	FGGGTKLTVL
bb)	LPVLTQAPS.ASGTPGQRVTISCSGS	SSNI....GSNT	VNWYQHLPGTAPKLLIY	SN.....N	QRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYC	AAWDDSLSGQV	CAAWDDSLSGQVF	VFGGGTKLTVL	FGGGTKLTVL
cc)	LPVLTQAPS.ASGTPGQRVTISCSGS	SSNI....GSNT	VNWYQHLPGTAPKLLIY	SN.....N	QRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYC	AAWDDSLSGQV	CAAWDDSLSGQVF	VFGGGTKLTVL	FGGGTKLTVL
dd)	QSVLTQPPS.ASGTPGQTVTITCSGS	DSNI....GSNY	VYWYQQLPGTAPKLLIY	RN.....N	QRPSGVP.DRFSGSK..SGTSASLAISGLRSEDEADYYC	AAWDDSLSGPV	CAAWDDSLSGPVF	VFGGGTKLTVL	FGGGTKLTVL
ee)	SSELTQDPA.VSVALGQTVRITCQGD	SLR.....RYY	ASWYQQKPGQAPLVVIF	GK.....D	KRPSGIP.DRFSGSR..SGNTASLTITATQAEDEADYYC	GSRDSSGTRVV	CGSRDSSGTRVVF	VVFGGGTKVTRP	FGGGTKVTRP
ff)	QPGLTQPPS.VSKGLRQTATLTCTGN	SNNV....GNQG	AAWLQQHQGHPPKLLFF	RN.....G	KRPSGIS.ERFSASR..SGSTASLTITELQPDDEADYYC	SAWDRSLVAWV	CSAWDRSLVAWVF	WVFGGGTRVTVL	FGGGTRVTVL
gg)	HPGLTHPPS.ESKGLIHTATLTCTGN	SNNV....GNQG	APWLHHHHGHPPKLLFF	IN.....G	KRPSWIS.KRFSASK..SRSTASLTITELQPDDDADYYC	TAWDRSLVAWV	CTAWDRSLVAWVF	WVFGGGTRVTVL	FGGGTRVTVL
hh)	SYELTQPPS.VSEGLRQTATLTCTGN	SNNV....GNQG	AAWLQQHQGHPPKLLSY	RN.....N	NRPSGIS.ERLSASR..SGNTASLTITGLQPEDEADYYC	SAWDSSLSAVI	CSAWDSSLSAVIF	VIFGGGTKLTVL	FGGGTKLTVL
ii)	QSALTQPAS.VSGSPGQSITISCTGT	SGDVG...AHDY	VSWYQQHPGKAPKLMIY	EG.....S	KRPSGVS.NRFSGSK..SGNTASLTVSGLQAEDEADYYC	SSFAGTNNYV	CSSFAGTNNYVF	YVFGTGTKVAVL	FGTGTKVAVL
jj)	QSVLTQPPS.VSGAPGQRVTISCTGS		VHWYQQLPGTAPKLLIY	GN.....S	SRPSGVP.DRFSGSK..SGTSPSLAISGLQSEDEADYYC	LSWDESLNAYV	CLSWDESLNAYVF	YVFGSGTKVTVL	FGSGTKVTVL
kk)	QTVVTQEPS.LTVSPGGTVTLTCGSS	TGAVT...SGHY	PYWFQQKPGQAPRTLIY	DT.....T	NRHSWTP.ARFSGSL..LGAKAALTLSGVQPEDEADYYC	LLSYSGDRV	CLLSYSGDRVF	VFGGETKLTVL	FGGETKLTVL
ll)	QPVLTQPHS.VSESPGKTVTISCTRS	GGSF....ADNY	VQWYQQRPGSAPTLMIY	EH.....H	QRPFGVP.DRFSGSIDSSSNSASLTISGLKTEDEADYYC	QSYDSSTPVV	CQSYDSSTPVVF	VVFGGGTKLTVL	FGGGTKLTVL

FIG. 68 CON'T

	Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele
aa)	hCTLA4-Rd3b-T1-E6_PelB-F_2021-02-10_E05	productive	Homsap IGHV4-30-4*08 (F)	Homsap IGHJ6*02 F	Homsap IGHD2-15*01 F
bb)	hCTLA4-Rd3b-E4-F2_PelB-F_2021-02-10_F06	productive	Homsap IGHV3-49*04 F	Homsap IGHJ3*01 F, or Homsap IGHJ3*02 F or Homsap IGHJ6*02 F or Homsap IGHJ6*03 F	Homsap IGHD5-18*01 F
cc)	hCTLA4-Rd3b-T1-A3_PelB-F_2021-02-10_B01	productive	Homsap IGHV3-49*04 F	Homsap IGHJ3*01 F, or Homsap IGHJ3*02 F or Homsap IGHJ6*02 F or Homsap IGHJ6*03 F	Homsap IGHD5-18*01 F
dd)	hCTLA4-T1-A6_PelB-F_2021-02-05_B04	productive	Homsap IGHV3-21*01 F	Homsap IGHJ4*01 F, or Homsap IGHJ4*03 F	Homsap IGHD1-26*01 F
ee)	hCTLA4-Rd3b-T1-A10_PelB-F_2021-02-10_F01	productive	Homsap IGHV3-7*03 F	Homsap IGHJ6*02 F	Homsap IGHD2-21*01 F
ff)	hCTLA4-Rd3b-E2-D5_PelB-F_2021-02-10_B05	productive	Homsap IGHV3-23*04 F	Homsap IGHJ3*01 F	Homsap IGHD4-23*01 ORF
gg)	hCTLA4-Rd3b-E2-G6_PelB-F_2021-02-10_C08	productive	Homsap IGHV3-23*01 F, or Homsap IGHV3-23D*01 F	Homsap IGHJ3*01 F	Homsap IGHD4-23*01 ORF
hh)	hCTLA4-Rd3b-E2-H3_PelB-F_2021-02-10_H08	productive	Homsap IGHV1-18*01 F	Homsap IGHJ3*01 F	Homsap IGHD4-17*01 F
ii)	CTLA4pmpl-Rd2-E2-H12_PelB-F_2021-08-06_H06	productive	Homsap IGHV3-53*01 F, or Homsap IGHV3-53*03 F	Homsap IGHJ1*01 F	Homsap IGHD5-24*01 ORF
jj)	CTLA4pmpl-Rd2-E2-H2_PelB-F_2021-08-06_H05	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*02 F, or Homsap IGHJ6*03 F	Homsap IGHD1-14*01 ORF
kk)	CTLA4pmpl-Rd2-E2-D10_PelB-F_2021-08-06_H02	productive	Homsap IGHV1-18*01 F	Homsap IGHJ6*04 F	Homsap IGHD2-15*01 F
ll)	CTLA4pmpl-Rd2-E2-D11_PelB-F_2021-08-06_A03	productive	Homsap IGHV1-46*01 F, or Homsap IGHV1-46*03 F	Homsap IGHJ6*02 F	Homsap IGHD1-1*01 F

FIG. 69

V-D-J-REGION V-J-REGION

aa) caggtgcagctgcaggagtcgggggga...ggcgtggtccagcctgggaggtctctgagactctcctgtgcagcctctggattcaccttc.....agcagctatggcatgcactgggtccgccagccccccaggggagggcctggagtggattgggcacatctcttacagt.....ggcaac
acttactacaacccgtcgctcaga...agtcgatttagtatttcaaaagacacgtccaagaatcagttctccctgcacctgaggtctgtgactgccgcagacacggccgtttattactgtgccagactgccatattgtagtggtggtaactgctacgatatggacgtctggggccaaggcaccctggtc
accgtctcctca

bb) caggtgcagctggtgcagtctgggggga...ggcttggtacagccagggcggtccctgagactctcctgtagaggttctggattcaccttt.....ggtgattatgctatgagctgggtccgccaggctccagggaagggggctggaatggatagctttcattacagccaaggctcacggtggggt
aacagaatatgccgcgtctgtgaaa...ggcagattcaccatctcaagagatgattcaaagaacacggcgtatctgcaaatgaacagcctgaaaaccgaggacacggccgtgtattactgcagtaatcaacgatggttgtcgtcgcctctctggggccaagggaccacggtcaccgtctcctc
ag

cc) caggtgcagctggtgcagtctgggggga...ggcttggtacagccagggcggtccctgagactctcctgtagaggttctggattcaccttt.....ggtgattatgctatgagctgggtccgccaggctccagggaagggggctggaatggatagctttcattagagccaaggctcacggtggggt
aacagaatatgccgcgtctgtgaaa...ggcagattcaccatctcaagagatgattcaaagaacacggcgtatctgcaaatgaacagcctgaaaaccgaggacacggccgtgtattactgcagtaatcaacgatggttgtcgtcgcctctctggggccaagggaccacggtcaccgtctcctc
ag

dd) caggtgcagctggtgcagtctgggggga...ggcttggtacagcctgggggtccctgagactctcctgtgcagcctctggattcaccttt.....agtagctatagcatgaactgggtccgccaggctccagggaagggggctggagtgggtctcatccattagtagtagt.....agtagttacata
tactacgcagactcagtgaag...ggccgattcaccatctccagagacaacgccaagaactcactgtatctgcaaatgaacagcctgagagacgaggacacggctgtgtattactgtgcgagaggtgtcgggggtactatgaagatggacgtctggggccaaggcaccctggtcaccgtctc
ctcag

ee) caggtgcagctggtgcagtctgggggga...ggcttggtccagccgggggggtccctgcgactctcctgtgcagcctctggattcgggttt.....aagaactactggatgacctgggtccgccaggccccagggaaggggctggagtgggtggccaatataaagaaagat.....ggaagt
gagaaatactatgtggactctgtgaag...ggccgattcaccagctccagagacaacgccaagaactcactgtatctccaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgaggggtcatttcggtatggacgtctggggcccagggaccacggtcaccgtctcctc
a

ff) caggtgcagctggtgcagtctgggggga...ggcttggtccagcctgggggggtccctgagactctcctgtgcagcctctggattcaccttt.....gtcagctatgccatgagctgggtccgccaggctccagggaaggggctggagtgggtctcaagtattagtggtagt.....ggtggtgacac
atactacgcagactccgtgaag...ggccggttcaccatctccagagacaattccgagagcaggctgtatttgcaaatgaacagcctgggacctgaggacacggcccttttattactgtgtgaagtcaaaaggggggaatacgaaagtatatggaggtctggggccaagggacaatggtcacc
gtctcttcag

gg) ...caggtgccctggtgcgtctgggggg...aggcttggtccagcctgggggggtccctgatactctcctgtgcgcctctggattcaccttt.....gtcaactatgccatgacctggatccgccaggctccagggaaggggctggagtgggtctcatgtattattggtagt.....ggtggtgacacatac
tacgcacactccgtgaag...gggcggatcaccatctccaaagacaattcccagagcaggctgtatttgctaatgaacatgctgggacctgaggactcggtcctttattactgtgtgaagtcaaaaggggggaatacgaaagtatatggaggtctggggccaagggacaatggtcaccgtctcttc
ag

hh) gaggtgcagctggtgcagtctgggcct...gaggtgaagaagcctggggactcagtgaaggtcccctgcaaggcttctggttacaccttc.....tccacttatggtatcagttgggtgcgacaggcccctggacaagggcttgagtggatgggatgggtcagcgcttac.....agacgtaac
gcaaactatgcacagaaattccag...gacagagtcaccatgaccacagacacatccacgaacacagcctacatggagctgaagagcctgagatctgacgacacggccatatatttctgtgcgagaaagcgctacggtgcttttgatgtctggggccaagggacaatggtcaccgtctcttc
ag

ii) gaggtgcagctggtgcagtctggagga...ggcttgatccagccgggggggtccctgagactctcctgcgcagcctctgggttcaccgtc.....agcagcgagtacatgacctgggtccgccaggctccagggaaggggctggagtgggtctcaaatatttatacaagt.....ggtccc
acctactacgcagactctgtgaag...ggccgattcaccatctccagggacaacgccaagaactcactgtatctgcaaatgaacagcctgagagccgaggacacggccgtgtattactgtgcgagagtagggaatggaggtggctacaatttgtggggccagggcaccctggtcaccgtctc
ctca

jj) caggtacagctgcagcagtcaggaact...gaggtgaagaagcctggggcctcagtgaaagtctcctgcaaggcttctggttacatcttt.....acgagttatggtttcacttgggtgcggcaggcccccggacaaggccttgagtggatgggatggatcagttcttac.....aatggtaacac
agactatgcacaaaagttcgag...ggcagagtcaccatgaccacagacacatccacgaccacagcctatatggagttgaggggtctgaaatctgacgacacggccatgtattattgtgcgagaggtccgcaaatggacgtctggggccaagggaccacggtcaccgtctcctca

kk) caggtgcagctggtgcagtctggaggt...gaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggtgacaccttt.....agcaggtatgggatcacctgggtgcgtcaggcccctggacaagggcttgagtggatgggatggatgagcaccgtc.....actggaa
acacaaactccgcgcagaagttccag...ggcagagtcttcttgaccagagacacatccacgagcacagcctacttggagctgaggagcctgagacctgacgacacggccgtctattactgtgcgagaggactatgtcgtgatagcagctgcctaacccctactactattacggtatggacg
tctggggcaaaggcaccctggtcaccgtctcctca

ll) gaggtgcagctggtgcagtctggggct...gaggtgaagaagcctggggcctcagtgaaggtttcctgcaaggcatctggatacaccttc.....accagctactatatgcactgggtgcgacaggcccctggacaagggcttgagtggatgggaataatcaaccctagt.....ggtggtag
cacaagctacgcacagaagttccag...ggcagagtcaccatgaccagggacacgtccacgagcacagtctacatggagctgagcagcctgagatctgaggacacggccgtgtattactgtgcgagagaactaaaacgcggggattactactactactacggtatggacgtctggggcc
aagggaccacggtcaccgtctcctca

FIG. 69 CON'T

V-REGION

aa) caggtgcagctgcaggagtcgggggga...ggcgtggtccagcctgggaggtctctgagactctcctgtgcagcctctggattcaccttc.....agcagctatggcatgcactgggtccgccagcccccaggggagggcctggagtggattgggcacatctcttacagt.....ggcaac
acttactacaacccgtcgctcaga...agtcgatttagtatttcaaaagacacgtccaagaatcagttctccctgcacctgaggtctgtgactgccgcagacacggccgtttattactgtgccaga

bb) caggtgcagctggtgcagtctgggggga...ggcttggtacagccagggcggtccctgagactctcctgtagaggttctggattcaccttt.....ggtgattatgctatgagctgggtccgccaggctccagggaaggggctggaatggatagctttcattacagccaaggctcacggtggggt
aacagaatatgccgcgtctgtgaaa...ggcagattcaccatctcaagagatgattcaaagaacacggcgtatctgcaaatgaacagcctgaaaaccgaggacacggccgtgtattactgcagta

cc) caggtgcagctggtgcagtctgggggga...ggcttggtacagccagggcggtccctgagactctcctgtagaggttctggattcaccttt.....ggtgattatgctatgagctgggtccgccaggctccagggaaggggctggaatggatagctttcattagagccaaggctcacggtggggt
aacagaatatgccgcgtctgtgaaa...ggcagattcaccatctcaagagatgattcaaagaacacggcgtatctgcaaatgaacagcctgaaaaccgaggacacggccgtgtattactgcagta

dd) caggtgcagctggtgcagtctgggggga...ggcttggtacagcctgggggggtccctgagactctcctgtgcagcctctggattcaccttt.....agtagctatagcatgaactgggtccgccaggctccagggaaggggctggagtgggtctcatccattagtagtagt.....agtagttacata
tactacgcagactcagtgaag...ggccgattcaccatctccagagacaacgccaagaactcactgtatctgcaaatgaacagcctgagagacgaggacacggctgtgtattactgtgcgagag

ee) caggtgcagctggtgcagtctgggggga...ggcttggtccagccgggggggtccctgcgactctcctgtgcagcctctggattcgggttt.....aagaactactggatgacctgggtccgccaggccccagggaaggggctggagtgggtggccaatataaagaaagat.....ggaagt
gagaaatactatgtggactctgtgaag...ggccgattcaccagctccagagacaacgccaagaactcactgtatctccaaatgaacagcctgagagccgaggacacggccgtatattactgtgcgag

ff) caggtgcagctggtgcagtctgggggga...ggcttggtccagcctgggggggtccctgagactctcctgtgcagcctctggattcaccttt.....gtcagctatgccatgagctgggtccgccaggctccagggaaggggctggagtgggtctcaagtattagtggtagt.....ggtggtgacac
atactacgcagactccgtgaag...ggccggttcaccatctccagagacaattccgagagcaggctgtatttgcaaatgaacagcctgggacctgaggacacggccctttattactgtgtgaa

gg) ...caggtgccctggtgcgtctggggg...aggcttggtccagcctgggggggtccctgatactctcctgtgcgcctctggattcaccttt.....gtcaactatgccatgacctggatccgccaggctccagggaaggggctggagtgggtctcatgtattattggtagt.....ggtggtgacacatac
tacgcacactccgtgaag...gggcggatcaccatctccaaagacaattcccagagcaggctgtatttgctaatgaacatgctgggacctgaggactcggtcctttattactgtgtgaa

hh) gaggtgcagctggtgcagtctgggcct...gaggtgaagaagcctggggactcagtgaaggtcccctgcaaggcttctggttacaccttc.....tccacttatggtatcagttgggtgcgacaggccccctggacaagggcttgagtggatgggatgggtcagcgcttac.....agacgtaac
gcaaactatgcacagaaattccag...gacagagtcaccatgaccacagacacatccacgaacacagcctacatggagctgaagagcctgagatctgacgacacggccatatatttctgtgcgaga

ii) gaggtgcagctggtgcagtctggagga...ggcttgatccagccgggggggtccctgagactctcctgcgcagcctctgggttcaccgtc.....agcagcgagtacatgacctgggtccgccaggctccagggaaggggctggagtgggtctcaaatatttatacaagt.....ggtccc
acctactacgcagactctgtgaag...ggccgattcaccatctccagggacaacgccaagaactcactgtatctgcaaatgaacagcctgagagccgaggacacggccgtgtattactgtgcgagag

jj) caggtacagctgcagcagtcaggaact...gaggtgaagaagcctggggcctcagtgaaagtctcctgcaaggcttctggttacatcttt.....acgagttatggtttcacttgggtgcggcaggcccccggacaaggccttgagtggatgggatggatcagttcttac.....aatggtaacac
agactatgcacaaaagttcgag...ggcagagtcaccatgaccacagacacatccacgaccacagcctatatggagttgaggggtctgaaatctgacgacacggccatgtattattgtgcgagag

kk) caggtgcagctggtgcagtctggaggt...gaggtgaagaagcctggggcctcagtgaaggtctcctgcaaggcttctggtgacaccttt.....agcaggtatgggatcacctgggtgcgtcaggcccctggacaagggcttgagtggatgggatggatgagcaccgtc.....actggaa
acacaaactccgcgcagaagttccag...ggcagagtcttcttgaccagagacacatccacgagcacagcctacttggagctgaggagcctgagacctgacgacacggccgtctattactgtgcgagag

ll) gaggtgcagctggtgcagtctggggct...gaggtgaagaagcctggggcctcagtgaaggtttcctgcaaggcatctggatacaccttc.....accagctactatatgcactgggtgcgacaggcccctggacaagggcttgagtggatgggaataatcaaccctagt.....ggtggtag
cacaagctacgcacagaagttccag...ggcagagtcaccatgaccagggacacgtccacgagcacagtctacatggagctgagcagcctgagatctgaggacacggccgtgtattactgtgcgagaga

FIG. 69 CON'T

	FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT	JUNCTION	J-REGION	FR4-IMGT
aa)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
bb)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
cc)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
dd)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
ee)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
ff)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
gg)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
hh)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
ii)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
jj)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
kk)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							
ll)	caggtgcagctgcaggagtcgggcccaggactggtgaagccttcg gagaccctgtccctcacctgcactgtctctggtggctccatcagcagtggtgattactactggagctggatccgccagcccccagggaaggggctggagtggattgggtatatctattacagtgggagcaccaactacaacccctccctcaagagtcgagtcaccatatcagtagagacacgtccaagaaccagttctccctgaagctgagctctgtgaccgccgcggacacggccgtgtattactgtgcgagacaccgtcgtgggagctatgctttttgatatctggggccaagggacaatggtcaccgtctcttca							

FIG. 69 CON'T

	Sequence ID	V-DOMAIN Functionality	V-GENE and allele	J-GENE and allele	D-GENE and allele
aa)	hCTLA4-Rd3b-T1-E6_PelB-F_2021-02-10_E05	productive	Homsap IGLV6-57*03 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F	
bb)	hCTLA4-Rd3b-E4-F2_PelB-F_2021-02-10_F06	productive	Homsap IGLV1-44*01 F	Homsap IGLJ3*02 F	
cc)	hCTLA4-Rd3b-T1-A3_PelB-F_2021-02-10_B01	productive	Homsap IGLV1-44*01 F	Homsap IGLJ3*02 F	
dd)	hCTLA4-T1-A6_PelB-F_2021-02-05_B04	productive	Homsap IGLV1-47*01 F	Homsap IGLJ3*02 F	
ee)	hCTLA4-Rd3b-T1-A10_PelB-F_2021-02-10_F01	productive	Homsap IGLV3-19*01 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F	
ff)	hCTLA4-Rd3b-E2-D5_PelB-F_2021-02-10_B05	productive	Homsap IGLV10-54*01 F	Homsap IGLJ3*02 F	
gg)	hCTLA4-Rd3b-E2-G6_PelB-F_2021-02-10_C08	productive	Homsap IGLV10-54*01 F	Homsap IGLJ3*02 F	
hh)	hCTLA4-Rd3b-E2-H3_PelB-F_2021-02-10_H08	productive	Homsap IGLV10-54*01 F	Homsap IGLJ2*01 F, or Homsap IGLJ3*01 F	
ii)	CTLA4pmpl-Rd2-E2-H12_PelB-F_2021-08-06_H06				
jj)	CTLA4pmpl-Rd2-E2-H2_PelB-F_2021-08-06_H05				
kk)	CTLA4pmpl-Rd2-E2-D10_PelB-F_2021-08-06_H02				
ll)	CTLA4pmpl-Rd2-E2-D11_PelB-F_2021-08-06_A03				

FIG. 69 CON'T

	V-D-J-REGION	V-J-REGION
aa)	aattttatgctgactcagccccactct...atgtcggagtctccggggaagacggtgaccatctcctgcacccgcagcagtggcagcatt.....gccagcaactatgtgcagtggttccagcagcgcccgggcagtgcccccaccactgtgatctatg aggat.....aaccaacgaccctctggggtccct...gatcggttctctggctccatcgacaggtcctccaactctgcctccctcatcatctctggactgaagactgaggacgaggctgactactactgtcattcttatgatagcaccaatgtggtat tcggcggagggaccaagctgaccgtcctgg	
bb)	ctgcctgtgctgactcaggcaccctca...gcgtctgggacccccgggcagagggtcaccatctcttgttctggaagcagctccaacatc.....ggaagtaatactgtaaactggtaccaacacctcccaggaacggcccccaaactcctcatctat agtaat.....aatcaacggccctcaggggtccct...gaccgattctctggctccaag.....tctggcacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgtgcagcatgggatgacagcctgagtgg tcaagtgttcggcggagggaccaagctgaccgtcctag	
cc)	ctgcctgtgctgactcaggcaccctca...gcgtctgggacccccgggcagagggtcaccatctcttgttctggaagcagctccaacatc.....ggaagtaatactgtaaactggtaccaacacctcccaggaacggcccccaaactcctcatctat agtaat.....aatcagcggccctcaggggtccct...gaccgattctctggctccaag.....tctggcacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgtgcagcatgggatgacagcctgagtgg tcaagtgttcggcggagggaccaagctgaccgtcctag	
dd)	cagtctgtgctgactcagccaccctca...gcgtctgggacccccgggcagacggtcaccatcacttgttctggaagcgactccaacatc.....ggaagtaattatgtatactggtaccagcagctcccaggaacggcccccaaactcctcatctata ggaat.....aatcagcggccctcaggggtccct...gaccgattctctggctccaag.....tctggcacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgtgcagcatgggatgacagcctgagtggt ccggtgttcggcggagggaccaagctgaccgtcctag	
ee)	tcttctgagctgactcaggaccctgct...gtgtctgtggccttgggacagacagtcaggatcacatgccaaggagacagcctcaga.....aggtattatgcaagctggtaccagcagaagccaggacaggccccttggttgtcatctttggca aa.....gacaagcggccctcggggatcccc...gaccgcttctctggctccagg.....tcaggaaacacagcttccttgaccataactgcgacccaggcggaggatgaggctgattattattgtggctcacgggacagcagtggcacccgt gtggtcttcggcggagggaccaaggtgacccgtccta	
ff)	cagcctgggctgactcagccaccctcg...gtgtccaagggcttgagacagaccgccacactcacctgcactgggaacagcaacaatgtt.....ggcaaccaaggagcagcttggctgcagcagcaccagggccacccctcccaaactcctcttc tttagaaat.....ggcaagcggccctcagggatctca...gagagattctctgcatccagg.....tcaggaagtacagcctccctgaccattactgaactccagcctgatgacgaggctgactattactgctcagcatgggacaggagcctcg tagcttgggtgttcggcggagggaccagggtgaccgtcctag	
gg)	catcctgggctgactcatccaccctcg...gagtccaagggtttgatacataccgccacactcacctgcactgggaacagcaacaatgtt.....ggcaaccaaggagcaccttggctgcatcaccaccatggccaccctcccaaactcctcttctttat aaat.....ggcaagcggccctcatggatctca...aagagattctctgcatccaag.....tcacgaagtacagcctccctgaccattactgaactccaacctgatgacgacgctgactattactgtacagcatgggacaggagcctcgtagct tgggtgttcggcggagggaccagggtgaccgtcctag	
hh)	tcctatgagctgactcagccaccctcg...gtgtccgagggcttgagacagaccgccacactcacctgcactgggaacagcaacaatgtt.....ggcaaccaaggagcagcttggctgcagcagcaccagggccaccctcccaaactcctatcc tacaggaat.....aacaaccggccctcagggatctca...gagagattatctgcatccagg.....tcaggaaacacagcctccctgaccattactggactccagcctgaggacgaggctgactattactgctcagcatgggacagcagcct cagtgctgtgatattcggcggagggaccaagctgaccgtcctag	
ii)	cagtctgccctgactcagcctgcctcc...gtgtcagggtctcctggacagtcgatcaccatctcctgcactggaaccagcggtgacgttggt.....gcgcatgactatgtctcgtggtaccaacaacacccgggcaaagcccccaaactcatgatttatg agggc.....agtaagcggccctcaggggtttct...aatcgcttctctggctccaag.....tctggcaacacggcctccctgaccgtctctgggctccaggctgaggatgaggctgattactactgcagctcatttgcaggaaccaacaattac gtcttcggaactgggaccaaggtcgccgtcctag	
jj)	gacatccagatgacccagtctccatcttctgtgtctgcatctataggagacagagtcaccatcacttgtcgggcgagtcaggatatt.....agcaactcgttagcctggtatcagcagaaaccagggaaagcccctaaactcctgatctatggtg ca.....tccaatttgcgaagtggggtccct...tcaaggttcagcggcggtgga.....tctgggacgtatttcactctcactatcagtagcctacagcctgaagattttgcgacttactattgtcaacagggtaacagtttcccgatcaccttcggcc aagggacgcgactggagattaaac	
kk)	cagacggtggtgactcaggagccctca...ctgactgtgtccccaggagggacagtcactctcacctgtggctccagcactggagctgtcacc.....agtggtcattatccctactggttccagcagaagcctggccaagcccccaggacactgatttat gataca.....accaacagacactcctggactcct...gcccggttctcaggctccctc.....cttggggccaaagctgccctgacactgtcaggtgtgcagcctgaggatgaggctgactattactgcttgctctcctatagtggtgatcgagtatt cggcggagagaccaaactgaccgtcctag	
ll)	cagcctgtgctgactcagccgcactct...gtgtcggagtctccggggaagacggtcaccatctcctgcacccgcagcggtggcagcttt.....gccgacaactatgtgcagtggtaccaacagcgcccgggcagtgcccccaccctatgatctat gaacat.....caccaaagaccctttggggtccct...gatcgattctctggctccatcgacagctcctccaactctgcctccctcaccatctctggactgaagactgaggacgaggctgactactactgtcagtcttatgatagcagcactcccgt ggtattcggcggagggaccaagctgaccgtcctag	

FIG. 69 CON'T

V-REGION

aa) aatttatgctgactcagccccactct...atgtcggagtctccgggagaagacggtgaccatcctcgcacccgcagcagtggcagcatt.....gccagcaactatgtgcagtggttccagcagccgcccgggcagtgccccaccactgtgatctatgaggat.....aaccaa
cgaccctctgggtcct...gatcggttctctggctccatcgacaggttcctccaactctgcctcctcatcatctctggactgaagactgaggacgaggctgactactactgtcaattctatgatagcaccaat

bb) ctgcctgtgctgactcaggcacccctca...gcgtctgggaccccgggcagaggtcaccatctcttgttctggaagcagctccaacatc.....ggaagtaatactgtaaactggtaccaacacctccaggaacggccccaaactcctcatctatagtaat.....aatcaa
cggccctcagggtcct...gaccgattctctggctccaag.....tctggcacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgtgcagcatgggatgacagcctgagtggtc

cc) ctgcctgtgctgactcaggcacccctca...gcgtctgggaccccgggcagaggtcaccatctcttgttctggaagcagctccaacatc.....ggaagtaatactgtaaactggtaccaacacctccaggaacggccccaaactcctcatctatagtaat.....aatcag
cggccctcagggtcct...gaccgattctctggctccaag.....tctggcacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgtgcagcatgggatgacagcctgagtggtc

dd) cagtctgtgctgactcagccacccctca...gcgtctgggaccccgggcagacggtcaccatcacttgttctggaagcgactccaacatc.....ggaagtaattatgtatactggtaccagcagctcccaggaacggccccaaactcctcatctataggaat.....aatcag
cggccctcagggtcct...gaccgattctctggctccaag.....tctggcacctcagcctccctggccatcagtgggctccggtccgaggatgaggctgattattactgtgcagcatgggatgacagcctgagtggtcc

ee) tcttctgagctgactcaggacacctgct...gtgtctgtggccttgggacagacaagtcaggatcacatgccaagggagacagcctcaga.....aggtattatgcaagctggtaccagcagaagccaggacagggcccctttggttgtcatctttggcaaa.....gacaagcgg
ccctcgggggatcccc...gaccgcttctctggctccagg.....tcaggaaacacagcttcctgacctaaactgcgacccaggcggaggatgaggctgattattattgtggctcacgggacagcagtggcaccc

ff) cagcctgggctgactcagccacccctcg...gtgtccaagggcttgagacagaccgccacactcacctgcactgggaacagcaacaatgtt.....ggcaaccaaggagcagcttggctgcagcagcaccagggccacctccaaactcctcttctttagaaat.....ggc
aagcggccctcagggatctca...gagagattctctgcatccagg.....tcaggaagtacagcctccctgaccattactgaactccagcctgatgacgaggctgactattactgctcagcatgggacaggagcctctgtagct

gg) catcctgggctgactcatccacccctcg...gagtccaagggtttgatacataccgccacactcacctgcactgggaacagcaacaatgtt.....ggcaaccaaggagcacctttggctgcatcaccactggccacctccaaactcctcttctttataaat.....ggcaagc
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FIG. 69 CON'T