

**PREFERENTIALLY EXPRESSED ANTIGEN IN MELANOMA (PRAME) T CELL
RECEPTORS AND METHODS OF USE THEREOF**

RELATED APPLICATIONS

- 5 **[0001]** This application claims the benefit of priority to U.S Provisional Application No. 62/965,231, filed on January 24, 2020, the entire contents of which are incorporated herein by reference.

SEQUENCE LISTING

- 10 **[0002]** 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 January 20, 2021, is named 118003-00520_SL.txt and is 461,085 bytes in size.

BACKGROUND

- 15 **[0003]** T cell receptors (TCRs) are membrane bound heterodimers comprising an α and β chain resembling an immunoglobulin variable (V) and constant (C) region. The TCR α chain includes a covalently linked V- α chain and C- α chain, whereas the β chain includes a V- β chain covalently linked to a C- β chain. The V- α and V- β chains form a pocket or cleft that can bind an antigen in the context of a major histocompatibility complex (MHC) (known in humans as an HLA complex). (Davis *Ann. Rev. of Immunology* 3: 537 (1985); *Fundamental Immunology* 3rd Ed., W. Paul Ed. New York (1993)).
- 20 **[0004]** TCRs are primary effectors of the immune system that have unique advantages as a platform for developing therapeutics. While antibody therapeutics are limited to recognition of pathogens in the blood and extracellular spaces, or to protein targets on the cell surface, T cell receptors can recognize antigens displayed with MHC molecules on the surface of cells, including antigens derived from
- 25 intracellular proteins. Depending on the subtype of T cells that recognize displayed antigen and become activated, TCRs can participate in controlling various immune responses. For instance, T cells are involved in regulation of the humoral immune response through induction of differentiation of B cells into antibody producing cells. In addition, activated T cells act to initiate cell-mediated immune responses. Thus, TCRs can recognize additional targets not available to antibodies. In
- 30 addition, TCRs have been reported to mediate cell killing, increase B cell proliferation, and impact the development and severity of various disorders including cancer, allergies, viral infections and autoimmune disorders.

- 35 **[0005]** In view of the function of TCRs, antigen-specific TCRs have been evaluated for use in immunotherapy for their ability to redirect T cells to tumors expressing the antigen. TCRs will bind to a small peptide, only 8-12 amino acids in length, which are bound on the surface of a target cell by the Major Histocompatibility Complex (MHC). TCRs can therefore recognize intracellular antigens

derived from cancer or viral proteins because these antigens are processed and displayed as peptides in the context of the surface MHC. Hence, TCRs can recognize additional internal cell targets not available to antibodies or therapies that cannot penetrate the cell.

[0006] However, the challenge of the industry is to engineer TCRs that lack immunogenicity when administered to a patient and have fine specificity to the particular peptide antigen of interest, without cross-reacting to other peptides on MHC or similar epitopes found in the natural protein repertoire.

[0007] Preferentially expressed antigen in melanoma, or PRAME, is a well-known cancer-testis antigen (CTA) encoded on the X chromosome. It was first identified as a tumor antigen that could be recognized by HLA-A*24 restricted cytotoxic T lymphocytes in metastatic cutaneous melanoma (Ikeda H., *et al.* (1997) *Immunity* 6:199–208). PRAME has been shown to act as a repressor of retinoic acid receptor and, thus, may confer a growth advantage to cancer cells via this mechanism (see, *e.g.*, Epping M.T., *et al.* (2005) *Cell* 122:835-847).

[0008] PRAME is abundantly re-expressed by many tumors of different histological types, including melanoma, renal cell cancer, non-small cell lung cancer (NSCLC), neuroblastoma, breast cancer, multiple myeloma, acute leukemia, chronic myeloid leukemia, multiple sarcoma subtypes, and primary and metastatic uveal melanoma but, in normal healthy adult tissues, PRAME expression is restricted to the testes.

[0009] There is an unmet need in the art for new targeting agents based on T cell receptors that specifically bind to PRAME antigens, as well as methods for producing and using such agents in therapeutic and diagnostic settings.

SUMMARY

[0010] The present invention provides T cell receptors (TCRs) that were generated against a PRAME peptide antigen in the context of MHC (HLA-A2). The unique TCR sequences identified have shown specific binding to a small peptide PRAME presented in the groove of an HLA molecule.

[0011] Accordingly, in one aspect, the present invention provides a T cell receptor (TCR) (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell) that binds specifically to an HLA-A2 presented cancer testis antigen preferentially expressed antigen in melanoma (PRAME) peptide comprising the amino acid sequence of RLDQLLRHV (SEQ ID NO:929) (PRAME 312-320) wherein the TCR comprises an alpha chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of any one of the alpha chain variable domain CDR3 amino acid sequences set forth in Table 3.

[0012] In another aspect, the present invention provides a T cell receptor (TCR) (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell) that binds specifically to an HLA-A2 presented cancer testis antigen preferentially expressed antigen in melanoma (PRAME) peptide comprising the amino acid sequence of RLDQLLRHV (SEQ ID NO:929) (PRAME 312-320), wherein the TCR comprises a

beta chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of any one of the beta chain variable domain CDR3 amino acid sequences set forth in Table 3.

5 [0013] In some embodiments, the alpha chain variable domain further comprises a CDR1 and a CDR2, wherein the CDR1 comprises any one of the alpha chain variable domain CDR1 amino acid sequences set forth in Table 3 and the CDR2 independently comprises any one of the alpha chain variable domain CDR2 amino acid sequences set forth in Table 3.

10 [0014] In some embodiments, the beta chain variable domain further comprises a CDR1 and a CDR2, wherein the CDR1 comprises any one of the beta chain variable CDR1 amino acid sequences set forth in Table 3 and the CDR2 independently comprises any one of the beta chain variable domain CDR2 amino acid sequences set forth in Table 3.

[0015] The TCR may include at least one TCR alpha chain variable domain and/or at least one beta chain variable domain; or the TCR may include a TCR alpha chain variable domain and a TCR beta chain variable domain.\

15 [0016] In some embodiments, the TCR comprises alpha chain variable domain CDR1, CDR2 and CDR3 contained within any one of the alpha chain variable domain sequences listed in Table 5; and beta chain variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 5.

20 [0017] In some embodiments, the TCR comprises an alpha chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 5.

25 [0018] In some embodiments, the TCR comprises a beta chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 5.

30 [0019] In some embodiments, the TCR comprises (a) an alpha chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 5; and (b) a beta chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 5.

35 [0020] In some embodiments, the TCR comprises (a) an alpha chain variable domain CDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 7, 13, 19, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, and 103; (b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 8, 14, 20, 26, 32, 38, 44, 50, 56, 62, 68, 74, 80, 86, 92, 98, and 104; (c) an alpha chain variable domain

CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99, and 105; (d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 16, 22, 28, 34, 40, 46, 52, 58, 64, 70, 76, 82, 88, 94, 100, and 106; (e) a beta chain variable domain CDR2
5 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, 17, 23, 29, 35, 41, 47, 53, 59, 65, 71, 77, 83, 89, 95, 101, and 107; and (f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, and 108.

[0021] In some embodiments, the TCR comprises an alpha chain variable domain/beta chain variable
10 domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 217/219, 229/231, 237/239, 241/243, and 285/287.

[0022] In some embodiments, the TCR comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 217/219, 221/223, 225/227, 229/231, 233/235, 237/239, 241/243, 245/247, 249/251, 253/255, 257/259,
15 261/263, 265/267, 269/271, 273/275, 277/279, 281/283, and 285/287.

[0023] The present invention also provides a TCR (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell) that complete for binding to any one or more of the TCRs of the invention.

[0024] In one aspect, the present invention provides a T cell receptor (TCR) (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell) that binds specifically to an HLA-A2 presented cancer testis
20 antigen preferentially expressed antigen in melanoma (PRAME) peptide comprising the amino acid sequence of SLLQHLIGL (SEQ ID NO:930) (PRAME 425-433), wherein the TCR comprises an alpha chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of any one of the alpha chain variable domain CDR3 amino acid sequences set forth in Table 6.

[0025] In another aspect, the present invention provides a T cell receptor (TCR) (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell) that binds specifically to an HLA-A2 presented preferentially expressed antigen in melanoma (PRAME) peptide comprising the amino acid sequence of SLLQHLIGL (SEQ ID NO:930) (PRAME 425-433), wherein the TCR comprises a beta chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3
30 comprises the amino acid sequence of any one of the beta chain variable domain CDR3 amino acid sequences set forth in Table 6.

[0026] In some embodiments, the alpha chain variable domain further comprises a CDR1 and a CDR2, wherein the CDR1 comprises any one of the alpha chain variable domain CDR1 amino acid sequences set forth in Table 6 and the CDR2 independently comprises any one of the alpha chain
35 variable domain CDR2 amino acid sequences set forth in Table 6.

[0027] In some embodiments, the beta chain variable domain further comprises a CDR1 and a CDR2, wherein the CDR1 comprises any one of the beta chain variable CDR1 amino acid sequences set forth in Table 6 and the CDR2 independently comprises any one of the beta chain variable domain CDR2 amino acid sequences set forth in Table 6.

- 5 **[0028]** The TCR may include at least one TCR alpha chain variable domain and/or at least one beta chain variable domain; or the TCR may include a TCR alpha chain variable domain and a TCR beta chain variable domain.

- [0029]** In some embodiments, the TCR comprises alpha chain variable domain CDR1, CDR2 and CDR3 contained within any one of the alpha chain variable domain sequences listed in Table 8; and
10 beta chain variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 8.

- [0030]** In some embodiments, the TCR comprises an alpha chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table
15 8.

[0031] In some embodiments, the TCR comprises a beta chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 8.

- [0032]** In some embodiments, the TCR comprises (a) an alpha chain variable domain having an
20 amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 8; and (b) a beta chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 8.

- 25 **[0033]** In some embodiments, the TCR comprises (a) an alpha chain variable domain CDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 385, 391, 397, 403, 409, 415, 421, 427, 433, 439, 445, 451, 457, 463, 469, 475, 481, 487, 493, 499, 505, 511, 517, and 523; (b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group
30 consisting of SEQ ID NOs: 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 386, 392, 398, 404, 410, 416, 422, 428, 434, 440, 446, 452, 458, 464, 470, 476, 482, 488, 494, 500, 506, 512, 518, and 524; (c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 387, 393, 399, 405, 411, 417, 423, 429, 435, 441, 447, 453,
35 459, 465, 471, 477, 483, 489, 495, 501, 507, 513, 519, and 525; (d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 292, 298,

304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, 400, 406, 412, 418, 424, 430, 436, 442, 448, 454, 460, 466, 472, 478, 484, 490, 496, 502, 508, 514, 520, and 526; (e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 389, 395, 401, 407, 413, 419, 425, 431, 437, 443, 449, 455, 461, 467, 473, 479, 485, 491, 497, 503, 509, 515, 521, and 527; and (f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 390, 396, 402, 408, 414, 420, 426, 432, 438, 444, 450, 456, 462, 468, 474, 480, 486, 492, 498, 504, 510, 516, 522, and 528.

10 **[0034]** In some embodiments, the TCR comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 825/827, 845/847, 853/855, 857/859, 865/867, 873/875, 885/887, 893/805, 897/899, 901/903, 913/915, and 925/927.

15 **[0035]** In some embodiments, the TCR comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 769/771, 773/775, 777/779, 781/783, 785/787, 789/791, 793/795, 797/799, 801/803, 805/807, 809/811, 813/815, 817/819, 821/823, 825/827, 829/831, 833/835, 837/839, 841/843, 845/847, 849/851, 853/855, 857/859, 861/863, 865/867, 869/871, 873/875, 877/879, 881/883, 885/887, 889/891, 893/805, 897/899, 901/903, 905/907, 909/911, 913/915, 917/919, 921/923, and 925/927.

20 **[0036]** The present invention also provides a TCR (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell) that complete for binding to any one or more of the TCRs of the invention.

[0037] In some embodiments, the TCRs of the invention further comprise a detectable moiety.

25 **[0038]** The present invention further provides pharmaceutical compositions comprising any of the TCRs of the invention, and a pharmaceutically acceptable carrier or diluent; as well as isolated cells presenting any of the TCRs of the invention.

[0039] In one aspect, the present invention provides isolated polynucleotide molecules comprising a polynucleotide sequence that encodes an alpha chain variable domain of any of the TCRs of the invention.

30 **[0040]** In another aspect, the present invention provides isolated polynucleotide molecules comprising a polynucleotide sequence that encodes a beta chain variable domain of any of the TCRs of the invention.

[0041] The present invention also provides vectors comprising the polynucleotide molecule of the invention; cells expressing the vectors of the invention.

35 **[0042]** In one aspect, the present invention provides a method of treating a subject having a PRAME-associated disease or disorder. The methods includes administering to the subject a therapeutically

effective amount of a TCR (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell), pharmaceutical composition, or a plurality of the cells of the invention, thereby treating the subject.

[0043] In some embodiments, the PRAME-associated disease or disorder is PRAME-associated cancer.

- 5 **[0044]** In some embodiments, the PRAME-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, testicular germ cell tumor, uveal
- 10 melanoma, kidney renal papillary cell carcinoma, kidney renal clear cell carcinoma, thymoma, colon adenocarcinoma, cervical squamous cell carcinoma, cervical tumor, pancreatic adenocarcinoma, liver cancer, hepatocellular carcinoma, mesothelioma, or a recurrent non-small cell lung cancer.
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- [0045]** In some embodiments of the invention, a TCR (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell), pharmaceutical composition, or a plurality of the cells of the invention is
- 20 administered to the subject in combination with a second therapeutic agent.

[0046] The TCR, the pharmaceutical composition, or the plurality of cells may be administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially to the subject.

- [0047]** In one aspect, the present invention provides an isolated nucleic acid molecule encoding a T cell receptor (TCR), wherein the TCR binds specifically to an HLA-A2 presented cancer testis antigen preferentially expressed antigen in melanoma (PRAME) peptide comprising the amino acid sequence of RLDQLLRHV (SEQ ID NO:929) (PRAME 312-320), wherein the TCR comprises an alpha chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of any one of the alpha chain variable domain CDR3 amino acid sequences set forth in Table 5.
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- [0048]** In another aspect, the present invention provides an isolated nucleic acid molecule encoding a T cell receptor (TCR), wherein the TCR binds specifically to an HLA-A2 presented cancer testis antigen preferentially expressed antigen in melanoma (PRAME) peptide comprising the amino acid sequence of RLDQLLRHV (SEQ ID NO:929) (PRAME 312-320), wherein the TCR comprises a beta
- 35 chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3

comprises the amino acid sequence of any one of the beta chain variable domain CDR3 amino acid sequences set forth in Table 5.

[0049] In some embodiments, the isolated nucleic acid molecule encodes at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.

- 5 **[0050]** In some embodiments, the TCR comprises alpha chain variable domain complementary determining regions (CDR) 1, CDR2, and CDR3 contained within any one of the alpha chain variable domain sequences listed in Table 5; and beta chain variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 5.

- 10 **[0051]** In some embodiments, the TCR (*e.g.*, isolated TCR or TCR expressed on an isolated cell) comprises alpha chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 5.

- 15 **[0052]** In some embodiments, the TCR comprises beta chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 5.

- 20 **[0053]** In some embodiments, the TCR comprises (a) an alpha chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 5; and (b) a beta chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 5.

- 25 **[0054]** In some embodiments, the isolated antigen-binding protein comprises (a) an alpha chain variable domain CDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 7, 13, 19, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, and 103; (b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 8, 14, 20, 26, 32, 38, 44, 50, 56, 62, 68, 74, 80, 86, 92, 98, and 104; (c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99, and 105; (d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 16, 22, 28, 34, 40, 46, 52, 58, 64, 70, 76, 82, 88, 94, 100, and 106; 30 (e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, 17, 23, 29, 35, 41, 47, 53, 59, 65, 71, 77, 83, 89, 95, 101, and 107; and (f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, and 108.

[0055] In some embodiments, the TCR comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 217/219, 229/231, 237/239, 241/243, and 285/287.

5 [0056] In some embodiments, the TCR comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 217/219, 221/223, 225/227, 229/231, 233/235, 237/239, 241/243, 245/247, 249/251, 253/255, 257/259, 261/263, 265/267, 269/271, 273/275, 277/279, 281/283, and 285/287.

[0057] In some embodiments, the isolated antigen-binding protein comprises (a) an alpha chain variable domain CDR1 encoded by a nucleic acid sequence selected from the group consisting of SEQ
10 ID NOs: 109, 115, 121, 127, 133, 139, 145, 151, 157, 163, 169, 175, 181, 187, 193, 199, 205, and 211; (b) an alpha chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 110, 116, 122, 128, 134, 140, 146, 152, 158, 164, 170, 176, 182, 188, 194, 200, 206, and 212; (c) an alpha chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 111, 117, 123, 129, 135, 141, 147, 153,
15 159, 165, 171, 177, 183, 189, 195, 201, 207, and 213; (d) a beta chain variable domain CDR1 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 112, 118, 124, 130, 136, 142, 148, 154, 160, 166, 172, 178, 184, 190, 196, 202, 208, and 214; (e) a beta chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 113, 119, 125, 131, 137, 143, 149, 155, 161, 167, 173, 179, 185, 191, 197, 203, 209, and 215;
20 and (f) a beta chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 114, 120, 126, 132, 138, 144, 150, 156, 162, 168, 174, 180, 186, 192, 198, 204, 210, and 216.

[0058] In some embodiments, the TCR comprises an alpha chain variable domain/beta chain variable domain nucleic acid sequence pair selected from the group consisting of SEQ ID NOs: 218/220,
25 222/224, 226/228, 230/232, 234/236, 238/240, 242/244, 246/248, 250/252, 254/256, 258/260, 262/264, 266/268, 270/272, 274/276, 278/280, 282/284, and 286/288.

[0059] The present invention also provides vectors comprising an isolated nucleic acid molecule of the invention and isolated cells comprising a vector of the invention.

[0060] In one aspect, the present invention provides isolated polynucleotide molecules comprising a
30 polynucleotide sequence that encodes an alpha chain variable domain of any of the TCRs of the invention.

[0061] In another aspect, the present invention provides isolated polynucleotide molecules comprising a polynucleotide sequence that encodes a beta chain variable domain of any of the TCRs of the invention.

35 [0062] The present invention also provides vectors comprising the polynucleotide molecule of the invention; cells expressing the vectors of the invention.

[0063] In one aspect, the present invention provides a method of treating a subject having a PRAME-associated disease or disorder. The methods includes administering to the subject a therapeutically effective amount of a TCR (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell), pharmaceutical composition, or a plurality of the cells of the invention, thereby treating the subject.

5 [0064] In some embodiments, the PRAME-associated disease or disorder is PRAME-associated cancer.

[0065] In some embodiments, the PRAME-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a
10 non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal
15 carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, testicular germ cell tumor, uveal melanoma, kidney renal papillary cell carcinoma, kidney renal clear cell carcinoma, thymoma, colon adenocarcinoma, cervical squamous cell carcinoma, cervical tumor, pancreatic adenocarcinoma, liver cancer, hepatocellular carcinoma, mesothelioma, or a recurrent non-small cell lung cancer.

20 [0066] In some embodiments of the invention, a TCR (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell), pharmaceutical composition, or a plurality of the cells of the invention is administered to the subject in combination with a second therapeutic agent.

[0067] The TCR, the pharmaceutical composition, or the plurality of cells may be administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or
25 intracranially to the subject.

[0068] In one aspect, the present invention provides an isolated nucleic acid molecule encoding a T cell receptor (TCR), wherein the TCR binds specifically to an HLA-A2 presented cancer testis antigen preferentially expressed antigen in melanoma (PRAME) peptide comprising the amino acid sequence of SLLQHLIGL (SEQ ID NO:930) (PRAME 425-433), wherein the TCR comprises an alpha chain
30 variable domain comprising a complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of any one of the alpha chain variable domain CDR3 amino acid sequences set forth in Table 8.

[0069] In another aspect, the present invention provides an isolated nucleic acid molecule encoding a T cell receptor (TCR), wherein the TCR binds specifically to an HLA-A2 presented cancer testis
35 antigen preferentially expressed antigen in melanoma (PRAME) peptide comprising the amino acid sequence of SLLQHLIGL (SEQ ID NO:930) (PRAME 425-433), wherein the TCR comprises a beta

chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of any one of the beta chain variable domain CDR3 amino acid sequences set forth in Table 8.

5 [0070] In some embodiments, the isolated nucleic acid molecule encodes at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.

[0071] In some embodiments, the TCR comprises alpha chain variable domain complementary determining regions (CDR) 1, CDR2, and CDR3 contained within any one of the alpha chain variable domain sequences listed in Table 8; and beta chain variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 8.

10 [0072] In some embodiments, the TCR (*e.g.*, isolated TCR or TCR expressed on an isolated cell) comprises alpha chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 8.

15 [0073] In some embodiments, the TCR comprises beta chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 8.

20 [0074] In some embodiments, the TCR comprises (a) an alpha chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 8; and (b) a beta chain variable domain having an amino acid sequence that has at least 85% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 8.

[0075] In some embodiments, the isolated antigen-binding protein comprises (a) an alpha chain variable domain CDR1 domain having an amino acid sequence selected from the group consisting of
 25 SEQ ID NOs: 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 385, 391, 397, 403, 409, 415, 421, 427, 433, 439, 445, 451, 457, 463, 469, 475, 481, 487, 493, 499, 505, 511, 517, and 523; (b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 386, 392, 398, 404, 410, 416, 422, 428, 434, 440, 446, 452, 458, 464,
 30 470, 476, 482, 488, 494, 500, 506, 512, 518, and 524; (c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 387, 393, 399, 405, 411, 417, 423, 429, 435, 441, 447, 453, 459, 465, 471, 477, 483, 489, 495, 501, 507, 513, 519, and 525; (d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of
 35 SEQ ID NOs: 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, 400, 406, 412, 418, 424, 430, 436, 442, 448, 454, 460, 466, 472, 478, 484, 490, 496, 502, 508,

514, 520, and 526; (e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 389, 395, 401, 407, 413, 419, 425, 431, 437, 443, 449, 455, 461, 467, 473, 479, 485, 491, 497, 503, 509, 515, 521, and 527; and (f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 390, 396, 402, 408, 414, 420, 426, 432, 438, 444, 450, 456, 462, 468, 474, 480, 486, 492, 498, 504, 510, 516, 522, and 528.

[0076] In some embodiments, the TCR comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 825/827, 845/847, 853/855, 857/859, 865/867, 873/875, 885/887, 893/805, 897/899, 901/903, 913/915, and 925/927.

[0077] In some embodiments, the TCR comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 769/771, 773/775, 777/779, 781/783, 785/787, 789/791, 793/795, 797/799, 801/803, 805/807, 809/811, 813/815, 817/819, 821/823, 825/827, 829/831, 833/835, 837/839, 841/843, 845/847, 849/851, 853/855, 857/859, 861/863, 865/867, 869/871, 873/875, 877/879, 881/883, 885/887, 889/891, 893/805, 897/899, 901/903, 905/907, 909/911, 913/915, 917/919, 921/923, and 925/927.

[0078] In some embodiments, the isolated antigen-binding protein comprises (a) an alpha chain variable domain CDR1 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 529, 535, 541, 547, 553, 559, 565, 571, 577, 583, 589, 595, 601, 607, 613, 619, 625, 631, 637, 643, 649, 655, 661, 667, 673, 679, 685, 691, 697, 703, 709, 715, 721, 727, 733, 739, 745, 751, 757, and 763; (b) an alpha chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 530, 536, 542, 548, 554, 560, 566, 572, 578, 584, 590, 596, 602, 608, 614, 620, 626, 632, 638, 644, 650, 656, 662, 668, 674, 680, 686, 692, 698, 704, 710, 716, 722, 728, 734, 740, 746, 752, 758, and 764; (c) an alpha chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 531, 537, 543, 549, 555, 561, 567, 573, 579, 585, 591, 597, 603, 609, 615, 621, 627, 633, 639, 645, 651, 657, 663, 669, 675, 681, 687, 693, 699, 705, 711, 717, 723, 729, 735, 741, 747, 753, 759, and 765; (d) a beta chain variable domain CDR1 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 532, 538, 544, 550, 556, 562, 568, 574, 580, 586, 592, 598, 604, 610, 616, 622, 628, 634, 640, 646, 652, 658, 664, 670, 676, 682, 688, 694, 700, 706, 712, 718, 724, 730, 736, 742, 748, 754, 760, and 766; (e) a beta chain variable domain CDR2 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 533, 539, 545, 551, 557, 563, 569, 575, 581, 587, 593, 599, 605, 611, 617, 623, 629, 635, 641, 647, 653, 659, 665, 671, 677, 683, 689, 695, 701, 707, 713, 719, 725, 731, 737, 743, 749, 755, 761, and 767; and (f) a beta chain variable domain CDR3 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 534, 540, 546, 552, 558,

564, 570, 576, 582, 588, 594, 600, 606, 612, 618, 624, 630, 636, 642, 648, 654, 660, 666, 672, 678, 684, 690, 696, 702, 708, 714, 720, 726, 732, 738, 744, 750, 756, 762, and 768.

[0079] In some embodiments, the TCR comprises an alpha chain variable domain/beta chain variable domain nucleic acid sequence pair selected from the group consisting of SEQ ID NOs: 770/772,

5 774/776, 778/780, 782/784, 786/788, 790/792, 794/796, 798/800, 802/804, 806/808, 810/812, 814/816, 818/820, 822/824, 826/828, 830/832, 834/836, 838/840, 842/844, 846/848, 850/852, 854/856, 858/860, 862/864, 866/868, 870/872, 874/876, 878/880, 882/884, 886/888, 890/892, 894/896, 898/900, 902/904, 906/908, 910/912, 914/916, 918/920, 922/924, and 926/928.

[0080] The present invention also provides vectors comprising an isolated nucleic acid molecule of
10 the invention and isolated cells comprising a vector of the invention.

[0081] In one aspect, the present invention provides a method of treating a subject having a PRAME-associated disease or disorder, comprising administering to the subject a plurality of the cells comprising a vector of the invention, thereby treating the subject.

[0082] In some embodiments, the PRAME-associated disease or disorder is PRAME-associated
15 cancer.

[0083] In some embodiments, the PRAME-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast
20 cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma,
25 uterine corpus endometrial carcinoma, uterine carcinosarcoma, testicular germ cell tumor, uveal melanoma, kidney renal papillary cell carcinoma, kidney renal clear cell carcinoma, thymoma, colon adenocarcinoma, cervical squamous cell carcinoma, cervical tumor, pancreatic adenocarcinoma, liver cancer, hepatocellular carcinoma, mesothelioma, or a recurrent non-small cell lung cancer.

[0084] In some embodiments, a plurality of cells is administered to the subject in combination with a
30 second therapeutic agent.

[0085] The present invention is further illustrated by the following detailed description.

DETAILED DESCRIPTION

[0086] The present invention provides T cell receptors (TCRs) that were generated against a PRAME
35 peptide antigen in the context of MHC (HLA-A2). The unique TCR sequences identified have shown specific binding to the small peptide PRAME presented in the groove of an HLA molecule.

I. Definitions

[0087] In order that the present invention may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also part of this invention.

[0088] In the following description, for purposes of explanation, specific numbers, materials and configurations are set forth in order to provide a thorough understanding of the invention. It will be apparent, however, to one having ordinary skill in the art that the invention may be practiced without these specific details. In some instances, well-known features may be omitted or simplified so as not to obscure the present invention. Furthermore, reference in the specification to phrases such as “one embodiment” or “an embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the invention. The appearances of phrases such as “in one embodiment” in various places in the specification are not necessarily all referring to the same embodiment.

[0089] The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

[0090] The term “comprising” or “comprises” is used herein in reference to compositions, methods, and respective component(s) thereof, that are essential to the disclosure, yet open to the inclusion of unspecified elements, whether essential or not.

[0091] The term “consisting of” refers to compositions, methods, and respective components thereof as described herein, which are exclusive of any element not recited in that description of the embodiment.

[0092] The term “T cell receptor” (TCR), as used herein, refers to an immunoglobulin superfamily member having a variable binding domain, a constant domain, a transmembrane region, and a short cytoplasmic tail; see, e.g., Janeway *et al.*, *Immunobiology: The Immune System in Health and Disease*, 3rd Ed., Current Biology Publications, p. 4:33, 1997) capable of specifically binding to an antigen peptide bound to a MHC receptor. A TCR can be found on the surface of a cell and generally is comprised of a heterodimer having α and β chains (also known as TCR α and TCR β , respectively), or γ and δ chains (also known as TCR γ and TCR δ , respectively). Like immunoglobulins, the extracellular portion of TCR chains (e.g., α -chain, β -chain) contain two immunoglobulin regions, a variable region (e.g., TCR variable α region or V α and TCR variable β region or V β ; typically amino acids 1 to 116 based on Kabat numbering at the N-terminus), and one constant region (e.g., TCR constant domain α or C α and typically amino acids 117 to 259 based on Kabat, TCR constant domain β or C β , typically amino acids 117 to 295 based on Kabat) adjacent to the cell membrane. Also, like immunoglobulins, the variable domains contain complementary determining regions (CDRs)

separated by framework regions (FRs). In certain embodiments, a TCR is found on the surface of T cells (or T lymphocytes) and associates with the CD3 complex. The source of a TCR of the present disclosure may be from various animal species, such as a human, mouse, rat, rabbit or other mammal. In preferred embodiments, the source of a TCR of the present invention is a mouse genetically engineered to produce TCRs comprising human alpha and beta chains (see, *e.g.*, PCT Publication No. WO 2016/164492, the entire contents of which are incorporated herein by reference).

[0093] The term “variable region” (variable region of an alpha chain ($V\alpha$), variable region of a beta chain ($V\beta$)) as used herein denotes each of the alpha and beta chains which is involved directly in binding the TCR to the antigen.

[0094] The “constant region” of the alpha chain and of the beta chain are not involved directly in binding of a TCR to an antigen, but exhibit various effector functions.

[0095] The term “antigen” as used herein is meant any substance that causes the immune system to produce antibodies or specific cell-mediated immune responses against it. A disease-associated antigen is any substance that is associated with any disease that causes the immune system to produce antibodies or a specific-cell mediated response against it.

[0096] The term “PRAME” or “preferentially expressed antigen in melanoma” refers to the well-known cancer-testis antigen (CTA) that is re-expressed in numerous cancer types.

[0097] The nucleotide sequence of PRAME is known and may be found in, for example, GenBank Accession Nos. NM_001291715.2 (SEQ ID NO: 931), NM_001291716.2 (SEQ ID NO: 932), NM_001291717.2 (SEQ ID NO: 933), NM_001291719.2 (SEQ ID NO: 934), NM_001318126.1 (SEQ ID NO: 935), NM_001318127.1 (SEQ ID NO: 936), NM_006115.5 (SEQ ID NO: 937), NM_206956.3 (SEQ ID NO: 938), NM_206955.2 (SEQ ID NO: 939), NM_206954.3 (SEQ ID NO: 940), and NM_206953.2 (SEQ ID NO: 941). The amino acid sequence of full-length PRAME is known and may be found in, for example, GenBank as Accession Nos. NP_001278646.1 (SEQ ID NO: 942), NP_006106.1 (SEQ ID NO: 943), NP_996837.1 (SEQ ID NO: 944), NP_996836.1 (SEQ ID NO: 945), NP_996839.1 (SEQ ID NO: 946), NP_996838.1 (SEQ ID NO: 947), NP_001278644.1 (SEQ ID NO: 948), NP_001305055.1 (SEQ ID NO: 949), NP_001305056.1 (SEQ ID NO: 950), NP_001278648.1 (SEQ ID NO: 951), and NP_001278645.1 (SEQ ID NO: 952). The term “PRAME” includes recombinant PRAME or a fragment thereof. The term also encompasses PRAME or a fragment thereof coupled to, for example, histidine tag, mouse or human Fc, or a signal sequence such as ROR1. In certain embodiments, the term comprises PRAME, or a fragment thereof, in the context of HLA-A2, linked to HLA-A2 or as displayed by HLA-A2. As used herein, the numbering of certain PRAME amino acid residues within the full-length PRAME sequence is with respect to SEQ ID NO: 944.

[0098] The term “HLA” refers to the human leukocyte antigen (HLA) system or complex, which is a gene complex encoding the major histocompatibility complex (MHC) proteins in humans. These cell-

surface proteins are responsible for the regulation of the immune system in humans. HLAs corresponding to MHC class I (A, B, and C) present peptides from inside the cell.

[0099] The term “HLA-A” refers to the group of human leukocyte antigens (HLA) that are coded for by the HLA-A locus. HLA-A is one of three major types of human MHC class I cell surface
5 receptors. The receptor is a heterodimer, and is composed of a heavy α chain and smaller β chain. The α chain is encoded by a variant HLA-A gene, and the β chain (β 2-microglobulin) is an invariant β 2 microglobulin molecule.

[00100] The term “HLA-A2” (which may also be referred to as HLA-A2*01 or HLA-A*0201 or HLA-A*02:01) is one particular class I major histocompatibility complex (MHC) allele group at
10 the HLA-A locus; the α chain is encoded by the HLA-A*02 gene and the β chain is encoded by the β 2-microglobulin or B2M locus.

[00101] The term “specifically binds,” or “binds specifically to”, or the like, means that TCR forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about 1×10^{-6} M or less,
15 for example, 1×10^{-8} M or less (*e.g.*, a smaller K_D denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. As described herein, the TCRs of the invention bind specifically to an HLA-A2 presented cancer testis preferentially expressed antigen in melanoma (PRAME) peptide, *e.g.*, a peptide comprising amino acid residues 312-320 or 425-433 of
20 PRAME (*e.g.*, of the full-length PRAME sequence of SEQ ID NO: 944).

[00102] The term “off-target peptide” refers to a peptide that differs by 1, 2, 3, 4, 5 or more amino acids from a target peptide (*e.g.*, a PRAME 312-320 peptide or a PRAME 425-433 peptide). In certain embodiments, the term includes a peptide that differs by less than or equal to 3 amino acids than the target peptide. For example, for a 9-mer peptide, if 1, 2, or 3 amino acids are not identical to
25 the target peptide, it is considered an “off-target” peptide. In certain embodiments, amino acid identity is expressed in terms of ‘degree of similarity’ (DoS). If 6 or more amino acids within a 9-mer peptide are identical, the DoS is 6. In certain embodiments, a peptide with $\text{DoS} \leq 6$ is considered an “off-target” peptide. The term “off-target” peptide also refers to a peptide that is similar to the target peptide based on sequence homology, is predicted to bind to HLA-A2 and is comprised in a protein
30 that is expressed in essential, normal tissues. Accordingly, in some embodiments a TCR of the present disclosure can bind to an HLA-A2-presented PRAME peptide (*e.g.*, a peptide comprising amino acid residues 312-320 or 425-433 of PRAME) with an affinity corresponding to a K_D value that is at least ten-fold lower than its affinity for binding to an off-target peptide.

[00103] The term “isolated” refers to a composition, compound, substance, or molecule
35 altered by the hand of man from the natural state. For example, a composition or substance that occurs in nature is isolated if it has been changed or removed from its original environment, or both.

For example, a polynucleotide or a polypeptide naturally present in a living animal is not isolated, but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is isolated, as the term is employed herein. More particularly, an isolated TCR can refer to a TCR that has been removed from a cell, for example, a TCR that has been purified. TCRs can also be expressed by an isolated cell, *e.g.*, a cell that has been isolated from an animal or a cell from cell culture. In this context, the isolated cell can express the TCR on its surface (*i.e.*, the cell can “present” the TCR).

[00104] The term “recombinant”, as used herein, refers to TCRs of the invention created, expressed, isolated or obtained by technologies or methods known in the art as recombinant DNA technology which include, *e.g.*, DNA splicing and transgenic expression. The term refers to TCRs expressed in a non-human mammal (including transgenic non-human mammals, *e.g.*, transgenic mice), or a cell (*e.g.*, CHO cells) expression system or isolated from a recombinant combinatorial human antibody library.

[00105] As used herein, the terms “polynucleotide” and “nucleic acid molecule” are used interchangeably to refer to polymeric forms of nucleotides of any length. The polynucleotides may contain deoxyribonucleotides, ribonucleotides, and/or their analogs. Nucleotides may have any three-dimensional structure, and may perform any function, known or unknown. The term “polynucleotide” includes, for example, single-, double-stranded and triple helical molecules, a gene or gene fragment, exons, introns, mRNA, tRNA, rRNA, ribozymes, antisense molecules, cDNA, recombinant polynucleotides, branched polynucleotides, aptamers, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A nucleic acid molecule may also comprise modified nucleic acid molecules (*e.g.*, comprising modified bases, sugars, and/or internucleotide linkers).

[00106] The term “polypeptide” is meant to refer to any polymer preferably consisting essentially of any of the 20 natural amino acids regardless of its size. Although the term “protein” is often used in reference to relatively large proteins, and “peptide” is often used in reference to small polypeptides, use of these terms in the field often overlaps. The term “polypeptide” refers generally to proteins, polypeptides, and peptides unless otherwise noted. Peptides useful in accordance with the present disclosure in general will be generally between about 0.1 to 100 kDa or greater up to about 1000 kDa, preferably between about 0.1, 0.2, 0.5, 1, 2, 5, 10, 20, 30 and 50 kDa as judged by standard molecule sizing techniques such as centrifugation or SDS-polyacrylamide gel electrophoresis.

[00107] The term “vector” is a nucleic acid molecule that is able to replicate autonomously in a host cell and can accept foreign DNA. A vector carries its own origin of replication, one or more unique recognition sites for restriction endonucleases which can be used for the insertion of foreign DNA, and usually selectable markers such as genes coding for antibiotic resistance, and often recognition sequences (*e.g.*, promoter) for the expression of the inserted DNA. Common vectors include plasmid vectors and phage vectors.

[00108] In some embodiments, TCRs of the invention may be conjugated to a moiety such as a ligand, a detectable moiety, or a therapeutic moiety (“immunoconjugate”), such as a cytotoxin, an anti-cancer drug, or any other therapeutic moiety useful for treating a disease or condition including PRAME-associated disease or disorder, such as a PRAME-associated cancer.

5 [00109] The term “surface plasmon resonance”, as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.).

[00110] The term “KD”, also known as K_D or K_d , is intended to refer to the equilibrium dissociation constant of a particular biomolecule and its binding partner. KD measurements are particularly useful for assessing protein-protein interactions, *e.g.* as in an antigen-binding protein-antigen interaction. The smaller the value of the KD, the greater (or *e.g.* stronger) the binding interaction or affinity between the antigen-binding protein and antigen (*e.g.* target). The larger the value of the KD, the weaker the binding interaction or affinity between the antigen-binding protein and antigen.

15 [00111] The term “substantial identity” or “substantially identical,” when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 20 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

[00112] Sequence identity can be calculated using an algorithm, for example, the Needleman Wunsch algorithm (Needleman and Wunsch 1970, *J. Mol. Biol.* 48: 443-453) for global alignment, or 25 the Smith Waterman algorithm (Smith and Waterman 1981, *J. Mol. Biol.* 147: 195-197) for local alignment. Another preferred algorithm is described by Dufresne *et al* in *Nature Biotechnology* in 2002 (vol. 20, pp. 1269-71) and is used in the software GenePAST (GQ Life Sciences, Inc. Boston, MA).

30 [00113] As applied to polypeptides, the term “substantial similarity” or “substantially similar” means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 90% sequence identity, even more preferably at least 95%, 96%, 97%, 98% or 99% sequence identity. Preferably, residue positions, which are not identical, differ by conservative amino acid substitutions. A “conservative amino acid substitution” is 35 one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (*e.g.*, charge or hydrophobicity). In general, a

conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. See, *e.g.*, Pearson (1994) *Methods Mol. Biol.* 24: 307-331, which is herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet *et al.* (1992) *Science* 256: 1443-45, herein incorporated by reference. A “moderately conservative” replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

[00114] Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, *e.g.*, GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (*e.g.*, FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) *supra*). Sequences also can be compared using the Smith-Waterman homology search algorithm using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 2, BLOSUM matrix of 62. Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. See, *e.g.*, Altschul *et al.* (1990) *J. Mol. Biol.* 215: 403-410 and (1997) *Nucleic Acids Res.* 25:3389-3402, each of which is herein incorporated by reference.

[00115] A “patient-derived TCR” is a TCR that is produced by isolating the alpha and beta chains of a PRAME reactive TCR isolated from the T-lymphocytes that mediated *in vivo* regression of a tumor in a subject having a PRAME-associated cancer.

[00116] An “affinity-matured TCR” is a TCR that is produced by mutagenesis and selection *in vitro*. For example, untargated or targated (*e.g.*, oligonucleotide-directed) mutagenesis can be performed to introduce variation in TCR sequences, and the subsequent TCRs can then be screened for affinity against a target, *e.g.*, by use of phage display.

5 [00117] The term “activates a T cell response having a signal to noise ratio stronger or equal to a patient-derived PRAME-specific TCR” or “activates a T cell response having a signal to noise ratio stronger or equal to an affinity-matured PRAME-specific TCR” is meant to refer to an increase, *i.e.*, about 2-fold or more, an amplification, *i.e.*, about 2-fold, an augmentation, *i.e.*, about 2-fold, or a boost of a physiological activity, *i.e.*, about 2-fold, *i.e.*, T cell signaling, as measured by, for example,
10 a luminescent bioassay. Reference to a greater T cell response, or a stronger T cell response or an activation signal, may be used interchangeably. Various measurements and assays of T cell response or T cell activation are well known to the skilled artisan.

[00118] By the phrase “therapeutically effective amount” is meant an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the
15 treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) *The Art, Science and Technology of Pharmaceutical Compounding*). The term “effective amount” is intended to encompass contexts such as a pharmaceutically effective amount or therapeutically effective amount. For example, in certain embodiments, the effective amount is capable of achieving a beneficial state, beneficial outcome, functional activity in a screening assay, or
20 improvement of a clinical condition.

[00119] As described herein, a TCR of the invention may be “administered” to a subject. “Administering” a TCR of the invention includes, but is not limited to, administration of a cell expressing a TCR of the invention (*e.g.*, an effector cell such as a T cell), administration of a nucleic acid expressing a TCR of the invention (*e.g.*, a vector expressing such a TCR), and administration of a
25 polypeptide comprising a TCR of the invention, wherein the polypeptide has been formatted for such administration (*e.g.*, a bispecific polypeptide comprising a TCR chain and a CD3-binding antibody chain).

[00120] As used herein, the term “subject” refers to an animal, preferably a mammal, in need of amelioration, prevention and/or treatment of a PRAME-associated disease or disorder, such as a
30 PRAME-associated cancer (*e.g.*, a PRAME-positive cancer). The term includes human subjects who have or are at risk of having a PRAME-associated disease or disorder, such as a PRAME-associated cancer.

[00121] As used herein, “anti-cancer drug” means any agent useful to treat or ameliorate or inhibit cancer including, but not limited to, cytotoxins and agents such as antimetabolites, alkylating
35 agents, anthracyclines, antibiotics, antimetotic agents, procarbazine, hydroxyurea, asparaginase, corticosteroids, cyclophosphamide, mytotane (O,P'-(DDD)), biologics (*e.g.*, antibodies and

interferons) and radioactive agents. As used herein, “a cytotoxin or cytotoxic agent”, also refers to a chemotherapeutic agent and means any agent that is detrimental to cells. Examples include Taxol® (paclitaxel), temozolamide, cytochalasin B, gramicidin D, ethidium bromide, emetine, cisplatin, mitomycin, etoposide, tenoposide, vincristine, vinblastine, coichicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof.

[00122] The terms “prevent”, “preventing”, “prevention”, “prophylactic treatment” and the like are meant to refer to reducing the probability of developing a disorder or condition in a subject, who does not have, but is at risk of or susceptible to developing a disorder or condition. Prevention and the like do not mean preventing a subject from ever getting the specific disease or disorder. Prevention may require the administration of multiple doses. Prevention can include the prevention of a recurrence of a disease in a subject for whom all disease symptoms were eliminated, or prevention of recurrence in a relapsing-remitting disease.

II. PRAME T Cell (TCRs) and Compositions Comprising PRAME TCRS

[00123] T cells are a subgroup of cells which, together with other immune cell types (polymorphonuclear, eosinophils, basophils, mast cells, B-cells, NK cells), constitute the cellular component of the immune system. Under physiological conditions T cells function in immune surveillance and in the elimination of foreign antigen. However, under pathological conditions there is compelling evidence that T cells play a major role in the causation and propagation of disease. In these disorders, breakdown of T cell immunological tolerance, either central or peripheral is a fundamental process in the causation of autoimmune disease.

[00124] T cells bind epitopes on small antigenic determinants on the surface of antigen-presenting cells that are associated with a major histocompatibility complex (MHC; in mice) or human leukocyte antigen (HLA; in humans) complex. T cells bind these epitopes through a T cell receptor (TCR) complex on the surface of the T cell. T cell receptors are heterodimeric structures composed of two types of chains: an α (alpha) and β (beta) chain, or a γ (gamma) and δ (delta) chain. The α chain is encoded by the nucleic acid sequence located within the α locus (on human or mouse chromosome 14), which also encompasses the entire δ locus, and the β chain is encoded by the nucleic acid sequence located within the β locus (on mouse chromosome 6 or human chromosome 7). The majority of T cells have an $\alpha\beta$ TCR; while a minority of T cells bears a $\gamma\delta$ TCR.

[00125] T cell receptor α and β polypeptides (and similarly γ and δ polypeptides) are linked to each other *via* a disulfide bond. Each of the two polypeptides that make up the TCR contains an extracellular domain comprising constant and variable regions, a transmembrane domain, and a cytoplasmic tail (the transmembrane domain and the cytoplasmic tail also being a part of the constant

region). The variable region of the TCR determines its antigen specificity, and similar to immunoglobulins, comprises three complementary determining regions (CDRs). The TCR is expressed on most T cells in the body and is known to be involved in the recognition of MHC-restricted antigens. The TCR α chain includes a covalently linked V α and C α region, whereas the β chain includes a V β region covalently linked to a C β region. The V α and V β regions form a pocket or cleft that can bind an antigen in the context of a major histocompatibility complex (MHC) (or HLA in humans). TCRs are detection molecules with exquisite specificity, and exhibit, like antibodies, an enormous diversity.

[00126] The general structure of TCR molecules and methods of making and using, including binding to a peptide:Major Histocompatibility Complex have been disclosed. See, for example PCT/US98/04274; PCT/US98/20263; WO99/60120.

[00127] Non-human animals (*e.g.*, rodents, *e.g.*, mice or rats) can be genetically engineered to express a human or humanized T cell receptor (TCR) comprising a variable domain encoded by at least one human TCR variable region gene segment, as described in, for example, PCT Publication No. WO 2016/164492, the entire contents of which are hereby incorporated herein by reference. For example, the VelociT® mouse technology (Regeneron), a genetically modified mouse that allows for the production of fully human therapeutic TCRs against tumor and/or viral antigens, can be used to produce the TCRs of the invention. Those of skill in the art, through standard mutagenesis techniques, in conjunction with the assays described herein, can obtain altered TCR sequences and test them for particular binding affinity and/or specificity. Useful mutagenesis techniques known in the art include, without limitation, *de novo* gene synthesis, oligonucleotide-directed mutagenesis, region-specific mutagenesis, linker-scanning mutagenesis, and site-directed mutagenesis by PCR (see, *e.g.*, Sambrook *et al.* (1989) and Ausubel *et al.* (1999)).

[00128] Briefly, in some embodiments, methods for generating a TCR to a PRAME 312-320 peptide or a PRAME 425-433 peptide may include immunizing a non-human animal (*e.g.*, a rodent, *e.g.*, a mouse or a rat), such as a genetically engineered non-human animal that comprises in its genome an un-rearranged human TCR variable gene locus, with a PRAME 312-320 peptide or a PRAME 425-433 peptide; allowing the animal to mount an immune response to the peptide; isolating from the animal a T cell reactive to the peptide; determining a nucleic acid sequence of a human TCR variable region expressed by the T cell; cloning the human TCR variable region into a nucleotide construct comprising a nucleic acid sequence of a human TCR constant region such that the human TCR variable region is operably linked to the human TCR constant region; and expressing from the construct a human T cell receptor specific for the PRAME 312-320 peptide or a PRAME 425-433 peptide, respectively. In some embodiments, the steps of isolating a T cell, determining a nucleic acid sequence of a human TCR variable region expressed by the T cell, cloning the human TCR variable region into a nucleotide construct comprising a nucleic acid sequence of a human TCR constant

region, and expressing a human T cell receptor are performed using standard techniques known to those of skill the art.

[00129] In some embodiments, the nucleotide sequence encoding a T cell receptor specific for an antigen of interest is expressed in a cell. In some embodiments, the cell expressing the TCR is selected from a CHO, COS, 293, HeLa, PERC.6™ cell, *etc.*

[00130] In obtaining variant TCR coding sequences, those of ordinary skill in the art will recognize that TCR-derived proteins may be modified by certain amino acid substitutions, additions, deletions, and post-translational modifications, without loss or reduction of biological activity. In particular, it is well known that conservative amino acid substitutions, that is, substitution of one amino acid for another amino acid of similar size, charge, polarity and conformation, are unlikely to significantly alter protein function. The 20 standard amino acids that are the constituents of proteins can be broadly categorized into four groups of conservative amino acids as follows: the nonpolar (hydrophobic) group includes alanine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan and valine; the polar (uncharged, neutral) group includes asparagine, cysteine, glutamine, glycine, serine, threonine and tyrosine; the positively charged (basic) group contains arginine, histidine and lysine; and the negatively charged (acidic) group contains aspartic acid and glutamic acid. Substitution in a protein of one amino acid for another within the same group is unlikely to have an adverse effect on the biological activity of the protein.

[00131] In some embodiments, a TCR of the present disclosure can comprise a CDR sequence (*e.g.*, a CDR3 sequence such as a V α CDR3 or a V β CDR3) with 1 or more substitutions as compared to a CDR sequence (*e.g.*, a CDR3 sequence such as a V α CDR3 or a V β CDR3) of Table 5 or Table 8. For example, a TCR of the present disclosure can comprise a CDR sequence with 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more substitutions as compared to a CDR sequence of Table 5 or Table 8. In general, the TCRs of the present invention function by binding to an HLA-A2 presented PRAME 312-320 peptide or a HLA-A2 presented PRAME 425-433 peptide. As used herein, an HLA presented peptide (such as an HLA-A2 presented peptide) can refer to a peptide that is bound to a human leukocyte antigen (HLA) protein, for example, an HLA protein expressed on the surface of a cell. Thus, a TCR that binds to an HLA presented peptide binds to the peptide that is bound by the HLA, and optionally also binds to the HLA itself. Interaction with the HLA can confer specificity for binding to a peptide presented by a particular HLA. In some embodiments, the TCR binds to an isolated HLA presented peptide. In some embodiments, the TCR binds to an HLA presented peptide on the surface of a cell.

[00132] In general, the TCRs of the present invention can function by binding to an HLA-A2-presented PRAME peptide (*e.g.*, PRAME 312-320 or PRAME 425-433).

[00133] The present invention includes PRAME TCRs that bind a PRAME 312-320 peptide or a PRAME 425-433 peptide in the context of HLA-A2 with high specificity. In some embodiments, the PRAME TCRs do not bind to the PRAME 312-320 peptide or the PRAME 425-433 peptide in the

absence of HLA-A2, or such binding is minimal. Further, in some embodiments, the PRAME TCRs do not bind to an off-target peptide in the context of HLA-A2, or such binding is minimal. As used herein, an off-target peptide can refer to a peptide that differs from a target peptide by 1, 2, 3, 4, 5, or more amino acids. In some embodiments, binding specificity can be determined by a) measuring on-target binding (e.g., binding to the HLA-A2 presented PRAME (312-320) peptide or the HLA-A2 presented PRAME (425-433) peptide), b) measuring off-target binding, and c) quantifying the difference between the two, e.g., by calculating a ratio. This ratio can be calculated, for example, by dividing the values obtained in a) and b). Measurement of on-target and off-target binding can be achieved, for example, by measuring % binding to a peptide/HLA tetramer reagent (e.g., a PRAME/HLA tetramer reagent), or by other techniques known in the art. In some embodiments, an on-target binding/off-target binding value (e.g., a value obtained by dividing the values obtained in a) and b) described above) of a TCR of the present disclosure can be greater than 5, greater than 6, greater than 7, greater than 8, greater than 9, greater than 10, greater than 11, greater than 12, greater than 13, greater than 14, greater than 15, greater than 16, greater than 17, greater than 18, greater than 19, greater than 20, greater than 21, greater than 22, greater than 23, greater than 24, greater than 25, greater than 26, greater than 27, greater than 28, greater than 29, greater than 30, greater than 35, greater than 40, greater than 45, greater than 50, greater than 55, greater than 60, greater than 65, greater than 70, greater than 75, greater than 80, greater than 85, greater than 90, greater than 95, greater than 100, greater than 110, greater than 120, greater than 130, greater than 140, greater than 150, greater than 160, greater than 170, greater than 180, greater than 190, greater than 200, greater than 225, greater than 250, greater than 275, greater than 300, greater than 325, greater than 350, greater than 375, greater than 400, greater than 425, greater than 450, greater than 475, greater than 500, greater than 550, greater than 600, greater than 650, greater than 700, greater than 750, greater than 800, greater than 850, greater than 900, greater than 950, greater than 1000, greater than 1100, greater than 1200, greater than 1300, greater than 1400, greater than 1500, greater than 1600, greater than 1700, greater than 1800, greater than 1900, or greater than 2000. In some embodiments, an on-target binding/off-target binding value (e.g., a value obtained by dividing the values obtained in a) and b) described above) can be about 5 to about 20, about 10 to about 30, about 20 to about 80, about 30 to about 70, about 40 to about 60, about 50 to about 250, about 100 to about 200, about 100 to about 1000, about 300 to about 700, about 500 to about 1500, about 800 to about 1200, about 900 to about 1100, about 800 to about 1500, about 1000 to about 1400, or about 1100 to about 1300.

[00134] In some embodiments, the invention provides a recombinant antigen-binding protein (e.g., an isolated antigen-binding protein) that binds specifically to a conformational epitope of an HLA-A2 presented human PRAME (312-320) peptide or to a conformational epitope of an HLA-A2 presented human PRAME (425-433) peptide, wherein the antigen-binding protein has a property selected from the group consisting of: (a) binds monomeric HLA-A2: PRAME (312-320) peptide or monomeric PRAME (312-320) peptide with a binding dissociation equilibrium constant (K_D) of less

than about 20nM as measured in a surface plasmon resonance assay at 25°C; (b) binds monomeric HLA-A2: PRAME (425-433) peptide or monomeric PRAME (425-433) peptide with a binding dissociation equilibrium constant (K_D) of less than about 25nM as measured in a surface plasmon resonance assay at 25°C; (c) binds to HLA-A2: PRAME (312-320) peptide-expressing cells or PRAME (425-433) peptide-expressing cells with an EC_{50} less than about 6 nM and does not bind to cells expressing predicted off-target peptides as determined by luminescence assay; (d) binds to HLA-A2: PRAME (312-320) peptide-expressing cells or PRAME (425-433) peptide-expressing cells with an EC_{50} less than about 1 nM and do not substantially bind to cells expressing predicted off-target peptides as determined by luminescence assay; (e) binds to HLA-A2: PRAME (312-320) peptide-expressing cells or PRAME (425-433) peptide-expressing cells with an EC_{50} less than about 30 nM as determined by flow cytometry assay; (f) binds to HLA-A2: PRAME (312-320) peptide-expressing cells or PRAME (425-433) peptide-expressing cells with an EC_{50} less than about 75nM as determined by flow cytometry assay; and (g) the conformational epitope comprises one or more amino acids of SEQ ID NO: 944.

[00135] In some embodiments, the PRAME TCRs of the present disclosure have specific activity or affinity for PRAME (312-320) or for PRAME (425-433) as measured by an *in vitro* assay. For example, cells (such as T2 cells) expressing an HLA can be pulsed with a PRAME (312-320) or for PRAME (425-433) polypeptide, or an off-target polypeptide thereby inducing the cells to present the polypeptide bound to the HLA. Alternatively or in addition to using an off-target polypeptide as a control, an off-target HLA (an HLA other than the HLA that is recognized by the TCR of interest) can be used. For example, an off-target HLA can be used to present the PRAME peptide to test for specificity of binding to the HLA-A2-presented PRAME peptide. In addition, a control can be a cell line that expresses neither PRAME nor the target HLA (*e.g.*, HLA-A2). Cells can be co-cultured with a T-cell population expressing the TCR of interest, and activity measured as a function of the amount of a cytokine (such as interferon gamma) produced by the cells. In certain embodiments, the assay can comprise *in vitro* co-cultures of a TCR-expressing T cell population with 10^{-10} M peptide-loaded T2 cells at an effector cell:target cell ratio of 1:1 (1×10^5 effector cells/96 well), and interferon gamma measurement 24 hours after co-culture (*e.g.*, by a Meso Scale Discovery (MSD®) Sector Imager). In certain embodiments, the assay can comprise *in vitro* co-cultures of a TCR-expressing T cell population and effector cell at an effector cell:target cell ratio of 5:1 (2.5×10^5 effector cells: 5×10^4 target cells), and interferon gamma measurement 24 hours after co-culture (*e.g.*, by a Meso Scale Discovery (MSD®) Sector Imager).

[00136] Increasing amounts of cytokine detected can serve as an indicator of activity. The activity or specificity of a TCR of interest to its target peptide in comparison to a control (off-target) polypeptide, or the activity or specificity of a TCR of interest to its on-target HLA-bound target peptide in comparison to an off-target HLA-bound target peptide can be 2-fold or greater, 3-fold or greater, 4-fold or greater, 5-fold or greater, 6-fold or greater, 7-fold or greater, 8-fold or greater, 9-fold

or greater, 10-fold or greater, 15-fold or greater, 20-fold or greater, 30-fold or greater, 40-fold or greater, 50-fold or greater, 100-fold or greater, 200-fold or greater, 300-fold or greater, 400-fold or greater, 500-fold or greater, 600-fold or greater, 700-fold or greater, 800-fold or greater, 900-fold or greater, 1,000-fold or greater, 1,500-fold or greater, 2,000-fold or greater, 2,500-fold or greater,
 5 3,000-fold or greater, 4,000-fold or greater, 5,000-fold or greater, 10,000-fold or greater, 20,000-fold or greater, 30,000-fold or greater, 40,000-fold or greater, 50,000-fold or greater, 60,000-fold or greater, 70,000-fold or greater, 80,000-fold or greater, 90,000-fold or greater, or 100,000-fold or greater.

[00137] In certain embodiments, the PRAME TCRs of the present disclosure are useful in
 10 inhibiting the growth of a tumor or delaying the progression of cancer when administered prophylactically to a subject in need thereof and may increase survival of the subject. For example, the administration of a PRAME TCR of the present invention may lead to shrinking of a primary tumor and may prevent metastasis or development of secondary tumors. In certain embodiments, the PRAME TCRs of the present invention are useful in inhibiting the growth of a tumor when
 15 administered therapeutically to a subject in need thereof and may increase survival of the subject. For example, the administration of a therapeutically effective amount of a PRAME TCR of the invention to a subject may lead to shrinking and disappearance of an established tumor in the subject.

[00138] In some embodiments, the invention provides a TCR (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell) that specifically binds to an HLA-A2 presented PRAME 312-320
 20 peptide, wherein the antigen-binding protein exhibits one or more of the following characteristics: (i) comprises an alpha chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of any one of the alpha chain variable domain CDR3 amino acid sequences set forth in Table 3; (ii) comprises a beta chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3 comprises the amino
 25 acid sequence of any one of the beta chain variable domain CDR3 amino acid sequences set forth in Table 3; (iii) comprises a CDR1 of the alpha chain variable domain comprising any one of the CDR1 amino acid sequences set forth in Table 3, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, and a CDR2 of the alpha chain variable domain independently comprising any one of the CDR2 amino acid
 30 sequences set forth in Table 3, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iv) comprises a CDR1 of a beta chain variable domain comprising any one of the CDR1 amino acid sequences set forth in Table 3, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, and a CDR2 of a beta chain
 35 variable domain independently comprising any one of the CDR2 amino acid sequences set forth in Table 3, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (v) comprises an alpha chain variable

domain CDR1, CDR2 and CDR3 contained within any one of the alpha chain variable domain sequences listed in Table 5, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and beta chain variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 5, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vi) comprises an alpha chain variable domain having an amino acid sequence that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or about 100% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 5; (vii) comprises a beta chain variable domain having an amino acid sequence that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or about 100% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 5; (viii) comprises (a) an alpha chain variable domain having an amino acid sequence that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or about 100% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 5; and (b) a beta chain variable domain having an amino acid sequence that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or about 100% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 5; (ix) comprises (a) an alpha chain variable domain CDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 7, 13, 19, 25, 31, 37, 43, 49, 55, 61, 67, 73, 79, 85, 91, 97, and 103, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 8, 14, 20, 26, 32, 38, 44, 50, 56, 62, 68, 74, 80, 86, 92, 98, and 104, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 9, 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99, and 105, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 10, 16, 22, 28, 34, 40, 46, 52, 58, 64, 70, 76, 82, 88, 94, 100, and 106, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 11, 17, 23, 29, 35, 41, 47, 53, 59, 65, 71, 77, 83, 89, 95, 101, and 107, or a substantially similar sequence

thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and (f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96, 102, and 108, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (x) comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 217/219, 229/231, 237/239, 241/243, and 285/287, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (xi) comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 217/219, 221/223, 225/227, 229/231, 233/235, 237/239, 241/243, 245/247, 249/251, 253/255, 257/259, 261/263, 265/267, 269/271, 273/275, 277/279, 281/283, and 285/287, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (xii) does not specifically bind to cells expressing predicted off-target peptides but not an HLA-A2 presented PRAME 312-320 peptide, as determined by a luminiscence assay; and/or (xiii) activates a T cell response about two times greater than a patient-derived PRAME-specific TCR, *e.g.*, activates a T cell response about two times greater, or about three times greater, or about four times greater than a patient-derived PRAME-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay.

20 **[00139]** In some embodiments, the invention provides a TCR (*e.g.*, an isolated TCR or a TCR expressed on an isolated cell) that specifically binds to an HLA-A2 presented PRAME 425-433 peptide, wherein the antigen-binding protein exhibits one or more of the following characteristics: (i) comprises an alpha chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of any one of the alpha chain variable domain CDR3 amino acid sequences set forth in Table 6; (ii) comprises a beta chain variable domain comprising a complementary determining region (CDR)3, wherein the CDR3 comprises the amino acid sequence of any one of the beta chain variable domain CDR3 amino acid sequences set forth in Table 6; (iii) comprises a CDR1 of the alpha chain variable domain comprising any one of the CDR1 amino acid sequences set forth in Table 6, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, and a CDR2 of the alpha chain variable domain independently comprising any one of the CDR2 amino acid sequences set forth in Table 6, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (iv) comprises a CDR1 of a beta chain variable domain comprising any one of the CDR1 amino acid sequences set forth in Table 6, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity, and a CDR2 of a beta chain variable domain independently comprising any one of the CDR2 amino acid sequences set forth in

Table 6, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (v) comprises an alpha chain variable domain CDR1, CDR2 and CDR3 contained within any one of the alpha chain variable domain sequences listed in Table 8, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and beta chain variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 8, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (vi) comprises an alpha chain variable domain having an amino acid sequence that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or about 100% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 8; (vii) comprises a beta chain variable domain having an amino acid sequence that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or about 100% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 8; (viii) comprises (a) an alpha chain variable domain having an amino acid sequence that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or about 100% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the alpha chain variable domain amino acid sequences listed in Table 8; and (b) a beta chain variable domain having an amino acid sequence that has at least 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or about 100% amino acid identity to the entire amino acid sequence of any one of the amino acid sequences of the beta chain variable domain amino acid sequences listed in Table 8; (ix) comprises (a) an alpha chain variable domain CDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 289, 295, 301, 307, 313, 319, 325, 331, 337, 343, 349, 355, 361, 367, 373, 379, 385, 391, 397, 403, 409, 415, 421, 427, 433, 439, 445, 451, 457, 463, 469, 475, 481, 487, 493, 499, 505, 511, 517, and 523, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (b) an alpha chain variable domain CDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 290, 296, 302, 308, 314, 320, 326, 332, 338, 344, 350, 356, 362, 368, 374, 380, 386, 392, 398, 404, 410, 416, 422, 428, 434, 440, 446, 452, 458, 464, 470, 476, 482, 488, 494, 500, 506, 512, 518, and 524, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (c) an alpha chain variable domain CDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 291, 297, 303, 309, 315, 321, 327, 333, 339, 345, 351, 357, 363, 369, 375, 381, 387, 393, 399, 405, 411, 417, 423, 429, 435, 441, 447, 453, 459, 465, 471, 477, 483, 489, 495, 501, 507, 513, 519, and 525, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least

- 99% sequence identity; (d) a beta chain variable domain CDR1 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 292, 298, 304, 310, 316, 322, 328, 334, 340, 346, 352, 358, 364, 370, 376, 382, 388, 394, 400, 406, 412, 418, 424, 430, 436, 442, 448, 454, 460, 466, 472, 478, 484, 490, 496, 502, 508, 514, 520, and 526, or a substantially similar sequence thereof
- 5 having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (e) a beta chain variable domain CDR2 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 293, 299, 305, 311, 317, 323, 329, 335, 341, 347, 353, 359, 365, 371, 377, 383, 389, 395, 401, 407, 413, 419, 425, 431, 437, 443, 449, 455, 461, 467, 473, 479, 485, 491, 497, 503, 509, 515, 521, and 527, or a substantially similar sequence thereof having at least 90%,
- 10 at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; and (f) a beta chain variable domain CDR3 having an amino acid sequence selected from the group consisting of SEQ ID NOs: 294, 300, 306, 312, 318, 324, 330, 336, 342, 348, 354, 360, 366, 372, 378, 384, 390, 396, 402, 408, 414, 420, 426, 432, 438, 444, 450, 456, 462, 468, 474, 480, 486, 492, 498, 504, 510, 516, 522, and 528, or a substantially similar sequence thereof having at least 90%, at least 95%, at
- 15 least 96%, at least 97%, at least 98% or at least 99% sequence identity; (x) comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 825/827, 845/847, 853/855, 857/859, 865/867, 873/875, 885/887, 893/805, 897/899, 901/903, 913/915, and 925/927, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity; (xi)
- 20 comprises an alpha chain variable domain/beta chain variable domain amino acid sequence pair selected from the group consisting of SEQ ID NOs: 769/771, 773/775, 777/779, 781/783, 785/787, 789/791, 793/795, 797/799, 801/803, 805/807, 809/811, 813/815, 817/819, 821/823, 825/827, 829/831, 833/835, 837/839, 841/843, 845/847, 849/851, 853/855, 857/859, 861/863, 865/867, 869/871, 873/875, 877/879, 881/883, 885/887, 889/891, 893/805, 897/899, 901/903, 905/907,
- 25 909/911, 913/915, 917/919, 921/923, and 925/927, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% sequence identity;
- (xii) does not specifically bind to cells expressing predicted off-target peptides but not an HLA-A2 presented PRAME 425-433 peptide, as determined by a luminescence assay; and/or (xiii) activates a T cell response about two times greater than a patient-derived PRAME-specific TCR, *e.g.*, activates a
- 30 T cell response about two times greater, or about three times greater, or about four times greater than a patient-derived PRAME-specific TCR as determined by a TCR-mediated T cell signaling luminescent bioassay.

[00140] The TCRs of the present invention may possess one or more of the aforementioned biological characteristics, or any combinations thereof. Other biological characteristics of the antigen-binding proteins of the present invention will be evident to a person of ordinary skill in the art from a review of the present disclosure including the working Examples herein.

35

[00141] In certain embodiments, a polynucleotide encoding a PRAME TCR described herein is inserted into a vector. The term "vector" as used herein refers to a vehicle into which a polynucleotide encoding a protein may be covalently inserted so as to bring about the expression of that protein and/or the cloning of the polynucleotide. Such vectors may also be referred to as "expression vectors". The isolated polynucleotide may be inserted into a vector using any suitable methods known in the art, for example, without limitation, the vector may be digested using appropriate restriction enzymes and then may be ligated with the isolated polynucleotide having matching restriction ends. Expression vectors have the ability to incorporate and express heterologous or modified nucleic acid sequences coding for at least part of a gene product capable of being transcribed in a cell. In most cases, RNA molecules are then translated into a protein. Expression vectors can contain a variety of control sequences, which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operatively linked coding sequence in a particular host organism. In addition to control sequences that govern transcription and translation, vectors and expression vectors may contain nucleic acid sequences that serve other functions as well and are discussed *infra*. An expression vector may comprise additional elements, for example, the expression vector may have two replication systems, thus allowing it to be maintained in two organisms, for example in human cells for expression and in a prokaryotic host for cloning and amplification.

[00142] The expression vector may have the necessary 5' upstream and 3' downstream regulatory elements such as promoter sequences such as CMV, PGK and EF1 α promoters, ribosome recognition and binding TATA box, and 3' UTR AAUAAA transcription termination sequence for the efficient gene transcription and translation in its respective host cell. Other suitable promoters include the constitutive promoter of simian virus 40 (SV40) early promoter, mouse mammary tumor virus (MMTV), HIV LTR promoter, MoMuLV promoter, avian leukemia virus promoter, EBV immediate early promoter, and rous sarcoma virus promoter. Human gene promoters may also be used, including, but not limited to the actin promoter, the myosin promoter, the hemoglobin promoter, and the creatine kinase promoter. In certain embodiments inducible promoters are also contemplated as part of the vectors expressing chimeric antigen receptor. This provides a molecular switch capable of turning on expression of the polynucleotide sequence of interest or turning off expression. Examples of inducible promoters include, but are not limited to a metallothionine promoter, a glucocorticoid promoter, a progesterone promoter, or a tetracycline promoter.

[00143] The expression vector may have additional sequence such as 6x-histidine (SEQ ID NO: 954), c-Myc, and FLAG tags which are incorporated into the expressed TCRs. Thus, the expression vector may be engineered to contain 5' and 3' untranslated regulatory sequences that sometimes can function as enhancer sequences, promoter regions and/or terminator sequences that can facilitate or enhance efficient transcription of the nucleic acid(s) of interest carried on the expression vector. An expression vector may also be engineered for replication and/or expression functionality

(e.g., transcription and translation) in a particular cell type, cell location, or tissue type. Expression vectors may include a selectable marker for maintenance of the vector in the host or recipient cell.

[00144] Examples of vectors are plasmid, autonomously replicating sequences, and transposable elements. Additional exemplary vectors include, without limitation, plasmids, phagemids, cosmids, artificial chromosomes such as yeast artificial chromosome (YAC), bacterial artificial chromosome (BAC), or P1-derived artificial chromosome (PAC), bacteriophages such as lambda phage or M13 phage, and animal viruses. Examples of categories of animal viruses useful as vectors include, without limitation, retrovirus (including lentivirus), adenovirus, adeno-associated virus, herpesvirus (e.g., herpes simplex virus), poxvirus, baculovirus, papillomavirus, and papovavirus (e.g., SV40). Examples of expression vectors are Lenti-X™ Bicistronic Expression System (Neo) vectors (Clontech), pCneo vectors (Promega) for expression in mammalian cells; pLenti4/V5-DEST™, pLenti6/V5-DEST™, and pLenti6.2N5-GW/lacZ (Invitrogen) for lentivirus-mediated gene transfer and expression in mammalian cells. The coding sequences of the TCRs disclosed herein can be ligated into such expression vectors for the expression of the chimeric protein in mammalian cells.

[00145] In certain embodiments, the nucleic acids encoding the TCR of the present invention are provided in a viral vector. A viral vector can be those derived from retrovirus, lentivirus, or foamy virus. As used herein, the term, "viral vector," refers 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 coding sequence for the various proteins described herein in place of nonessential viral genes. The vector and/or particle can be utilized for the purpose of transferring DNA, RNA or other nucleic acids into cells either *in vitro* or *in vivo*. Numerous forms of viral vectors are known in the art.

[00146] In certain embodiments, the viral vector containing the coding sequence for a TCR described herein is a retroviral vector or a lentiviral vector. The term "retroviral vector" refers to a vector containing structural and functional genetic elements that are primarily derived from a retrovirus. The term "lentiviral vector" refers to a vector containing structural and functional genetic elements outside the LTRs that are primarily derived from a lentivirus.

[00147] The retroviral vectors for use herein can be derived from any known retrovirus (e.g., type c retroviruses, such as 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 Stem Cell Virus (MSCV) and Rous Sarcoma Virus (RSV)). Retroviruses of the invention also include human T cell leukemia viruses, HTLV-1 and HTLV-2, and the lentiviral family of retroviruses, such as Human Immunodeficiency Viruses, HIV-1, HIV-2, simian immunodeficiency virus (SIV), feline immunodeficiency virus (FIV), equine immunodeficiency virus (EIV), and other classes of retroviruses.

[00148] A lentiviral vector for use herein refers to a vector derived from a lentivirus, a group (or genus) of retroviruses that give rise to slowly developing disease. Viruses included within this group include HIV (human immunodeficiency virus; including HIV type 1, and HIV type 2); visna-maedi; a caprine arthritis-encephalitis virus; equine infectious anemia virus; feline immunodeficiency virus (FIV); bovine immune deficiency virus (BIV); and simian immunodeficiency virus (SIV). Preparation of the recombinant lentivirus can be achieved using the methods according to Dull *et al.* and Zufferey *et al.* (Dull *et al.*, *J. Virol.*, 1998; 72: 8463-8471 and Zufferey *et al.*, *J. Virol.* 1998; 72:9873-9880).

[00149] Retroviral vectors (*i.e.*, both lentiviral and non-lentiviral) for use in the present invention can be formed using standard cloning techniques by combining the desired DNA sequences in the order and orientation described herein (*Current Protocols in Molecular Biology*, Ausubel, F. M. *et al.* (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14 and other standard laboratory manuals; Eglitis, *et al.* (1985) *Science* 230:1395-1398; Danos and Mulligan (1988) *Proc. Natl. Acad. Sci. USA* 85:6460-6464; Wilson *et al.* (1988) *Proc. Natl. Acad. Sci. USA* 85:3014-3018; Armentano *et al.* (1990) *Proc. Natl. Acad. Sci. USA* 87:6141-6145; Huber *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:8039-8043; Ferry *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:8377-8381; Chowdhury *et al.* (1991) *Science* 254:1802-1805; van Beusechem *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:7640-7644; Kay *et al.* (1992) *Human Gene Therapy* 3:641-647; Dai *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:10892-10895; Hwu *et al.* (1993) *J. Immunol* 150:4104-4115; U.S. Pat. No. 4,868,116; U.S. Pat. No. 4,980,286; PCT Application WO 89/07136; PCT Application WO 89/02468; PCT Application WO 89/05345; and PCT Application WO 92/07573).

[00150] Suitable sources for obtaining retroviral (*i.e.*, both lentiviral and non-lentiviral) sequences for use in forming the vectors include, for example, genomic RNA and cDNAs available from commercially available sources, including the Type Culture Collection (ATCC), Rockville, Md. The sequences also can be synthesized chemically.

[00151] For expression of a PRAME TCR, the vector may be introduced into a host cell to allow expression of the polypeptide within the host cell. The expression vectors may contain a variety of elements for controlling expression, including without limitation, promoter sequences, transcription initiation sequences, enhancer sequences, selectable markers, and signal sequences. These elements may be selected as appropriate by a person of ordinary skill in the art, as described above. For example, the promoter sequences may be selected to promote the transcription of the polynucleotide in the vector. Suitable promoter sequences include, without limitation, T7 promoter, T3 promoter, SP6 promoter, beta-actin promoter, EF1a promoter, CMV promoter, and SV40 promoter. Enhancer sequences may be selected to enhance the transcription of the polynucleotide. Selectable markers may be selected to allow selection of the host cells inserted with the vector from those not, for example, the selectable markers may be genes that confer antibiotic resistance. Signal sequences may be

selected to allow the expressed polypeptide to be transported outside of the host cell.

[00152] For cloning of the polynucleotide, the vector may be introduced into a host cell (an isolated host cell) to allow replication of the vector itself and thereby amplify the copies of the polynucleotide contained therein. The cloning vectors may contain sequence components generally include, without limitation, an origin of replication, promoter sequences, transcription initiation sequences, enhancer sequences, and selectable markers. These elements may be selected as appropriate by a person of ordinary skill in the art. For example, the origin of replication may be selected to promote autonomous replication of the vector in the host cell.

[00153] In certain embodiments, the present disclosure provides isolated host cells containing the vectors provided herein. The host cells containing the vector may be useful in expression or cloning of the polynucleotide contained in the vector. Suitable host cells can include, without limitation, prokaryotic cells, fungal cells, yeast cells, or higher eukaryotic cells such as mammalian cells. Suitable prokaryotic cells for this purpose include, without limitation, eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescans*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis*, *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*.

[00154] The TCRs of the present invention are introduced into a host cell using transfection and/or transduction techniques known in the art. As used herein, the terms, "transfection," and "transduction," refer to the processes by which an exogenous nucleic acid sequence is introduced into a host cell. The nucleic acid may be integrated into the host cell DNA or may be maintained extrachromosomally. The nucleic acid may be maintained transiently or may be a stable introduction. Transfection may be accomplished by a variety of means known in the art including but not limited to calcium phosphate-DNA co-precipitation, DEAE-dextran-mediated transfection, polybrene-mediated transfection, electroporation, microinjection, liposome fusion, lipofection, protoplast fusion, retroviral infection, and biolistics. Transduction refers to the delivery of a gene(s) using a viral or retroviral vector by means of viral infection rather than by transfection. In certain embodiments, retroviral vectors are transduced by packaging the vectors into virions prior to contact with a cell. For example, a nucleic acid encoding a PRAME TCR of the invention carried by a retroviral vector can be transduced into a cell through infection and pro virus integration.

[00155] As used herein, the term "genetically engineered" or "genetically modified" refers to the addition of extra genetic material in the form of DNA or RNA into the total genetic material in a cell. The terms, "genetically modified cells," "modified cells," and, "redirected cells," are used interchangeably.

[00156] In particular, the TCRs of the present invention are introduced and expressed in immune effector cells so as to redirect their specificity to a target antigen of interest, e.g., an HLA-A2

displayed PRAME peptide, *e.g.*, amino acid residues 312-320 or 425-433 of PRAME.

[00157] The present invention provides methods for making the immune effector cells which express the TCRs as described herein. In some embodiments, the method comprises transfecting or transducing immune effector cells, *e.g.*, immune effector cells isolated from a subject, such as a
5 subject having a PRAME-associated disease or disorder, such that the immune effector cells express one or more TCR as described herein. In certain embodiments, the immune effector cells are isolated from an individual and genetically modified without further manipulation *in vitro*. Such cells can then be directly re-administered into the individual. In further embodiments, the immune effector cells are first activated and stimulated to proliferate *in vitro* prior to being genetically modified to express a
10 TCR. In this regard, the immune effector cells may be cultured before or after being genetically modified (*i.e.*, transduced or transfected to express a TCR as described herein).

[00158] Prior to *in vitro* manipulation or genetic modification of the immune effector cells described herein, the source of cells may be obtained from a subject. In particular, the immune effector cells for use with the TCRs as described herein comprise T cells.

15 [00159] T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph nodes tissue, cord blood, thymus issue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments, T cell can be obtained from a unit of blood collected from the subject using any number of techniques known to the skilled person, such as FICOLL separation. In some embodiments, cells from the circulating blood of
20 an individual are obtained by apheresis. The apheresis product typically contains lymphocytes, including T cells, monocytes, granulocyte, B cells, other nucleated white blood cells, red blood cells, and platelets. In some embodiments, the cells collected by apheresis may be washed to remove the plasma fraction and to place the cells in an appropriate buffer or media for subsequent processing. In some embodiments of the invention, the cells are washed with PBS. In alternative embodiments, the
25 washed solution lacks calcium and may lack magnesium or may lack many if not all divalent cations. As would be appreciated by those of ordinary skill in the art, a washing step may be accomplished by methods known to those in the art, such as by using a semiautomated flow-through centrifuge. After washing, the cells may 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
30 may be removed in the cell directly resuspended culture media.

[00160] In certain embodiments, T cells are isolated from peripheral blood mononuclear cells (PBMCs) by lysing the red blood cells and depleting the monocytes, for example, by centrifugation through a PERCOLLTM gradient. A specific subpopulation of T cells, such as CD28+, CD4+, CD8+, CD45RA+, and CD45RO+ T cells, can be further isolated by positive or negative selection techniques.
35 For example, enrichment of a T cell population by negative selection can be accomplished with a combination of antibodies directed to surface markers unique to the negatively selected cells. One

method for use herein is cell sorting and/or selection via negative magnetic immunoadherence or flow cytometry that uses a cocktail of monoclonal antibodies directed to cell surface markers present on the cells negatively selected. For example, to enrich for CD4⁺ cells by negative selection, a monoclonal antibody cocktail typically includes antibodies to CD14, CD20, CD11b, CD16, HLA-DR, and CD8.

5 Flow cytometry and cell sorting may also be used to isolate cell populations of interest for use in the present invention.

[00161] PBMC may be used directly for genetic modification with the TCRs using methods as described herein. In certain embodiments, after isolation of PBMC, T lymphocytes are further isolated and in certain embodiments, both cytotoxic and helper T lymphocytes can be sorted into naive,
10 memory, and effector T cell subpopulations either before or after genetic modification and/or expansion.

[00162] The immune effector cells, such as T cells, can be genetically modified following isolation using known methods, or the immune effector cells can be activated and expanded (or differentiated in the case of progenitors) *in vitro* prior to being genetically modified. In some
15 embodiments, the immune effector cells, such as T cells, are genetically modified with the chimeric antigen receptors described herein (*e.g.*, transduced with a viral vector comprising a nucleic acid encoding a TCR) and then are activated and expanded *in vitro*. Methods for activating and expanding T cells are known in the art and are described, for example, in U.S. Pat. No. 6,905,874; U.S. Pat. No. 6,867,041; U.S. Pat. No. 6,797,514; WO2012079000, US 2016/0175358.

20 [00163] The invention provides a population of modified immune effector cells for the treatment of a PRAME-associated disease or disorder, *e.g.*, cancer, the modified immune effector cells comprising a PRAME TCR as disclosed herein.

[00164] TCR-expressing immune effector cells prepared as described herein can be utilized in methods and compositions for adoptive immunotherapy in accordance with known techniques, or
25 variations thereof that will be apparent to those skilled in the art based on the instant disclosure. See, *e.g.*, US Patent Application Publication No. 2003/0170238 to Gruenberg *et al*; see also U.S. Pat. No. 4,690,915 to Rosenberg.

III. Pharmaceutical Compositions

30 [00165] The invention provides therapeutic compositions comprising the PRAME TCRs of the invention or immune effector cells comprising the PRAME TCRs of the invention. Therapeutic compositions in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known
35 to all pharmaceutical chemists: *Remington's Pharmaceutical Sciences*, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils,

lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell *et al.* "Compendium of excipients for parenteral formulations"

5 PDA (1998) *J Pharm Sci Technol* 52:238-311.

[00166] Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted.

[00167] In certain embodiments, the initial dose may be followed by administration of a second or a plurality of subsequent doses of PRAME TCRs of the invention or immune effector cells comprising the PRAME TCRs of the invention in an amount that can be approximately the same or
10 less than that of the initial dose,

[00168] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In some embodiments, a pump may be used.

[00169] Injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous, intracranial, intraperitoneal and intramuscular injections, drip infusions, *etc.* The TCRs, pharmaceutical compositions, and cells described herein can be administered via parenteral administration. The preparations of the present disclosure may be prepared by methods publicly known. For example, the preparations may be prepared, *e.g.*, by dissolving, suspending or emulsifying the antigen-binding protein or its salt described above in a sterile aqueous medium or an oily medium
15 conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, *etc.*, which may be used in combination with an appropriate solubilizing agent such as an alcohol (*e.g.*, ethanol), a polyalcohol (*e.g.*, propylene glycol, polyethylene glycol), a nonionic surfactant [*e.g.*, polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], *etc.* As the oily medium,
20 there are employed, *e.g.*, sesame oil, soybean oil, *etc.*, which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, *etc.* The injection thus prepared is preferably filled in an appropriate ampoule.

[00170] In some embodiments, TCR-expressing immune effector cells are formulated by first harvesting them from their culture medium, and then washing and concentrating the cells in a medium and container system suitable for administration (a "pharmaceutically acceptable" carrier) in a
30 treatment-effective amount. Suitable infusion medium can be any isotonic medium formulation, typically normal saline, Normosol R (Abbott) or Plasma-Lyte A (Baxter), but also 5% dextrose in water or Ringer's lactate can be utilized. The infusion medium can be supplemented with human serum albumin.

35 **[00171]** A treatment-effective number of cells in the composition is typically greater than 10^2 cells, and up to 10^6 up to and including 10^8 or 10^9 cells and can be more than 10^{10} cells. The number

of cells will depend upon the ultimate use for which the composition is intended as will the type of cells included therein.

[00172] The cells may be autologous or heterologous to the patient undergoing therapy. If desired, the treatment may also include administration of mitogens (*e.g.*, PHA) or lymphokines, cytokines, and/or chemokines (*e.g.*, IFN- γ , IL-2, IL-12, TNF- α , IL-18, and TNF- β , GM-CSF, IL-4, IL-13, Flt3-L, RANTES, MIP1 α , *etc.*) as described herein to enhance induction of the immune response.

[00173] The TCR expressing immune effector cell populations of the present invention may be administered either alone, or as a pharmaceutical composition in combination with diluents and/or with other components such as IL-2 or other cytokines or cell populations. Briefly, pharmaceutical compositions of the present invention may comprise a TCR-expressing immune effector cell population, such as T cells, as described herein, in combination with one or more pharmaceutically or physiologically acceptable carriers, diluents or excipients. Such compositions may comprise buffers such as neutral buffered saline, phosphate buffered saline and the like; carbohydrates such as glucose, mannose, sucrose or dextrans, mannitol; proteins; polypeptides or amino acids such as glycine; antioxidants; chelating agents such as EDTA or glutathione; adjuvants (*e.g.*, aluminum hydroxide); and preservatives. Compositions of the present invention are preferably formulated for intravenous administration.

IV. Therapeutic Uses of PRAME TCRs or Immune Effector Cells Comprising PRAME TCRs

[00174] The anti-tumor immune response induced in a subject by administering TCR expressing T cells described herein using the methods described herein, or other methods known in the art, may include cellular immune responses mediated by cytotoxic T cells capable of killing infected cells, regulatory T cells, and helper T cell responses. Humoral immune responses, mediated primarily by helper T cells capable of activating B cells thus leading to antibody production, may also be induced. A variety of techniques may be used for analyzing the type of immune responses induced by the compositions of the present invention, which are well described in the art; *e.g.*, *Current Protocols in Immunology*, Edited by: John E. Coligan, Ada M. Kruisbeek, David H. Margulies, Ethan M. Shevach, Warren Strober (2001) John Wiley & Sons, NY, N.Y.

[00175] Thus, the PRAME TCRs of the invention are useful, *inter alia*, for the treatment, prevention and/or amelioration of any disease or disorder associated with or mediated by PRAME. For example, the present invention provides methods for treating a PRAME-associated disease or disorder, such as a PRAME-associated cancer (*e.g.*, a PRAME-positive cancer) (tumor growth inhibition) by administering a PRAME TCR (or pharmaceutical composition comprising a PRAME TCR or a plurality of cells comprising a PRAME TCR) as described herein to a patient in need of such treatment, and PRAME TCRs (or pharmaceutical composition comprising a PRAME TCR) for

use in the treatment of a PRAME-associated cancer. The antigen-binding proteins of the present invention are useful for the treatment, prevention, and/or amelioration of disease or disorder or condition such as a PRAME-associated cancer and/or for ameliorating at least one symptom associated with such disease, disorder or condition. In the context of the methods of treatment described herein, the PRAME TCR (or pharmaceutical composition or plurality of cells) may be administered as a monotherapy (*i.e.*, as the only therapeutic agent) or in combination with one or more additional therapeutic agents (examples of which are described elsewhere herein).

[00176] Accordingly, the present invention provides for methods of treating an individual diagnosed with or suspected of having, or at risk of developing, a PRAME-associated disease or disorder, *e.g.*, a PRAME-associated cancer, comprising administering the individual a therapeutically effective amount of the TCR-expressing immune effector cells as described herein.

[00177] In some embodiments, the invention provides a method of treating a subject diagnosed with a PRAME-positive cancer comprising removing immune effector cells from a subject diagnosed with a PRAME-positive cancer, genetically modifying said immune effector cells with a vector comprising a nucleic acid encoding a TCR of the instant invention, thereby producing a population of modified immune effector cells, and administering the population of modified immune effector cells to the same subject. In some embodiments, the immune effector cells comprise T cells.

[00178] The methods for administering the cell compositions described herein includes any method which is effective to result in reintroduction of *ex vivo* genetically modified immune effector cells that either directly express a TCR of the invention in the subject or on reintroduction of the genetically modified progenitors of immune effector cells that on introduction into a subject differentiate into mature immune effector cells that express the TCR. One method comprises transducing peripheral blood T cells *ex vivo* with a nucleic acid construct in accordance with the invention and returning the transduced cells into the subject.

[00179] In some embodiments of the invention, the compositions described herein are useful for treating subjects suffering from primary or recurrent cancer, including, but not limited to, PRAME-associated cancer, *e.g.*, PRAME-associated cancer is a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, or a recurrent non-small cell lung cancer. In some embodiments, the PRAME-associated cancer is an

ovarian cancer, a melanoma, a non-small cell lung carcinoma, a hepatocellular carcinoma, a colorectal carcinoma, an esophageal squamous cell carcinoma, an esophageal adenocarcinoma, a stomach cancer, a bladder cancer, a head and neck cancer, a gastric cancer, a synovial sarcoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, testicular germ cell tumor, uveal melanoma, kidney renal papillary cell carcinoma, kidney renal clear cell carcinoma, thymoma, colon adenocarcinoma, cervical squamous cell carcinoma, cervical tumor, pancreatic adenocarcinoma, liver cancer, hepatocellular carcinoma, mesothelioma, or a myxoid round cell liposarcoma.

5 [00180] The TCRs may be used to treat early stage or late-stage symptoms of the PRAME-associated cancer. In some embodiments, a TCR of the invention may be used to treat advanced or metastatic cancer. The TCRs are useful in reducing or inhibiting or shrinking tumor growth. In certain
10 embodiments, treatment with a TCR of the invention leads to more than 40% regression, more than 50% regression, more than 60% regression, more than 70% regression, more than 80% regression or more than 90% regression of a tumor in a subject. In certain embodiments, the TCRs may be used to prevent relapse of a tumor. In certain embodiments, the TCRs are useful in extending progression-free
15 survival or overall survival in a subject with PRAME-associated cancer. In some embodiments, the TCRs are useful in reducing toxicity due to chemotherapy or radiotherapy while maintaining long-term survival in a patient suffering from PRAME-associated cancer.

[00181] One or more TCRs of the present invention may be administered to relieve or prevent or decrease the severity of one or more of the symptoms or conditions of the disease or disorder.

20 [00182] It is also contemplated herein to use one or more TCRs of the present invention prophylactically to patients at risk for developing a disease or disorder such as PRAME-associated disease or disorder, such as a PRAME-associated cancer.

[00183] In further embodiments of the invention, the present TCRs are used for the preparation of a pharmaceutical composition for treating patients suffering from PRAME-associated
25 disease or disorder, such as a PRAME-associated cancer. In some embodiments of the invention, the present TCRs are used as adjunct therapy with any other agent or any other therapy known to those skilled in the art useful for treating PRAME-associated cancer.

[00184] Combination therapies may include a PRAME TCR of the invention, such as immune effector cell comprising a TCR of the invention, or a pharmaceutical composition of the invention,
30 and any additional therapeutic agent that may be advantageously combined with a TCR of the invention. The TCRs of the present invention may be combined synergistically with one or more anti-cancer drugs or therapy used to treat or inhibit a PRAME-associated disease or disorder, such as PRAME-positive cancer, *e.g.*, a liposarcoma, a neuroblastoma, a myeloma, a melanoma, a metastatic melanoma, a synovial sarcoma, a bladder cancer, an esophageal cancer, an esophageal squamous cell carcinoma, a hepatocellular cancer, a head and neck cancer, a non-small cell lung cancer, an ovarian
35 cancer, an ovarian epithelial cancer, a prostate cancer, a breast cancer, an astrocytic tumor, a

glioblastoma multiforme, an anaplastic astrocytoma, a brain tumor, a fallopian tube cancer, primary peritoneal cavity cancer, advanced solid tumors, soft tissue sarcoma, a sarcoma, a myelodysplastic syndrome, an acute myeloid leukemia, a Hodgkin lymphoma, a non-Hodgkin lymphoma, a Hodgkin disease, a multiple myeloma, a metastatic solid tumors, a colorectal carcinoma, a stomach cancer, a gastric cancer, a rhabdomyosarcoma, a myxoid round cell liposarcoma, uterine corpus endometrial carcinoma, uterine carcinosarcoma, testicular germ cell tumor, uveal melanoma, kidney renal papillary cell carcinoma, kidney renal clear cell carcinoma, thymoma, colon adenocarcinoma, cervical squamous cell carcinoma, cervical tumor, pancreatic adenocarcinoma, liver cancer, hepatocellular carcinoma, mesothelioma, or a recurrent non-small cell lung cancer.

10 **[00185]** It is contemplated herein to use the TCRs of the invention in combination with immunostimulatory and/or immunosupportive therapies to inhibit tumor growth, and/or enhance survival of cancer patients. The immunostimulatory therapies include direct immunostimulatory therapies to augment immune cell activity by either “releasing the brake” on suppressed immune cells or “stepping on the gas” to activate an immune response. Examples include targeting other checkpoint
15 receptors, vaccination and adjuvants. The immunosupportive modalities may increase antigenicity of the tumor by promoting immunogenic cell death, inflammation or have other indirect effects that promote an anti-tumor immune response. Examples include radiation, chemotherapy, anti-angiogenic agents, and surgery.

[00186] In various embodiments, one or more TCRs of the present invention may be used in
20 combination with a PD-1 inhibitor (*e.g.*, an anti-PD-1 antibody such as nivolumab, pembrolizumab, pidilizumab, BGB-A317 or REGN2810), a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody such as avelumab, atezolizumab, durvalumab, MDX-1105, or REGN3504), a CTLA-4 inhibitor (*e.g.*, ipilimumab), a TIM3 inhibitor, a BTLA inhibitor, a TIGIT inhibitor, a CD47 inhibitor, a GITR inhibitor, an antagonist of another T cell co-inhibitor or ligand (*e.g.*, an antibody to CD-28, 2B4,
25 LY108, LAIR1, ICOS, CD160 or VISTA), an indoleamine-2,3-dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist [*e.g.*, a “VEGF-Trap” such as aflibercept or other VEGF-inhibiting fusion protein as set forth in US 7,087,411, or an anti-VEGF antibody or antigen-binding fragment thereof (*e.g.*, bevacizumab, or ranibizumab) or a small molecule kinase inhibitor of VEGF receptor (*e.g.*, sunitinib, sorafenib, or pazopanib)], an Ang2 inhibitor (*e.g.*,
30 nesvacumab), a transforming growth factor beta (TGF β) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor (*e.g.*, erlotinib, cetuximab), an NY-ESO-1 inhibitor (*e.g.*, an anti-NY-ESO-1 antibody), a CD20 inhibitor (*e.g.*, an anti-CD20 antibody such as rituximab), an antibody to a tumor-specific antigen [*e.g.*, CA9, CA125, melanoma-associated antigen 3 (MAGE3), carcinoembryonic antigen (CEA), vimentin, tumor-M2-PK, prostate-specific antigen (PSA), mucin-1,
35 MART-1, and CA19-9], a vaccine (*e.g.*, Bacillus Calmette-Guerin, a cancer vaccine), an adjuvant to increase antigen presentation (*e.g.*, granulocyte-macrophage colony-stimulating factor), a costimulatory agent, a bispecific antibody (*e.g.*, CD3xCD20 bispecific antibody, a PSMAxCD3

bispecific antibody, or a bispecific antibody that acts as a costimulatory agent, such as a bispecific antibody that binds a tumor antigen and has costimulatory activity), a cytotoxin, a chemotherapeutic agent (*e.g.*, dacarbazine, temozolomide, cyclophosphamide, docetaxel, doxorubicin, daunorubicin, cisplatin, carboplatin, gemcitabine, methotrexate, mitoxantrone, oxaliplatin, paclitaxel, and vincristine), cyclophosphamide, radiotherapy, surgery, an IL-6R inhibitor (*e.g.*, sarilumab), an IL-4R inhibitor (*e.g.*, dupilumab), an IL-10 inhibitor, a cytokine such as IL-2, IL-7, IL-21, and IL-15, an antibody-drug conjugate (ADC) (*e.g.*, anti-CD19-DM4 ADC, and anti-DS6-DM4 ADC), an anti-inflammatory drug (*e.g.*, corticosteroids, and non-steroidal anti-inflammatory drugs), a dietary supplement such as anti-oxidants or any other therapy care to treat cancer. In certain embodiments, the TCRs of the present invention may be used in combination with cancer vaccines including dendritic cell vaccines, oncolytic viruses, tumor cell vaccines, etc. to augment the anti-tumor response.

[00187] Examples of cancer vaccines that can be used in combination with TCRs of the present invention include MAGE3 vaccine for melanoma and bladder cancer, MUC1 vaccine for breast cancer, EGFRv3 (*e.g.*, Rindopepimut) for brain cancer (including glioblastoma multiforme), ALVAC-CEA (for CEA+ cancers), and NY-ESO-1 vaccine (*e.g.*, for melanoma).

[00188] In certain embodiments, the PRAME TCRs of the invention may be administered in combination with radiation therapy in methods to generate long-term durable anti-tumor responses and/or enhance survival of patients with cancer. In some embodiments, the PRAME TCRs of the invention may be administered prior to, concomitantly or after administering radiation therapy to a cancer patient. For example, radiation therapy may be administered in one or more doses to tumor lesions followed by administration of one or more doses of PRAME TCRs of the invention. In some embodiments, radiation therapy may be administered locally to a tumor lesion to enhance the local immunogenicity of a patient's tumor (adjuvinating radiation) and/or to kill tumor cells (ablative radiation) followed by systemic administration of a PRAME TCRs of the invention.

[00189] The additional therapeutically active agent(s)/component(s) may be administered prior to, concurrent with, or after the administration of the PRAME TCRs of the present invention. For purposes of the present disclosure, such administration regimens are considered the administration of a PRAME TCR "in combination with" a second therapeutically active component.

[00190] The additional therapeutically active component(s) may be administered to a subject prior to administration of a PRAME TCR of the present invention. In other embodiments, the additional therapeutically active component(s) may be administered to a subject after administration of a PRAME TCR of the present invention. In yet other embodiments, the additional therapeutically active component(s) may be administered to a subject concurrent with administration of a PRAME TCR of the present invention. "Concurrent" administration, for purposes of the present invention, includes, *e.g.*, administration of a PRAME TCR and an additional therapeutically active component to a subject in a single dosage form (*e.g.*, co-formulated), or in separate dosage forms administered to

the subject within about 30 minutes or less of each other. If administered in separate dosage forms, each dosage form may be administered via the same route; alternatively, each dosage form may be administered via a different route. In any event, administering the components in a single dosage form, in separate dosage forms by the same route, or in separate dosage forms by different routes are all considered "concurrent administration," for purposes of the present disclosure. For purposes of the present disclosure, administration of a PRAME TCR "prior to", "concurrent with," or "after" (as those terms are defined herein above) administration of an additional therapeutically active component is considered administration of a PRAME TCR "in combination with" an additional therapeutically active component).

[00191] The present invention is further illustrated by the following Examples, which are not intended to be limiting in any way. The entire contents of all references, patents and published patent applications cited throughout this application are hereby incorporated herein by reference.

EXAMPLES

Example 1. Identification of PRAME specific T cell receptors

[00192] Mice humanized for cellular immune system components, VelociT mice (see, *e.g.*, PCT Publication No. WO 2016/164492, the entire contents of which are incorporated herein by reference), were immunized with either a PRAME (312-320) peptide (RLDQLLRHV); SEQ ID NO:929) or a PRAME (425-433) peptide (SLLQHLIGL); SEQ ID NO:930) presented specifically by human HLA-A2, diluted in PBS and mixed with adjuvant, *e.g.* in equal volume with Complete Freund's Adjuvant (CFA; Chondrex, Inc.). Spleen suspensions from mice immunized with either peptide were separately obtained and dissociated. Red blood cells were lysed in ACK lysis buffer (Life Technologies), and splenocytes were suspended in RPMI complete media. Isolated splenocytes were sorted and single T cells that bind the PRAME peptide used for immunization (either PRAME (312-320) or PRAME (425-433) in the context of MHC were isolated by fluorescent-activated cell sorting (FACS). Isolated T cells were single well plated and mixed with TCR alpha and beta variable region-specific PCR primers. cDNAs for each single T cell were synthesized *via* a reverse transcriptase (RT) reaction. Each resulting RT product was then split and transferred into two corresponding wells for subsequent TCR beta and alpha PCRs. One set of the resulting RT products was first amplified by PCR using a 5' degenerate primer specific for TCR beta variable region leader sequence or a 5' degenerate primer specific for TCR alpha chain variable region leader sequence and a 3' primer specific for TCR constant region, to form an amplicon. The amplicons were then amplified again by PCR using a 5' degenerate primer specific for TCR beta variable region framework 1 or a 5' degenerate primer specific for TCR alpha chain variable region framework 1 and a 3' primer specific for TCR constant region, to generate amplicons for cloning. The TCR beta and alpha derived PCR products were cloned into expression vectors containing beta constant region and

alpha constant region, respectively. Expression vectors expressing full-length beta and alpha chain pairs were transfected into CHO cells and tested for binding to commercial PRAME/HLA tetramer reagent. CHO cells were incubated with soluble HLA-A2:PRAME (312-320) or HLA:A2:PRAME (425-433) (MBL International, Woburn, MA) tetramer and an antibody specific for mouse TCR constant region (clone H57-597) (Biolegend, San Diego, CA). Samples were then analyzed on an LSRFortessa X-20 (BD Biosciences, San Jose, CA). To calculate percentage of tetramer positive cells, antigen positive (Ag+) gates were set based on a negative control TCR that does not bind to the HLA-A2:PRAME (312-320) or HLA:A2:PRAME (425-433) (MBL International, Woburn, MA) tetramer using FlowJo (LLC, Ashland, OR). All Ag+ TCRs had a FlowJo criteria of $\geq 1\%$ of cells in Ag+ gate with the mean fluorescence intensity (MFI) ≥ 1000 . Ag+ TCRs were determined by Next Generation Sequencing. The total number of TCRs that were identified with PRAME (312-320) and that express identical TCR alpha and beta nucleotide sequences are shown in Table 1 below. Cell frequency, or % tetramer positive cells in the Ag+ gate, is representative of the TCR shown in the first column of Table 1. The total number of TCRs that were identified with PRAME (425-433) and that express identical TCR alpha and beta nucleotide sequences are shown in Table 2 below. Cell frequency, or % tetramer positive cells in the Ag+ gate, is representative of the TCR shown in the first column of Table 2.

[00193] A detailed list of the beta chain variable domain CDR1, CDR2, and CDR3 amino acid sequences, and the alpha chain variable domain CDR1, CDR2, and CDR3 amino acid sequences of the TCRs that were identified with PRAME (312-320) as described above are provided in Table 3. A detailed list of the beta chain variable domain CDR1, CDR2, and CDR3 polynucleic acid sequences, and the alpha chain variable domain CDR1, CDR2, and CDR3 polynucleic acid sequences of the TCRs that were identified with PRAME (312-320) as described above are provided in Table 4. Table 5 provides the amino acid and nucleotide sequences of the beta chain variable and alpha chain variable regions of the TCRs that were identified with PRAME (312-320).

[00194] A detailed list of the beta chain variable domain CDR1, CDR2, and CDR3 amino acid sequences, and the alpha chain variable domain CDR1, CDR2, and CDR3 amino acid sequences of the TCRs that were identified with PRAME (425-433) as described above are provided in Table 6. A detailed list of the beta chain variable domain CDR1, CDR2, and CDR3 polynucleic acid sequences, and the alpha chain variable domain CDR1, CDR2, and CDR3 polynucleic acid sequences of the TCRs that were identified with PRAME (425-433) as described above are provided in Table 7. Table 8 provides the amino acid and nucleotide sequences of the beta chain variable and alpha chain variable regions of the TCRs that were identified with PRAME (425-433).

[00195] Table 9 provides the TCR gene families for the alpha and beta variable and joining regions of the isolated TCRs that were identified with PRAME (312-320) and Table 11 provides the

amino acid and polynucleic acid sequence identifiers for alpha and beta variable chains and CDRs of the TCRs that were identified with PRAME (312-320).

- [00196]** Table 10 provides the TCR gene families for the alpha and beta variable and joining regions of the isolated TCRs that were identified with PRAME (425-433) and Table 12 provides the amino acid and polynucleic acid sequence identifiers for alpha and beta variable chains and CDRs of the TCRs that were identified with PRAME (425-433).

Table 1.

TCR ID	Total Ag+ TCRs	Cell Frequency ≥ 1000 MFI, $\geq 1\%$
PN46909	21	52.60
PN46889	21	92.50
PN46733	2	87.90
PN46723	52	72.50
PN46714	1	62.10
PN46735	1	17.90
PN46678	1	11.00
PN46884	3	59.00
PN46914	1	11.50
PN46883	13	64.70
PN46857	1	53.90
PN46880	5	31.90
PN46871	2	44.70
PN46853	2	35.40
PN46731	1	15.70
PN46777	99	98.90
PN46797	1	57.30
PN46738	1	23.00

Table 2.

TCR ID	Total Ag+ TCRs	Cell Frequency ≥ 1000 MFI, $\geq 1\%$
PN42365	96	95.80
PN42879	1	93.10
PN42774	3	91.60
PN42498	30	90.30
PN42558	1	85.70
PN42386	1	82.20
PN42378	2	77.50
PN42776	1	60.20
PN42455	1	53.00
PN42840	21	52.50
PN42795	14	49.40
PN42870	8	7.27
PN42689	21	4.92

PN42888	22	87.40
PN42450	4	62.20
PN42750	2	40.80
PN42562	5	92.00
PN42483	29	86.40
PN42712	11	80.70
PN42561	150	80.20
PN42442	3	61.30
PN42476	1	54.20
PN42496	1	45.00
PN42655	7	27.00
PN42677	1	25.30
PN42706	1	24.70
PN42654	1	20.10
PN42441	1	15.50
PN42683	2	11.10
PN42845	1	10.50
PN42826	1	9.26
PN42707	10	7.28
PN42833	2	6.86
PN42762	12	4.95
PN42780	1	4.89
PN42746	1	4.39
PN42815	30	4.35
PN42711	1	4.26
PN42895	3	4.09
PN42610	1	6.08

Table 3. Amino acid CDR sequences for VelociT TCRs specific for PRAME (312-320) / HLA-A2

TCR ID	V α CDR1	SEQ ID NO:	V α CDR2	SEQ ID NO:	V α CDR3	SEQ ID NO:	V β CDR1	SEQ ID NO:	V β CDR2	SEQ ID NO:	V β CDR3	SEQ ID NO:
PN46678	TRDTTYY	1	RNSFDEQN	2	ALSEFDRGSTLGRLY	3	SGHKS	4	YYEKEE	5	ASSRDINEKLF	6
PN46714	VSGLRG	7	LYSAGEE	8	AVQADGGSQGNLI	9	SGHKS	10	YYEKEE	11	ASSLDINSPLH	12
PN46723	VSGLRG	13	LYSAGEE	14	AVQEDGGSQGNLI	15	SGHKS	16	YYEKEE	17	ASSRDINEKLF	18
PN46731	DSASNY	19	IRSNVGE	20	AAWNYGQNFV	21	PRHDT	22	FYEKMV	23	ASSLEGSEAF	24
PN46733	NSASDY	25	IRSNMDK	26	AENNYGQNFV	27	MNHNS	28	SASEGT	29	ASSDWGQGVVEAF	30
PN46735	TISGTDY	31	GLTSN	32	ILREYMYSGGGADGLT	33	SGHKS	34	YYEKEE	35	ASSFQAGVNYGYT	36
PN46738	TSENNYY	37	QEAYKQQN	38	AFGMYSGGGADGLT	39	WSHSY	40	SAAADI	41	ASSDGTGYGYT	42
PN46777	TSENNYY	43	QEAYKQQN	44	ALMEYGNKLV	45	WSHSY	46	SAAADI	47	ASSDGTGYGYT	48
PN46797	TSENNYY	49	QEAYKQQN	50	ALMEYENKLV	51	WSHSY	52	SAAADI	53	ASSDGTGYGYT	54
PN46853	SSNFYA	55	MTLNGDE	56	ACGGSGNTGKLI	57	PRHDT	58	FYEKMV	59	ASSSQGQPQH	60
PN46857	TRDTTYY	61	RNSFDEQN	62	ALSEGYGNKLV	63	KGHSH	64	LQENI	65	ASSHRDDTEAF	66
PN46871	DSAIYN	67	IQSSQRE	68	AVEGTTDSWGKFO	69	PRHDT	70	FYEKMV	71	ASSSQGQPQH	72
PN46880	YSGSPE	73	HISR	74	ALSGASGGSYIPT	75	KGHSH	76	LQENI	77	ASSHRDDTEAF	78
PN46883	TRDTTYY	79	RNSFDEQN	80	ALSVSSYNTDKLI	81	KGHSH	82	LQENI	83	ASSHRDDTEAF	84
PN46884	TRDTTYY	85	RNSFDEQN	86	ALSEGYNTDKLI	87	MDHEN	88	SYDVKM	89	ASSLGGANTIY	90
PN46889	DRGSQS	91	IYSNGD	92	AVNIPNSGYSTLT	93	MNHEY	94	SVGEGT	95	ASSYWEGTEAF	96
PN46909	TSENNYY	97	QEAYKQQN	98	AFDYGQNFV	99	MNHNY	100	SVGAGI	101	ASSYGGGQTEAF	102
PN46914	TRDTTYY	103	RNSFDEQN	104	ALSEGYNQGGKLI	105	MDHEN	106	SYDVKM	107	ASGADSNQPQH	108

Table 4. Nucleic acid CDR sequences for VelociT TCRs specific for PRAME (312-320) / HLA-A2

TCR ID	V α CDR1	SEQ ID NO:	V α CDR2	SEQ ID NO:	V α CDR3	SEQ ID NO:	V β CDR1	SEQ ID NO:	V β CDR2	SEQ ID NO:	V β CDR3	SEQ ID NO:
PN46678	ACCCGTG ATACTAC TTATTAC	109	CGGAACTCT TTTGATGAG CAAAAT	110	GCTCTGAGTGAGTTTG ACAGAGGCTCAACCC TGGGGAGGCTATAC	111	TCTGGGC ACAAGA GT	112	TATTATG AGAAAGA AGAG	113	GCCAGCAGCCGGGA CATTAAATGAAAAAC TGTTT	114
PN46714	GTCAGCG GTTTAAG AGG	115	CTGTATTCA GCTGGGGAA GAA	116	GCTGTGCAGGCCGAT GGAGGAAGCCCAAGGA AATCTCATC	117	TCTGGGC ACAAGA GT	118	TATTATG AGAAAGA AGAG	119	GCCAGCAGCTTGGA CATTAAATTCACCCCT CCAC	120
PN46723	GTCAGCG GTTTAAG AGG	121	CTGTATTCA GCTGGGGAA GAA	122	GCTGTGCAGGAGGAT GGAGGAAGCCCAAGGA AATCTCATC	123	TCTGGGC ACAAGA GT	124	TATTATG AGAAAGA AGAG	125	GCCAGCAGCCGGGA CATTAAATGAAAAAC TGTTT	126
PN46731	GACAGTG CCTCAA CTAC	127	ATTCGTTCA AATGTGGGC GAA	128	GCAGCATGGAACTAT GGTCAGAAATTTTGTG	129	CCTAGAC ACGACA CT	130	TTTTATG AAAAAGAT GCAG	131	GCCAGCAGCTTAGA GGGTCTGAAAGCTT TC	132
PN46733	AACAGCG CCTCAGA CTAC	133	ATTCGTTCA AATATGGAC AAA	134	GCAGAGAATAAATCTAT GGTCAGAAATTTTGTG	135	ATGAAC CATAACT CC	136	TCAGCTT CTGAGGG TACC	137	GCCAGCAGTGACTG GGGACAGGGGGTTG AAGCTTTC	138
PN46735	ACAATCA GTGGAAC TGATTAC	139	GGTCTTACA AGCAAT AAA	140	ATCCTGAGAGAATAAC ATGTAATTCAGGAGGA GGTGCTGACGGACTC ACC	141	TCTGGGC ACAAGA GT	142	TATTATG AGAAAGA AGAG	143	GCCAGCAGCTTCCA AGCAGGGGTAACT ATGGCTACACC	144
PN46738	ACCAGTG AGAATAA TTATTAT	145	CAAGAAAGCT TATAAGCAA CAGAAAT	146	GCTTTCGGTATGTATT CAGGAGGAGGTGCTG ACGGACTCAC	147	TGGAGC CACAGCT AT	148	TCAGCAG CTGCTGA TATT	149	GCCAGCAGTGATGG GACAGGGTACTATG GCTACACC	150
PN46777	ACCAGTG AGAATAA TTATTAT	151	CAAGAAAGCT TATAAGCAA CAGAAAT	152	GCCCTTATGGAATATG GAAACAAAACCTGGTC	153	TGGAGC CACAGCT AT	154	TCAGCAG CTGCTGA TATT	155	GCCAGCAGTGATGG GACAGGGTACTATG GCTACACC	156
PN46797	ACCAGTG AGAATAA TTATTAT	157	CAAGAAAGCT TATAAGCAA CAGAAAT	158	GCCCTTATGGAATATG AAAACAAAACCTGGTC	159	TGGAGC CACAGCT AT	160	TCAGCAG CTGCTGA TATT	161	GCCAGCAGTGATGG GACAGGGTACTATG GCTACACC	162

TCR ID	V α CDR1	SEQ ID NO:	V α CDR2	SEQ ID NO:	V α CDR3	SEQ ID NO:	V β CDR1	SEQ ID NO:	V β CDR2	SEQ ID NO:	V β CDR3	SEQ ID NO:
PN46853	TCCAGCA ATTTTAT GCC	163	ATGACTTTA AATGGGAT	164	GCCTGTGGGGTTCTG GCAACACAGGCAAAAC TAATC	165	CCTAGAC ACGACA CT	166	TTTTATG AAAAGAT GCAG	167	GCCAGCAGCTCCCA GGGTACAGCCCCAGC AT	168
PN46857	ACCCGTG ATACTAC TTATTAC	169	CGGAACTCT TTTGATGAG CAAAAT	170	GCTCTGAGTGAGGGA TATGGAACAAACTG GTC	171	AAAGGA CACAGTC AT	172	CTCCAGA AAGAAAA TATC	173	GCCAGCTCACACAG GGACGACACTGAAG CTTTC	174
PN46871	GATAGCG CTATTTA CAAC	175	ATTCAGTCA AGTCAGAGA GAG	176	GCTGTGGAGGGGACA ACTGACAGCTGGGG AAATTCAG	177	CCTAGAC ACGACA CT	178	TTTTATG AAAAGAT GCAG	179	GCCAGCAGCTCCCA GGGTACAGCCCCAGC AT	180
PN46880	TATTCTG GGAGTCC TGAA	181	CACATCTCT AGA	182	GCTCTAAGTGGGGCAT CAGGAGGAAGCTACA TACCTACA	183	AAAGGA CACAGTC AT	184	CTCCAGA AAGAAAA TATC	185	GCCAGCTCACACAG GGACGACACTGAAG CTTTC	186
PN46883	ACCCGTG ATACTAC TTATTAC	187	CGGAACTCT TTTGATGAG CAAAAT	188	GCTCTGAGTGATCAT CTTATAACACCGACAA GCTCATC	189	AAAGGA CACAGTC AT	190	CTCCAGA AAGAAAA TATC	191	GCCAGCTCACACAG GGATGACACTGAAG CTTTC	192
PN46884	ACCCGTG ATACTAC TTATTAC	193	CGGAACTCT TTTGATGAG CAAAAT	194	GCTCTGAGTGAGGGG TATAACACCGACAA CTCATC	195	ATGGAC CATGAA AAT	196	TCATATG ATGTTAA AATG	197	GCCAGCAGTTTAGG GGGGCGAACACCA TATAT	198
PN46889	GACCGAG GTTCCCA GTCC	199	ATATACTCC AATGGTGAC	200	GCCGTGAACATTCGGA ATTCAGGATACAGCA CCCTCACC	201	ATGAAC CATGAAT AC	202	TCAGTTG GTGAGGG TACA	203	GCCAGCAGTTACTG GGAGGGCACTGAAG CTTTC	204
PN46909	ACCAAGT AGAAATA TTATTAT	205	CAAGAAAGCT TATAAGCAA CAGAAAT	206	GCTTTCGACTATGGTC AGAAATTTTGTC	207	ATGAAC CATAACT AC	208	TCAGTTG GTGCTGG TATC	209	GCCAGCAGTTACGG GGGGGGCAGACTG AAGCTTTC	210
PN46914	ACCCGTG ATACTAC TTATTAC	211	CGGAACTCT TTTGATGAG CAAAAT	212	GCTCTGAGTGAGGGTT ATAACCGAGGAGGAA AGCTTATC	213	ATGGAC CATGAA AAT	214	TCATATG ATGTTAA AATG	215	GCCAGCGGGGCGAGA TAGCAATCAGCCCC AGCAT	216

Table 5: Amino acid and nucleic acid sequences for VelociT TCRs specific for PRAME (312-320) / HLA-A2

Domain name	Domain Sequences Amino Acid Sequence (SEQ ID NO); CDR1, CDR2, and CDR3 sequences are <u>underlined</u> Nucleic Acid Sequence (SEQ ID NO) ; CDR1, CDR2, and CDR3 sequences are <u>underlined</u>
PN46678 V α	AQKVTQAQPEISVVEKEDVTLDCVYETRD <u>TTYLFWYKQPPSGELVFLIRNSFD</u> <u>EQNEISGRYSWNFQKSTSSFNFTITASQVVDSAVYFC</u> <u>ALSEFDRGSTLGRLYFGR</u> GTQLTVWP (SEQ ID NO: 217) GCTCAGAAGGTAAGTCAAGCGCAGCCTGAAATTTCTGTGGTGGAGAAGGAG GATGTGACCTTGGACTGTGTGTATGAA <u>ACCCGTGATACTACTTATTACTTATT</u> CTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCTTATTCTGTC <u>CGGAAC</u> <u>TCTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTTGGAACCTCCAGA</u> AATCCACCAGTTCCTTCAACTTCACCATCACAGCCTCACAAAGTCGTGGACTCA GCAGTATACTTCTGTGCTCTGAGTGAGTTTGACAGAGGCTCAACCCTGGGGA <u>GGCTATACTTTGGAAGAGGAACTCAGTTGACTGTCTGGCCT</u> (SEQ ID NO: 218)
PN46678 V β	DAGVTQSPTHLIKTRGQQVTLRCSPIS <u>GHKS</u> SVSWYQQVLGQGPQFIFQYYEKEER GRGNFPDRFSARQFPNYSSELNVNALLGDSALYLC <u>ASSRDINEKLEFGSGTQLS</u> VL (SEQ ID NO: 219) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCTATCTCTGGGCACAAGAGTGTGTCTCTGGTA CCAACAGGTCCTGGGTCAGGGGCCCCAGTTTATCTTTTCACTATTATGAGAAA <u>GAAGAGAGAGGAAGAGGAACTTCCCTGATCGATTCTCAGCTCGCCAGTTCC</u> CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTGCTGGGGGACTCGGC CCTGTATCTCTGTG <u>CCAGCAGCCGGGACATTAATGAAAACTGTTTTTTGGCA</u> GTGGAACCCAGCTCTCTGTCTTG (SEQ ID NO: 220)
PN46714 V α	EDQVTQSPEALRLQEGESSLNCSYTVSGLRGLFWYRQDPGKGPEFLFTLYSAGE <u>EKEKERLKA TLTKESFLHITAPKPEDSATYLC</u> <u>AVQADGGSQGNLIFGKGTKLSV</u> KP (SEQ ID NO: 221) GAAGACCAGGTGACGCAGAGTCCCGAGGCCCTGAGACTCCAGGAGGGAGAG AGTAGCAGTCTCAACTGCAGTTACACAGT <u>CAGCGGTTTAAGAGGGCTGTTCT</u> GGTATAGGCAAGATCCTGGGAAAGGCCCTGAATTCCTCTTACCCTGTATTC <u>AGCTGGGGAAGAAAAGGAGAAAGAAAGGCTAAAAGCCACATTAACAAAGA</u> AGGAAAGCTTTCTGCACATCACAGCCCTAAACCTGAAGACTCAGCCACTTA TCTCTGTGCTGTGCAGGCCGATGGAGGAAGCCAAGGAAATCTCATCTTTGGA AAAGGCACTAAACTCTCTGTAAACCA (SEQ ID NO: 222)
PN46714 V β	DAGVTQSPTHLIKTRGQQVTLRCSPIS <u>GHKS</u> SVSWYQQVLGQGPQFIFQYYEKEER GRGNFPDRFSARQFPNYSSELNVNALLGDSALYLC <u>ASSLDINSPLHFGNGTRLT</u> VT (SEQ ID NO: 223) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCTATCTCTGGGCACAAGAGTGTGTCTCTGGTA CCAACAGGTCCTGGGTCAGGGGCCCCAGTTTATCTTTTCACTATTATGAGAAA <u>GAAGAGAGAGGAAGAGGAACTTCCCTGATCGATTCTCAGCTCGCCAGTTCC</u> CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTGCTGGGGGACTCGGC

	CCTGTATCTCTGTGCCAGCAGCTTGGACATTAATTCACCCCTCCACTTTGGGA ACGGGACCAGGCTCACTGTGACA (SEQ ID NO: 224)
PN46723 V α	EDQVTQSPEALRLQEGESSLNCSYTVSGLRGLFWYRQDPGKGPEFLFTLYSAGE EKEKERLKATLTKKESFLHITAPKPEDSATYLC <u>AVQEDGGSQGNLIFGKGTKLSV</u> KP (SEQ ID NO: 225) GAAGACCAGGTGACGCAGAGTCCCGAGGCCCTGAGACTCCAGGAGGGAGAG AGTAGCAGTCTCAACTGCAGTTACACAGTCAGCGGTTTAAGAGGGCTGTTCT GGTATAGGCAAGATCCTGGGAAAGGCCCTGAATTCCTCTTCACCCCTGTATTC <u>AGCTGGGGAAGAAAAGGAGAAAGAAAGGCTAAAAGCCACATTAACAAAGA</u> AGGAAAGCTTTCTGCACATCACAGCCCCTAAACCTGAAGACTCAGCCACTTA TCTCTGTGCTGTGCAGGAGGATGGAGGAAGCCAAGGAAATCTCATCTTTGGA AAAGGCACTAAACTCTCTGTAAACCA (SEQ ID NO: 226)
PN46723 V β	DAGVTQSPTHLIKTRGQQVTLRCSPISGHKSWSWYQQVLGQGPQFIFQYYEKEER GRGNFPDRFSARQFPNYSELNVNALLGDSALYLC <u>CASSRDINEKLFFGSGTQLS</u> VL (SEQ ID NO: 227) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTATCTCTGGGCACAAGAGTGTGTCTTGTA CCAACAGGTCCTGGGTGAGGGGCCCCAGTTTATCTTTTCAGTATTATGAGAAA <u>GAAGAGAGAGGAAGAGGAACTTCCCTGATCGATTCTCAGCTCGCCAGTTCC</u> CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTTGCTGGGGGACTCGGC CCTGTATCTCTGTGCCAGCAGCCGGGACATTAATGAAAACTGTTTTTTGGCA GTGGAACCCAGCTCTCTGTCTTG (SEQ ID NO: 228)
PN46731 V α	GENVEQHPSTLSVQEGDSAVIKCTYSDSASNYFPWYKQELGKRQPQLIIDIRSNVG EKKDQRIAVTLNKTAKHFSLHITETQPEDSAVYFCAAWNYGQNFVFGPGTRLVS LP (SEQ ID NO: 229) GGAGAGAATGTGGAGCAGCATCCTTCAACCCTGAGTGTCCAGGAGGGAGAC AGCGCTGTTATCAAGTGTAATTATTCAGACAGTGCCTCAAACCTACTTCCCTTG GTATAAGCAAGAACTTGGAAGAAAGACCTCAGCTTATTATAGACATTCGTTCA <u>AATGTGGGCGAAAAGAAAGACCAACGAATTGCTGTTACATTGAACAAGACA</u> <u>GCCAAACATTTCTCCCTGCACATCACAGAGACCCAACCTGAAGACTCGGCTG</u> TCTACTTCTGTGCAGCATGGAACTATGGTCAGAAATTTGTCTTTGGTCCCGGA ACCAGATTGTCCGTGCTGCCC (SEQ ID NO: 230)
PN46731 V β	AAGVIQSPRHLIKEKRETATLKCYPPIPRHDTVYWYQQGPGQDPQFLISFYEKMQS DKGSIPDRFSAQQFSDYHSELNMSLELGDALYFC <u>ASSLEGSEAFFGQGTRLTV</u> V (SEQ ID NO: 231) GCTGCTGGAGTCATCCAGTCCCCAAGACATCTGATCAAAGAAAAGAGGGAA ACAGCCACTCTGAAATGCTATCCTATCCCTAGACACGACACTGTCTACTGGTA CCAGCAGGGTCCAGGTCAGGACCCCCAGTTCCTCATTTCTGTTTTATGAAAAG <u>ATGCAGAGCGATAAAGGAAGCATCCCTGATCGATTCTCAGCTCAACAGTTCA</u> GTGACTATCATTCTGAACTGAACATGAGCTCCTTGAGCTGGGGGACTCAGC CCTGTACTTCTGTGCCAGCAGCTTAGAGGGGTCTGAAGCTTCTTTGGACAAG GCACCAGACTCACAGTTGTA (SEQ ID NO: 232)
PN46733 V α	GESVGLHLPTLSVQEGDNSIINCAYSNSASDYFIWYKQESGKGPPQFIIDIRSNMDK RQGQRVTVLLNKTVKHLSLQIAATQPGDSAVYFCAENNYGQNFVFGPGTRLVSVL P (SEQ ID NO: 233)

	GGAGAGAGTGTGGGGCTGCATCTTCCTACCCTGAGTGTCCAGGAGGGTGACA ACTCTATTATCAACTGTGCTTATTCAAACAGCGCCTCAGACTACTTCATTTGG TACAAGCAAGAATCTGGAAAAGGTCTCAATTCATTATAGACATTCGTTCAA ATATGGACAAAAGGCAAGGCCAAAGAGTCACCGTTTTATTGAATAAGACAGT GAAACATCTCTCTCTGCAAATTGCAGCTACTCAACCTGGAGACTCAGCTGTCT ACTTTTGTGCAGAGAATAACTATGGTCAGAATTTTGTCTTTGGTCCCGGAACC AGATTGTCCGTGCTGCCC (SEQ ID NO: 234)
PN46733 Vβ	NAGVTQTPKFQVLKTGQSMTLQCAQDMNHNSMYWYRQDPGMGLRLIYYSAE GTTDKGEVPNGYNVSRNLKREFSLRLESAAPSQTSVYFCASSDWGQGVEAFFGQ GTRLTVV (SEQ ID NO: 235) AATGCTGGTGTCACTCAGACCCCCAAAATTCAGGTCTGAAGACAGGACAGA GCATGACACTGCAGTGTGCCCAGGATATGAACCATAACTCCATGTACTGGTA TCGACAAGACCCAGGCATGGGACTGAGGCTGATTTATTACTCAGCTTCTGAG GGTACCACTGACAAAGGAGAAGTCCCCAATGGCTACAATGTCTCCAGATTAA ACAAACGGGAGTTCTCGCTCAGGCTGGAGTCGGCTGCTCCCTCCAGACATC TGTGTACTTCTGTGCCAGCAGTGAAGTGGGGACAGGGGGTTGAAGCTTTCTTTG GACAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 236)
PN46735 Vα	DAKTTQPNSMESNEEPPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSTLILHRATLRDAAVYYCILREYMYSGGGADGLTFGKGT HLIIQP (SEQ ID NO: 237) GATGCTAAGACCACACAGCCAAATTCATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTCATGGTCTTACAA GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC CAGTACCTTGATCCTGCACCGTGCTACCTTGAGAGATGCTGCTGTGTACTACT GCATCCTGAGAGAATACATGTATTTCAGGAGGAGGTGCTGACGGACTCACCTT TGGCAAAGGGACTCATCTAATCATCCAGCCC (SEQ ID NO: 238)
PN46735 Vβ	DAGVTQSPTHLIKTRGQQVTLRCSPISGHKS VSWYQQVLGQGPQFIFQYYEKEER GRGNFPDRFSARQFPNYSSELNVNALLGDSALYLCASSFQAGVNYGYTFGSGT RLTVV (SEQ ID NO: 239) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCTATCTCTGGGCACAAGAGTGTGTCTCTGGTA CCAACAGGTCCTGGGTGAGGGGCCCCAGTTTATCTTTTCAGTATTATGAGAAA GAAGAGAGAGGAAGAGGAACTTCCCTGATCGATTCTCAGCTCGCCAGTTCC CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTTGCTGGGGGACTCGGC CCTGTATCTCTGTGCCAGCAGCTTCCAAGCAGGGGTAACTATGGCTACACCT TCGGTTCGGGGACCAGGTAAACCGTTGTA (SEQ ID NO: 240)
PN46738 Vα	AQTVTQSQPEMSVQEAETVTLSTYDTSENNYYLFWYKQPPSRQMILVIRQEAY KQQNATENRFSVNFQKAASFSLSKISDSQLGDTAMYFCAFGMYSGGGADGLTF GKGTHLIIQP (SEQ ID NO: 241) GCCCAGACAGTCACTCAGTCTCAACCAGAGATGTCTGTGCAGGAGGCAGAGA CTGTGACCCTGAGTTGCACATATGACACCAGTGAGAATAATTATTATTTGTTT TGGTACAAGCAGCCTCCAGCAGGCAGATGATTCTCGTTATTCGCCAAGAAG CTTATAAGCAACAGAATGCAACGGAGAATCGTTTCTCTGTGAACCTTCCAGAA AGCAGCCAAATCCTTCAGTCTCAAGATCTCAGACTCACAGCTGGGGGACACT

	<u>GCGATGTATTTCTGTGCTTTCGGTATGTATTCAGGAGGAGGTGCTGACGGACTCACCTTTGGCAAAGGGACTCATCTAATCATCCAGCCC</u> (SEQ ID NO: 242)
PN46738 V β	DAGITQSPRYKITETGRQVTLMCHQTWSHSYMFWYRQDLGHGLRLIYY <u>SAAADI</u> TDKGEVPDGYVVSRSKTENFPLTLESATRSQTSVYFC <u>ASSDGTGYGYT</u> FGSGTRLTVV (SEQ ID NO: 243) GATGCTGGAATCACCCAGAGCCCAAGATACAAGATCACAGAGACAGGAAGG CAGGTGACCTTGATGTGTACACAGACTTGGAGCCACAGCTATATGTTCTGGT ATCGACAAGACCTGGGACATGGGCTGAGGCTGATCTATTACTCAGCAGCTGC <u>TGATATTACAGATAAAGGAGAAGTCCCCGATGGCTATGTTGTCTCCAGATCC</u> AAGACAGAGAATTTCCCCCTCACTCTGGAGTCAGCTACCCGCTCCCAGACAT CTGTGTATTTCTGCGCCAGCAGTGATGGGACAGGGTACTATGGCTACACCTTC GGTTCGGGGACCAGGTAAACCGTTGTA (SEQ ID NO: 244)
PN46777 V α	AQTVTQSQPEMSVQEAETVTLSTYDTSENNYYLFWYKQPPSRQMILVIRQEAY <u>KQQNATENRFSVNFQKA</u> AKSFSLKISDSQLGDTAMYFC <u>ALMEYGNKLV</u> FGAGTILRVKS (SEQ ID NO: 245) GCCCAGACAGTCACTCAGTCTCAACCAGAGATGTCTGTGCAGGAGGCAGAGA CTGTGACCCTGAGTTGCACATATGAC <u>ACCAGTGAGAATAATTATTATTTGTTCT</u> TGGTACAAGCAGCCTCCAGCAGGCAGATGATTCTCGTTATTCGCCAAGAAG <u>CTTATAAGCAACAGAATGCAACGGAGAATCGTTTCTCTGTGAACTTCCAGAA</u> AGCAGCCAAATCCTTCAGTCTCAAGATCTCAGACTCACAGCTGGGGGACACT GCGATGTATTTCTGTGCCCTTATGGAATATGGAAACAACTGGTCTTTGGCGC AGGAACCATCTGAGAGTCAAGTCC (SEQ ID NO: 246)
PN46777 V β	DAGITQSPRYKITETGRQVTLMCHQTWSHSYMFWYRQDLGHGLRLIYY <u>SAAADI</u> TDKGEVPDGYVVSRSKTENFPLTLESATRSQTSVYFC <u>ASSDGTGYGYT</u> FGSGTRLTVV (SEQ ID NO: 247) GATGCTGGAATCACCCAGAGCCCAAGATACAAGATCACAGAGACAGGAAGG CAGGTGACCTTGATGTGTACACAGACTTGGAGCCACAGCTATATGTTCTGGT ATCGACAAGACCTGGGACATGGGCTGAGGCTGATCTATTACTCAGCAGCTGC <u>TGATATTACAGATAAAGGAGAAGTCCCCGATGGCTATGTTGTCTCCAGATCC</u> AAGACAGAGAATTTCCCCCTCACTCTGGAGTCAGCTACCCGCTCCCAGACAT CTGTGTATTTCTGCGCCAGCAGTGATGGGACAGGGTACTATGGCTACACCTTC GGTTCGGGGACCAGGTAAACCGTTGTA (SEQ ID NO: 248)
PN46797 V α	AQTVTQSQPEMSVQEAETVTLSTYDTSENNYYLFWYKQPPSRQMILVIRQEAY <u>KQQNATENRFSVNFQKA</u> AKSFSLKISDSQLGDTAMYFC <u>ALMEYENKLV</u> FGAGTILRVKS (SEQ ID NO: 249) GCCCAGACAGTCACTCAGTCTCAACCAGAGATGTCTGTGCAGGAGGCAGAGA CTGTGACCCTGAGTTGCACATATGAC <u>ACCAGTGAGAATAATTATTATTTGTTCT</u> TGGTACAAGCAGCCTCCAGCAGGCAGATGATTCTCGTTATTCGCCAAGAAG <u>CTTATAAGCAACAGAATGCAACGGAGAATCGTTTCTCTGTGAACTTCCAGAA</u> AGCAGCCAAATCCTTCAGTCTCAAGATCTCAGACTCACAGCTGGGGGACACT GCGATGTATTTCTGTGCCCTTATGGAATATGAAAACAACTGGTCTTTGGCGC AGGAACCATCTGAGAGTCAAGTCC (SEQ ID NO: 250)
PN46797 V β	DAGITQSPRYKITETGRQVTLMCHQTWSHSYMFWYRQDLGHGLRLIYY <u>SAAADI</u> TDKGEVPDGYVVSRSKTENFPLTLESATRSQTSVYFC <u>ASSDGTGYGYT</u> FGSGTRLTVV (SEQ ID NO: 251)

	GATGCTGGAATCACCCAGAGCCCAAGATACAAGATCACAGAGACAGGAAGG CAGGTGACCTTGATGTGTACCAGACTTGGAGCCACAGCTATATGTTCTGGT ATCGACAAGACCTGGGACATGGGCTGAGGCTGATCTATTACTCAGCAGCTGC TGATATTACAGATAAAGGAGAAGTCCCCGATGGCTATGTTGTCTCCAGATCC AAGACAGAGAATTTCCCCCTCACTCTGGAGTCAGCTACCCGCTCCCAGACAT CTGTGTATTTCTGCGCCAGCAGTGATGGGACAGGGTACTATGGCTACACCTTC GGTTCGGGGACCAGGTAAACCGTTGTA (SEQ ID NO: 252)
PN46853 V α	ILNVEQSPQSLHVQEGDSTNFTCSFPSSNFYALHWYRWETAKSPEALFVMTLNG DEKKKGRISATLNTKEGYSYLYIKGSQPEDSATYLCACGSGSNTGKLIFGQGTTL QVKP (SEQ ID NO: 253) ATACTGAACGTGGAACAAAGTCCTCAGTCAGTCATGTTTCAGGAGGGAGACA GCACCAATTTACCTGCAGCTTCCCTTCCAGCAATTTTATGCCTTACACTGG TACAGATGGGAAACTGCAAAAAGCCCCGAGGCCTTGTTTGTAATGACTTTAA ATGGGGATGAAAAGAAGAAAGGACGAATAAGTGCCACTCTTAATACCAAGG AGGGTTACAGCTATTTGTACATCAAAGGATCCCAGCCTGAAGACTCAGCCAC ATACCTCTGTGCTGTGGGGGTTCTGGCAACACAGGCAAATAATCTTTGGG CAAGGGACAACCTTACAAGTAAACCA (SEQ ID NO: 254)
PN46853 V β	AAGVIOSPRHLIKEKRETATLKCYPPIRHDTVYWYQQGPGQDPQFLISFYEQMQS DKGSIPDRFSAQQFSDYHSELNMSSELGDSALYFCASSSQGPQHFGDGTLSIL (SEQ ID NO: 255) GCTGCTGGAGTCATCCAGTCCCCAAGACATCTGATCAAAGAAAAGAGGGAA ACAGCCACTCTGAAATGCTATCCTATCCCTAGACACGACACTGTCTACTGGTA CCAGCAGGGTCCAGGTCAGGACCCCCAGTTCCTCATTTCGTTTTATGAAAAG ATGCAGAGCGATAAAGGAAGCATCCCTGATCGATTCTCAGCTCAACAGTTCA GTGACTATCATTCTGAACTGAACATGAGCTCCTTGAGCTGGGGGACTCAGC CCTGTACTTCTGTGCCAGCAGCTCCCAGGGTCAGCCCCAGCATTTTGGTGATG GACTCGACTCTCCATCCTA (SEQ ID NO: 256)
PN46857 V α	AQKVTQATREISVVEKEDVTLDVCYETRDTTYLFWYKQPPSGELVFLIRNSFD EQNEISGRYSWNFQKSTSSFNFTITASQVVDSAVYFCALSEGYGNKLVFGAGTIL RVKS (SEQ ID NO: 257) GCTCAGAAGGTAAGTCAAGCGACTAGAGAAATTTCTGTGGTGGAGAAGGAG GATGTGACCTTGGACTGTGTGTATGAAACCCGTGATACTACTTATTACTTATT CTGGTACAAGCAACCAAGTGGAGAATTGGTTTTCTTATTCGTCCGAAC TCTTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTTGAACTTCCAGA AATCCACCAGTTCCTTCAACTTCACCATCACAGCCTCACAAGTCGTGGACTCA GCAGTATACTTCTGTGCTCTGAGTGAGGGATATGGAAACAACTGGTCTTTG GCGCAGGAACCATCTGAGAGTCAAGTCC (SEQ ID NO: 258)
PN46857 V β	NAGVMQNPRHLVRRRGQEARLRCSPMKGHSHVYWYRQLPEEGLKFMVYLQKE NIIDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYFCASSHRDDTEAFFGQGT RLTVV (SEQ ID NO: 259) AATGCCGGCGTCATGCAGAACCCAAGACACCTGGTCAGGAGGAGGGGACAG GAGGCAAGACTGAGATGCAGCCAATGAAAGGACACAGTCATGTTTACTGGT ATCGGCAGCTCCCAGAGGAAGGTCTGAAATTCATGGTTTATCTCCAGAAAGA AAATATCATAGATGAGTCAGGAATGCCAAAGGAACGATTTTCTGCTGAATTT CCCAAAGAGGGCCCCAGCATCCTGAGGATCCAGCAGGTAGTGCGAGGAGAT

	TCGGCAGCTTATTTCTGTGCCAGCTCACACAGGGACGACACTGAAGCTTCTT TGGACAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 260)
PN46871 V α	KQEVTVIPAALSVPEGENLVNCSFTDSAIYNLQWFRQDPGKGLTSLLLIQSSQRE QTSGRLNASLDKSSGRSTLYIAASQPGDSATYLC AVEGTTDSWGKFQFGAGTQV VVTP (SEQ ID NO: 261) AAACAGGAGGTGACGCAGATTCTGTCAGCTCTGAGTGTCCCAGAAGGAGAA AACTTGTTCTCAACTGCAGTTTCACTGATAGCGCTATTTACAACCTCCAGTG GTTTAGGCAGGACCCTGGGAAAGGTCTCACATCTCTGTTGCTTATTCAGTCAA GTCAGAGAGAGCAAACAAGTGGAAGACTTAATGCCTCGCTGGATAAATCATC AGGACGTAGTACTTTATACATTGCAGCTTCTCAGCCTGGTGACTCAGCCACCT ACCTCTGTGCTGTGGAGGGGACAACCTGACAGCTGGGGGAAATTCAGTTTGG AGCAGGGACCCAGGTTGTGGTCACCCCA (SEQ ID NO: 262)
PN46871 V β	AAGVIQSPRHLIKEKRETATLKCYPPIRHDTVYVYQQGPGQDPQFLISFYEKMQS DKGSIPDRFSAQQFSDYHSELNMSSELGDSALYFCASSSQGPQHFGDGTLSIL (SEQ ID NO: 263) GCTGCTGGAGTCATCCAGTCCCCAAGACATCTGATCAAAGAAAAGAGGGAA ACAGCCACTCTGAAATGCTATCCTATCCCTAGACACGACACTGTCTACTGGTA CCAGCAGGGTCCAGGTCCAGGACCCCCAGTTCTCTATTTCTGTTTATGAAAAG ATGCAGAGCGATAAAGGAAGCATCCCTGATCGATTCTCAGCTCAACAGTTCA GTGACTATCATTCTGAACTGAACATGAGCTCCTTGAGCTGGGGGACTCAGC CCTGTACTTCTGTGCCAGCAGCTCCAGGGTCAGCCCCAGCATTTTGGTGATG GGACTCGACTCTCCATCCTA (SEQ ID NO: 264)
PN46880 V α	AQRVTQPEKLLSVFKGAPVELKCNYSYSGSPELFWYVQYSRQRLQLLLRHISRES IKGFTADLNKGETSFHLKKPFAQEEDSAMYYCALSGASGGSYIPTFGRGTS LIVH P (SEQ ID NO: 265) GCCCAGAGAGTGACTCAGCCCGAGAAGCTCCTCTCTGTCTTTAAAGGGGCCC CAGTGGAGCTGAAGTGCAACTATTCCTATTCTGGGAGTCCTGAACTCTTCTGG TATGTCCAGTACTCCAGACAACGCCTCCAGTTACTCTTGAGACACATCTCTAG AGAGAGCATCAAAGGCTTCACTGCTGACCTTAACAAAGGCGAGACATCTTTC CACCTGAAGAAACCATTTGCTCAAGAGGAAGACTCAGCCATGTATTACTGTG CTCTAAGTGGGGCATCAGGAGGAAGCTACATACCTACATTTGGAAGAGGAAC CAGCCTTATTGTTTCATCCG (SEQ ID NO: 266)
PN46880 V β	NAGVMQNPRHLVRRRGQEARLRCSPMKGHSHVYVYRQLPEEGLKFMVYLOKE NIIDESGMPKERFSAEFPKEGPSILRIQQVVRGDSAAYFCASSHRDDTEAFFGQGT RLTVV (SEQ ID NO: 267) AATGCCGGCGTCATGCAGAACCCAAGACACCTGGTCAGGAGGAGGGGACAG GAGGCAAGACTGAGATGCAGCCAATGAAAGGACACAGTCATGTTTACTGGT ATCGGCAGCTCCCAGAGGAAGGTCTGAAATTCATGGTTTATCTCCAGAAAGA AAATATCATAGATGAGTCAGGAATGCCAAAGGAACGATTTTCTGCTGAATTT CCCAAAGAGGGGCCCCAGCATCTGAGGATCCAGCAGGTAGTGCGAGGAGAT TCGGCAGCTTATTTCTGTGCCAGCTCACACAGGGACGACACTGAAGCTTCTT TGGACAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 268)
PN46883 V α	AQKVTQAQTEISVVEKEDVTLDVCVYETRDTTYLLFWYKQPPSGELVFLIRNSF DEQNEISGRYSWNFQKSTSSFNFTITASQVVDSAVYFCALSVSSYNTDKLIFGTGT RLQVFP (SEQ ID NO: 269)

	GCTCAGAAGGTAAGTCAAGCGCAGACTGAAATTTCTGTGGTGGAGAAGGAG GATGTGACCTTGGACTGTGTGTATGAAACCCGTGATACTACTTATTACTTATT CTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCTTATTTCGT<u>CGGAAC</u> <u>TCTTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTTGGAACCTCCAGA</u> AATCCACCAGTTCCTTCAACTTCACCATCACAGCCTCACAAGTCGTGGACTCA GCAGTATACTTCTGT<u>GCTCTGAGTGTATCATCTTATAACACCGACAAGCTCAT</u> <u>CTTTGGGACTGGGACCAGATTACAAGTCTTTCCA</u> (SEQ ID NO: 270)
PN46883 Vβ	NAGVMQNPRHLVRRRGQEARLRCSMPK<u>GHSHVY</u>WYRQLPEEGLKFMVY<u>LQKE</u> <u>NI</u>IDESGMPKERFSAEFPKEGPSILRIQVVVRGDSAAYFC<u>ASSHRDDTEAFFGQGT</u> RLTVV (SEQ ID NO: 271) AATGCCGGCGTCATGCAGAACCCAAGACACCTGGTCAGGAGGAGGGGACAG GAGGCAAGACTGAGATGCAGCCCAATGAAAGGACACAGTCATGTTTACTGGT ATCGGCAGCTCCCAGAGGAAGGTCTGAAATTCATGGTTTATCTCCAGAAAGA <u>AAATATCATAGATGAGTCAGGAATGCCAAAGGAACGATTTTCTGCTGAATTT</u> CCCAAAGAGGGCCCCAGCATCCTGAGGATCCAGCAGGTAGTGCGAGGAGAT TCGGCAGCTTATTTCTGT<u>GCCAGCTCACACAGGGATGACACTGAAGCTTTCTT</u> TGGACAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 272)
PN46884 Vα	AQKVTQAQPEISVVEKEDVTLDCVYETRD<u>TTY</u>YLFWYKQPPSGELVFLIRNSFD <u>EQNE</u>ISGRYSWNFQKSTSSFNTITASQVVDSAVYFC<u>ALSEGYNTDKLIFGTGTRL</u> QVFP (SEQ ID NO: 273) GCTCAGAAGGTAAGTCAAGCGCAGCCTGAAATTTCTGTGGTGGAGAAGGAG GATGTGACCTTGGACTGTGTGTATGAAACCCGTGATACTACTTATTACTTATT CTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCTTATTTCGT<u>CGGAAC</u> <u>TCTTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTTGGAACCTCCAGA</u> AATCCACCAGTTCCTTCAACTTCACCATCACAGCCTCACAAGTCGTGGACTCA GCAGTATACTTCTGT<u>GCTCTGAGTGAGGGGTATAACACCGACAAGCTCATCT</u> TTGGGACTGGGACCAGATTACAAGTCTTTCCA (SEQ ID NO: 274)
PN46884 Vβ	DVKVTQSSRYLVKRTGEKVFLFCVQDMD<u>HEN</u>MFWYRQDPGLGLRLIYFSYDVK <u>MKE</u>KGDIPEGYSVSREKKERFSLILESASTNQTSMYLC<u>ASSLGGANTIYFGE</u>GSW LTVV (SEQ ID NO: 275) GATGTGAAAGTAACCCAGAGCTCGAGATATCTAGTCAAAAGGACGGGAGAG AAAGTTTTCTGGAATGTGTCCAGGATATGGACCATGAAAATATGTTCTGGTA TCGACAAGACCCAGGTCTGGGGCTACGGCTGATCTATTTCTCATATGATGTTA <u>AAATGAAAGAAAAAGGAGATATTCCTGAGGGGTACAGTGTCTTAGAGAGA</u> AGAAGGAGCGCTTCTCCCTGATTCTGGAGTCCGCCAGCACCAACCAGACATC TATGTACCTCTGT<u>GCCAGCAGTTT</u>AGGGGGGGCGAACACCATATATTTTGA GAGGGAAGTTGGCTCACTGTTGTA (SEQ ID NO: 276)
PN46889 Vα	QKEVEQNSGPLSVPEGAIASLNCTYS<u>DRGSQS</u>FFWYRQYSGKSPELIMSIY<u>SNGD</u> KEDGRFTAQLNKASQYVSLIRDSQPSDSATYLC<u>AVNIPNSGYSTLTFGKGTMLL</u> VSP (SEQ ID NO: 277) CAGAAGGAGGTGGAGCAGAATTCTGGACCCCTCAGTGTTCCAGAGGGAGCC ATTGCCTCTCTCAACTGCATTACAGTGACCGAGGTTCCAGTCCCTTCTTG GTACAGACAATATTCTGGGAAAAGCCCTGAGTTGATAATGTCCATATACTCC <u>AATGGTGACAAAGAAGATGGAAGGTTTACAGCACAGCTCAATAAAGCCAGC</u> CAGTATGTTTCTCTGCTCATCAGAGACTCCCAGCCCAGTGATTCAGCCACCTA

	CCTCTGTGCCGTGAACATTCCGAATTCAGGATACAGCACCCCTCACCTTTGGGAAGGGGACTATGCTTCTAGTCTCTCCA (SEQ ID NO: 278)
PN46889 Vβ	NAGVTQTPKFRVLKTGQSM TLLCAQDMNHEYMYWYRQDPGMGLRLIHYSVGE GTTAKGEVPDGYNVSRLLKKQNFLLGLESAAPSQTSVYFCASSYWEGTEAFFGQG TRLTVV (SEQ ID NO: 279) AATGCTGGTGTCACTCAGACCCCCAAAATTCCGGGTCTCTGAAGACAGGACAGA GCATGACACTGCTGTGTGCCCAGGATATGAACCATGAATACATGTACTGGTA TCGACAAGACCCAGGCATGGGGCTGAGGCTGATTCACTCAGTTGGTGAG GGTACAAGTCCAAAGGAGAGGTCCCTGATGGCTACAATGTCTCCAGATTAA AAAAACAGAATTTCTGTGCTGGGGTTGGAGTCGGCTGCTCCCTCCCAAACATC TGTGTACTTCTGTGCCAGCAGTTACTGGGAGGGCACTGAAGCTTTCTTTGGAC AAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 280)
PN46909 Vα	AQTVTQSQPEMSVQEAETVTLSTYDTSNNYYLFWYKQPPSRQMILVIRQEA YKQONATENRFSVNFQKAASFSLKISDSQLGDTAMYFCAFDYQGFVFGPGTRL SVLP (SEQ ID NO: 281) GCCCAGACAGTCACTCAGTCTCAACCAGAGATGTCTGTGCAGGAGGCAGAGA CTGTGACCCTGAGTTGCACATATGACACCAGTGAGAATAATTATTATTGTTT TGGTACAAGCAGCCTCCAGCAGGCAGATGATTCTCGTTATTCGCCAAGAAG CTTATAAGCAACAGAATGCAACGGAGAATCGTTTCTCTGTGAACCTCCAGAA AGCAGCCAAATCCTTCAGTCTCAAGATCTCAGACTCACAGCTGGGGGACACT GCGATGTATTTCTGTGCTTTCCAGTATGGTCAGAAATTTGTCTTTGGTCCCGG AACCAGATTGTCCGTGCTGCCC (SEQ ID NO: 282)
PN46909 Vβ	NAGVTQTPKFRILKIGQSM TLLCAQDMNHNMYWYRQDPGMGLKLIYYSVGA GITDKGEVPNGYNVSRSTTEYFPLRLELAAPSQTSVYFCASSYGGGQTEAFFGQG TRLTVV (SEQ ID NO: 283) AATGCTGGTGTCACTCAGACCCCCAAAATTCCGCATCCTGAAGATAGGACAGA GCATGACACTGCAGTGTGCCCAGGATATGAACCATAACTACATGTACTGGTA TCGACAAGACCCAGGCATGGGGCTGAAGCTGATTTATTATTCACTTGGTGCT GGTATCACTGATAAAGGAGAAGTCCCGAATGGCTACAACGTCTCCAGATCAA CCACAGAGTATTTCCCGCTCAGGCTGGAGTTGGCTGCTCCCTCCAGACATCT GTGTACTTCTGTGCCAGCAGTTACGGGGGGGGGCGAGACTGAAGCTTTCTTTG GACAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 284)
PN46914 Vα	AQKVTQAQPEISVVEKEDVTLDCVYETRD TTYLFWYKQPPSGELVFLIRNSFD EQNEISGRYSWNFQKSTSSFNFTITASQVVDSAVYFCALSEGYNQGGKLIFGQGT ELSVKP (SEQ ID NO: 285) GCTCAGAAGGTAAGTCAAGCGCAGCCTGAAATTTCTGTGGTGGAGAAGGAG GATGTGACCTTGGACTGTGTGTATGAAACCCGTGATACTACTTATTACTTATT CTGGTACAAGCAACCACCAAGTGGAGAATTGGTTTTCTTATTCTCGTCGGAAC TCTTTTGATGAGCAAAATGAAATAAGTGGTCGGTATTCTTGGAACCTCCAGA AATCCACCAGTTCCTTCAACTTCACCATCACAGCCTCACAAGTCGTGGACTCA GCAGTATACTTCTGTGCTCTGAGTGAGGGTTATAACCAGGGAGGAAAGCTTA TCTTCGGACAGGGAACGGAGTTATCTGTGAAACCC (SEQ ID NO: 286)
PN46914 Vβ	DVKVTQSSRYLVKRTGEKVFLCVQDMDHENMFWYRQDPGLGLRLIYFSYDVK MKEKGDIEGYSVSREKKERFSLILESASTNQTSMYLCASGADSNQPHFGDGTR LSIL (SEQ ID NO: 287)

	GATGTGAAAGTAACCCAGAGCTCGAGATATCTAGTCAAAAGGACGGGAGAG AAAGTTTTTCTGGAATGTGTCCAGGATATGGACCATGAAAATATGTTCTGGTA TCGACAAGACCCAGGTCTGGGGCTACGGCTGATCTATTTCTCATATGATGTTA <u>AAATGAAAGAAAAAGGAGATATTCCTGAGGGGTACAGTGTCTCTAGAGAGA</u> AGAAGGAGCGCTTCTCCCTGATTCTGGAGTCCGCCAGCACCAACCAGACATC TATGTACCTCTGTGCCAGCGGGGCAGATAGCAATCAGCCCCAGCATTTTGGT GATGGGACTCGACTCTCCATCCTA (SEQ ID NO: 288)
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Table 6. Amino acid CDR sequences for VelociT TCRs specific for PRAME (425-433) / HLA-A2

TCR ID	V α CDR1	SEQ ID NO:	V α CDR2	SEQ ID NO:	V α CDR3	SEQ ID NO:	V β CDR1	SEQ ID NO:	V β CDR2	SEQ ID NO:	V β CDR3	SEQ ID NO:
PN42365	SVFSS	289	VVTGGEV	290	AANGGSQGNLI	291	SGHDT	292	YEEEE	293	ASSLQDYGYT	294
PN42378	TISGTDY	295	GLTSN	296	ILRPDSWGKFK	297	SGHDT	298	YEEEE	299	ASSLQDYGYT	300
PN42386	SVFSS	301	VVTGGEV	302	ATNGGSQGNLI	303	SGHDT	304	YEEEE	305	ASSLQDYGYT	306
PN42441	TISGTDY	307	GLTSN	308	IRRPNGQFY	309	MNHEY	310	SMNVEV	311	ASSLWTGSEAF	312
PN42442	SVFSS	313	VVTGGEV	314	AGTSGTYKYI	315	MNHEY	316	SMNVEV	317	ASSPGTANYGYT	318
PN42450	YSGSPE	319	HISR	320	ALGNTDKLI	321	MDHEN	322	SYDVKM	323	ASSSPRTGWYGYT	324
PN42455	TISGTDY	325	GLTSN	326	ILRPDSWGKFK	327	SGHDT	328	YEEEE	329	ASSLVDYGYT	330
PN42476	TISGTDY	331	GLTSN	332	ILRPDSWGKFK	333	MDHEY	334	SMNVEV	335	ASSLGGVDERLS	336
PN42483	SVFSS	337	VVTGGEV	338	AGDGSQGNLI	339	MNHEY	340	SMNVEV	341	ASSLGGADEKLF	342
PN42496	TISGTDY	343	GLTSN	344	ILGQGAQKLV	345	MNHEY	346	SMNVEV	347	ASSLWTGGGYT	348
PN42498	SVFSS	349	VVTGGEV	350	AGDGSQGNLI	351	SGHDT	352	YEEEE	353	ASSLVDYGYT	354
PN42558	DSVNN	355	IPSGT	356	VLGGGSQGNLI	357	SGHDT	358	YEEEE	359	ASSFTDYGYT	360
PN42561	TISGTDY	361	GLTSN	362	ILRDGTGNQFY	363	MNHEY	364	SMNVEV	365	ASSLWTGGGYT	366
PN42562	SVFSS	367	VVTGGEV	368	AGGPGSPTYKYI	369	MNHEY	370	SMNVEV	371	ASSPGTPNYGYT	372
PN42610	DRGSQS	373	IYSNGD	374	AGNYGQNFV	375	PRHDT	376	FYEKMQ	377	ASSIGLNQPH	378
PN42654	TISGTDY	379	GLTSN	380	ILRDGIGNQFY	381	MNHEY	382	SMNVEV	383	ASSLWTGGGYT	384
PN42655	TISGTDY	385	GLTSN	386	ILRPDSWGKFK	387	MNHEY	388	SMNVEV	389	ASSLWTGGGYT	390
PN42677	TISGTDY	391	GLTSN	392	ILRDGTGNQFY	393	MNHEY	394	SMNVEV	395	ASSSTGYGYT	396
PN42683	TISGTDY	397	GLTSN	398	ILRDREYGNKLV	399	MNHEY	400	SMNVEV	401	ASSLWTGGGYT	402
PN42689	SVFSS	403	VVTGGEV	404	AEDGSQGNLI	405	SGHDT	406	YEEEE	407	ASSLSDYGYT	408
PN42706	DSVNN	409	IPSGT	410	AVEASGTYKYI	411	MNHEY	412	SMNVEV	413	ASSWGTGGGYT	414
PN42707	NSASDY	415	IRSNMDK	416	AENKRDNYGQNFV	417	MNHEY	418	SMNVEV	419	ASSFWVNTAF	420
PN42711	DSVNN	421	IPSGT	422	AVGSSNGYKLS	423	MNHEY	424	SMNVEV	425	ASSPGTGGFSPH	426
PN42712	DSVNN	427	IPSGT	428	AVGSSNDYKLS	429	MNHEY	430	SMNVEV	431	ASSPGTGGFSPH	432
PN42746	NSASDY	433	IRSNMDK	434	AENRQDNYGQNFV	435	MNHEY	436	SMNVEV	437	ASSLWVNTAF	438
PN42750	TISGTDY	439	GLTSN	440	ILRPDSWGKFK	441	MDHEN	442	SYDVKM	443	ASSTVRQNGYGYT	444
PN42762	TISGTDY	445	GLTSN	446	ILNTGTASKLT	447	MNHEY	448	SMNVEV	449	ASSLSSNTEAF	450

TCR ID	V α CDR1	SEQ ID NO:	V α CDR2	SEQ ID NO:	V α CDR3	SEQ ID NO:	V β CDR1	SEQ ID NO:	V β CDR2	SEQ ID NO:	V β CDR3	SEQ ID NO:
PN42774	DRGSQS	451	IYSNGD	452	AVNRGTDKLI	453	SGHDT	454	YEEEE	455	ASSWTDYGYT	456
PN42776	TISGTDY	457	GLTSN	458	ILRPDSWGKFK	459	SGHDT	460	YEEEE	461	ASSWTDYGYT	462
PN42780	SVFSS	463	VVTGGEV	464	AGGTSGTYKYI	465	MNHEY	466	SMNVEV	467	ASSPGTPTYGYT	468
PN42795	NSASQS	469	VYSSGN	470	VVNGGSQGNLI	471	SGHDT	472	YEEEE	473	ASSVGDYGYT	474
PN42815	NSASDY	475	IRSNMDK	476	AENNYGQNFV	477	MNHEY	478	SMNVEV	479	ASSLWDSPLH	480
PN42826	NSMFDY	481	ISSIKDK	482	AASAGSARQLT	483	MNHEY	484	SMNVEV	485	ASSLYTHTEAF	486
PN42833	TISGNEY	487	GLKNN	488	IVRDTTSGTYKYI	489	MNHEY	490	SMNVEV	491	ASSLSSTGFSPLH	492
PN42840	SVFSS	493	VVTGGEV	494	AEGGGSQGNLI	495	SGHDT	496	YEEEE	497	ASSWTDYGYT	498
PN42845	SVFSS	499	VVTGGEV	500	AGIRSNQYKLS	501	MNHEY	502	SMNVEV	503	ASSSWTAHTEAF	504
PN42870	SVFSS	505	VVTGGEV	506	AENSGGGADGLT	507	SGHDT	508	YEEEE	509	ASSFTDYGYT	510
PN42879	SVFSS	511	VVTGGEV	512	AGEDFGNEKLT	513	SGHDT	514	YEEEE	515	ASSWADYGYT	516
PN42888	SSNFYA	517	MTLNGDE	518	AFLTGNQFY	519	MDHEN	520	SYDVVKM	521	ASSTVRQGNVGYT	522
PN42895	NSMFDY	523	ISSIKDK	524	AASAGSARQLT	525	MNHEY	526	SMNVEV	527	ASSLWSNTEAF	528

Table 7. Nucleic acid CDR sequences for VelociT TCRs specific for PRAME (425-433) / HLA-A2

TCR ID	V α CDR1	SEQ ID NO:	V α CDR2	SEQ ID NO:	V α CDR3	SEQ ID NO:	V β CDR1	SEQ ID NO:	V β CDR2	SEQ ID NO:	V β CDR3	SEQ ID NO:
PN42365	AGTGTTT TTTCCAG C	529	GTAGTTACG GGTGAGAA GTG	530	GCCGCTAATGGAGGA AGCCAAGGAAATCTC ATC	531	TCTGGGC ATGACA CT	532	TATTATG AGGAGGA AGAG	533	GCCAGCAGCTTACA GGACTATGGCTACA CC	534
PN42378	ACAATCA GTGGAAC TGATTAC	535	GGTCTTACA AGCAAT	536	ATCTGCGGCTGACA GCTGGGGGAAATTC AG	537	TCTGGGC ATGACA CT	538	TATTATG AGGAGGA AGAG	539	GCCAGCAGCTTACA GGACTATGGCTACA CC	540
PN42386	AGTGTTT TTTCCAG C	541	GTAGTTACG GGTGAGAA GTG	542	GCCACTAATGGAGGA AGCCAAGGAAATCTC ATC	543	TCTGGGC ATGACA CT	544	TATTATG AGGAGGA AGAG	545	GCCAGCAGCTTACA GGACTATGGCTACA CC	546

TCR ID	V α CDR1	SEQ ID NO:	V α CDR2	SEQ ID NO:	V α CDR3	SEQ ID NO:	V β CDR1	SEQ ID NO:	V β CDR2	SEQ ID NO:	V β CDR3	SEQ ID NO:
PN42441	ACAATCA GTGGAAC TGATTAC	547	GGTCTTACA AGCAAT	548	ATCAGGCGGCCGGT AACCAGTTCTAT	549	ATGAAC CATGAGT AT	550	TCAATGA ATGTTGA GGTG	551	GCCAGCAGTTTATG GACAGGGTCTGAAG CTTTC	552
PN42442	AGTGTTT TTTCCAG C	553	GTAGTTACT GGTGGAGAA GTG	554	GCAGGAGGGACCTCA GGAACCTACAAATAC ATC	555	ATGAAC CATGAGT AT	556	TCAATGA ATGTTGA GGTG	557	GCCAGCAGTCCAGG GACAGCTAACTATG GCTACACC	558
PN42450	TATTCGT GGAGTCC TGAA	559	CACATCTCT AGA	560	GCTCTAGGGAACACC GACAAGCTCATC	561	ATGGAC CATGAA AAT	562	TCATATG ATGTTAA AATG	563	GCCAGCAGTTCGCC CAGGACAGGGTGGT ATGGCTACACC	564
PN42455	ACAATCA GTGGAAC TGATTAC	565	GGTCTTACA AGCAAT	566	ATCCTGCGGCCCTGACA GCTGGGGGAAATTCC AG	567	TCTGGGC ATGACA CT	568	TATTATG AGGAGGA AGAG	569	GCCAGCAGCTTGGT GGATTATGGCTACA CC	570
PN42476	ACAATCA GTGGAAC TGATTAC	571	GGTCTTACA AGCAAT	572	ATCCTGCGGCCCTGACA GCTGGGGGAAATTCC AG	573	ATGGAC CATGAGT AT	574	TCAATGA ATGTTGA GGTG	575	GCCAGCAGTTTAGG GGGCGTGATGAAA GACTGTCT	576
PN42483	AGTGTTT TTTCCAG C	577	GTAGTTACG GGTGGAGAA GTG	578	GCAGGGGATGGAGGA AGCCAAGGAAATCTC ATC	579	ATGAAC CATGAGT AT	580	TCAATGA ATGTTGA GGTG	581	GCCAGCAGTTTAGG GGGCGCGGATGAAA AACTGTTT	582
PN42496	ACAATCA GTGGAAC TGATTAC	583	GGTCTTACA AGCAAT	584	ATCCTGGGTCAGGGA GCCCAGAAAGCTGGTA	585	ATGAAC CATGAGT AT	586	TCAATGA ATGTTGA GGTG	587	GCCAGCAGTTTATG GACAGGGGGCGGCT ACACC	588
PN42498	AGTGTTT TTTCCAG C	589	GTAGTTACG GGTGGAGAA GTG	590	GCAGGGGATGGAGGA AGCCAAGGAAATCTC ATC	591	TCTGGGC ATGACA CT	592	TATTATG AGGAGGA AGAG	593	GCCAGCAGCTTGGT GGATTATGGCTACA CC	594
PN42558	GACTCTG TGAACAA T	595	ATTCCTTCA GGGACA	596	GTCCTAGGGGGAGGA AGCCAAGGAAATCTC ATC	597	TCTGGGC ATGACA CT	598	TATTATG AGGAGGA AGAG	599	GCCAGCAGCTTATG AGACTATGGCTACA CC	600
PN42561	ACAATCA GTGGAAC TGATTAC	601	GGTCTTACA AGCAAT	602	ATCCTGAGAGACGGG ACCGTAACCACTTCT AT	603	ATGAAC CATGAGT AT	604	TCAATGA ATGTTGA GGTG	605	GCCAGCAGTTTATG GACAGGGGGTGGCT ACACC	606

TCR ID	V α CDR1	SEQ ID NO:	V α CDR2	SEQ ID NO:	V α CDR3	SEQ ID NO:	V β CDR1	SEQ ID NO:	V β CDR2	SEQ ID NO:	V β CDR3	SEQ ID NO:
PN42562	AGTGTTT TTTCCAG C	607	GTAGTTACG GGTGGAGAA GTG	608	GCAGGAGACCCCTCA GGAACCTACAAATAC ATC	609	ATGAAC CATGAGT AT	610	TCAATGA ATGTTGA GGTG	611	GCCAGCAGTCCCGG GACACCTAACTATG GCTACACC	612
PN42610	GACCGAG GTTCCCA GTCC	613	ATATACTCC AATGGTGAC	614	GCCGGGAACTATGGT CAGAAATTTGTC	615	CCTAGAC ACGACA CT	616	TTTTATG AAAAGAT GCAG	617	GCCAGCAGCATCGG ACTTAATCAGCCCC AGCAT	618
PN42654	ACAATCA GTGGAAC TGATTAC	619	GGTCTTACA AGCAAT	620	ATCCTGAGAGACGGC ATCGGTAACCAAGTTCT AT	621	ATGAAC CATGAGT AT	622	TCAATGA ATGTTGA GGTG	623	GCCAGCAGTTTATG GACAGGGGGAGGCT ACACC	624
PN42655	ACAATCA GTGGAAC TGATTAC	625	GGTCTTACA AGCAAT	626	ATCCTGCGGCTTGACA GCTGGGGAAATTCC AG	627	ATGAAC CATGAGT AT	628	TCAATGA ATGTTGA GGTG	629	GCCAGCAGTTTATG GACAGGGGGAGGCT ACACC	630
PN42677	ACAATCA GTGGAAC TGATTAC	631	GGTCTTACA AGCAAT	632	ATCCTGAGAGACGGC ACCGTAACCAAGTTCT AT	633	ATGAAC CATGAGT AT	634	TCAATGA ATGTTGA GGTG	635	GCCAGCAGTTCGAC AGGTACTATGGCT ACACC	636
PN42683	ACAATCA GTGGAAC TGATTAC	637	GGTCTTACA AGCAAT	638	ATCCTGAGAGACCGG GAATATGAAACAAA CTGGTC	639	ATGAAC CATGAGT AT	640	TCAATGA ATGTTGA GGTG	641	GCCAGCAGTTTATG GACAGGGGGCGGCT ACACC	642
PN42689	AGTGTTT TTTCCAG C	643	GTAGTTACG GGTGGAGAA GTG	644	GCAGAAAGATGGAGGA AGCCAAGGAAATCTC ATC	645	TCTGGGC ATGACA CT	646	TATTATG AGGAGGA AGAG	647	GCCAGCAGCTTATC AGACTATGGCTACA CC	648
PN42706	GACTCTG TGAACAA T	649	ATTCCCTCA GGGACA	650	GCTGTGGAGGCCCTCA GGAACCTACAAATAC ATC	651	ATGAAC CATGAGT AT	652	TCAATGA ATGTTGA GGTG	653	GCCAGCAGTTGGGG GACAGGGGGCTATG GCTACACC	654
PN42707	AACAGCG CCTCAGA CTAC	655	ATTCTGTTCA AATATGGAC AAA	656	GCAGAGAAATAAGCGG GATAACTATGTCAG AATTTGTC	657	ATGAAC CATGAGT AT	658	TCAATGA ATGTTGA GGTG	659	GCCAGCAGTTTCTG GGTGAACACTGAAG CTTTC	660
PN42711	GACTCTG TGAACAA T	661	ATTCCCTCA GGGACA	662	GCTGTGGGAGTTCTA ACGGCTACAAAGCTCA GC	663	ATGAAC CATGAGT AT	664	TCAATGA ATGTTGA GGTG	665	GCCAGCAGTCCCGG GACAGGGGGATTTT CACCCCTCCAC	666

TCR ID	V α CDR1	SEQ ID NO:	V α CDR2	SEQ ID NO:	V α CDR3	SEQ ID NO:	V β CDR1	SEQ ID NO:	V β CDR2	SEQ ID NO:	V β CDR3	SEQ ID NO:
PN42712	GACTCTG TGAACAA T	667	ATCCCTCA GGGACA	668	GCTGTGGGAGTTCTA ACGACTACAAAGCTCA GC	669	ATGAAC CATGAGT AT	670	TCAATGA ATGTTGA GGTG	671	GCCAGCAGTCCCGG GACAGGGGGATTTT CACCCCTCCAC	672
PN42746	AACAGCG CCTCAGA CTAC	673	ATTCGTTCA AATATGGAC AAA	674	GCAGAGAAATAGGCAG GATAACTATGCTCAG AATTTTGTG	675	ATGAAC CATGAGT AT	676	TCAATGA ATGTTGA GGTG	677	GCCAGCAGTTTATG GGTTAACACTGAAG CTTTC	678
PN42750	ACAATCA GTGGAAC TGATTAC	679	GGTCTTACA AGCAAT	680	ATCCTGCGGCTTGACA GCTGGGGAAAGTTCC AG	681	ATGGAC CATGAA AAT	682	TCATATG ATGTTAA AATG	683	GCCAGCAGTACCGT GAGGCAGGGGAACT ATGGCTACACC	684
PN42762	ACAATCA GTGGAAC TGATTAC	685	GGTCTTACA AGCAAT	686	ATCCTGAATACCGGCA CTGCCAGTAACTCAC C	687	ATGAAC CATGAGT AT	688	TCAATGA ATGTTGA GGTG	689	GCCAGCAGTTTATC GTCGAACACTGAAG CTTTC	690
PN42774	GACCGAG GTTCCCA GTCC	691	ATATACTCC AATGGTGAC	692	GCCGTGAACAGAGGC ACCGACAAGTCTATC ATC	693	TCTGGGC ATGACA CT	694	TATTATG AGGAGGA AGAG	695	GCCAGCAGCTGGAC AGACTATGGCTACA CC	696
PN42776	ACAATCA GTGGAAC TGATTAC	697	GGTCTTACA AGCAAT	698	ATCCTGCGGCTTGACA GCTGGGGAAATTC AG	699	TCTGGGC ATGACA CT	700	TATTATG AGGAGGA AGAG	701	GCCAGCAGCTGGAC AGACTATGGCTACA CC	702
PN42780	AGTGTTT TTTCCAG C	703	GTAGTTACG GGTGAGAA GTG	704	GCAGGAGGAACCTCA GGAACCTACAAATAC ATC	705	ATGAAC CATGAGT AT	706	TCAATGA ATGTTGA GGTG	707	GCCAGCAGTCCCGG GACACCCAACTATG GCTACACC	708
PN42795	AACAGTG CTTCTCA GTCT	709	GTATACTCC AGTGGTAAT	710	GTGGTGAATGGAGGA AGCCAAGGAAATCTC ATC	711	TCTGGGC ATGACA CT	712	TATTATG AGGAGGA AGAG	713	GCCAGCAGCTAGG GGACTATGGCTACA CC	714
PN42815	AACAGCG CCTCAGA CTAC	715	ATTCGTTCA AATATGGAC AAA	716	GCAGAGAACAACTAT GGTCAGAAATTTGTC ATC	717	ATGAAC CATGAGT AT	718	TCAATGA ATGTTGA GGTG	719	GCCAGCAGTTTATG GGACAGTTCACCCC TCCAC	720
PN42826	AACAGCA TGTTTGA TTAT	721	ATAAGTTCC ATTAAGGAT AAA	722	GCAGCAAGCGCCGGT TCTGCAAGGCAACTG ACC	723	ATGAAC CATGAGT AT	724	TCAATGA ATGTTGA GGTG	725	GCCAGCAGTTTATA CACCCACACTGAAG CTTTC	726

TCR ID	V α CDR1	SEQ ID NO:	V α CDR2	SEQ ID NO:	V α CDR3	SEQ ID NO:	V β CDR1	SEQ ID NO:	V β CDR2	SEQ ID NO:	V β CDR3	SEQ ID NO:
PN42833	ACCATCA GTGGAAA TGAGTAT	727	GGTCTAAAA AACAAAT	728	ATCGTCAGAGACACT ACCTCAGGAACCTAC AAATACATC	729	ATGAAC CATGAGT AT	730	TCAATGA ATGTTGA GGTG	731	GCCAGCAGTTTATC CTCGACAGGTTTTTC ACCCCTCCAC	732
PN42840	AGTGTTT TTTCCAG C	733	GTAGTTACG GGTGGAGAA GTG	734	GCAGAGGGGGAGGA AGCCAAGGAAATCTC ATC	735	TCTGGGC ATGACA CT	736	TATTATG AGGAGGA AGAG	737	GCCAGCAGCTGGAC AGACTATGGCTACA CC	738
PN42845	AGTGTTT TTTCCAG C	739	GTAGTTACG GGTGGAGAA GTG	740	GCAGGGATACGTTCTA ACGACTACAAAGCTCA GC	741	ATGAAC CATGAGT AT	742	TCAATGA ATGTTGA GGTG	743	GCCAGCAGTTCCCTG GACAGCCACACTG AAGCTTTC	744
PN42870	AGTGTTT TTTCCAG C	745	GTAGTTACG GGTGGAGAA GTG	746	GCAGAAAATTTCAGGA GGAGGTGCTGACGGA CTCACC	747	TCTGGGC ATGACA CT	748	TATTATG AGGAGGA AGAG	749	GCCAGCAGCTTCAC AGACTATGGCTACA CC	750
PN42879	AGTGTTT TTTCCAG C	751	GTAGTTACG GGTGGAGAA GTG	752	GCAGGAGAGGACTTT GGAAATGAGAAAATTA ACC	753	TCTGGGC ATGACA CT	754	TATTATG AGGAGGA AGAG	755	GCCAGCAGCTGGGC GGATTATGGCTACA CC	756
PN42888	TCCAGCA ATTTTAT GCC	757	ATGACTTTA AATGGGGAT GAA	758	GCCTTTCTCACCGGTA ACCAGTTCTAT	759	ATGGAC CATGAA AAT	760	TCATATG ATGTTAA AATG	761	GCCAGCAGTACCGT GAGGCAGGGGAACT ATGGCTACAC	762
PN42895	AACAGCA TGTTTGA TTAT	763	ATAAGTTCC ATTAAGGAT AAA	764	GCAGCAAGCGCCGGT TCTGCAAGGCAACTG ACC	765	ATGAAC CATGAGT AT	766	TCAATGA ATGTTGA GGTG	767	GCCAGCAGTTTATG GTCGAACACTGAAG CTTTC	768

Table 8: Amino acid and nucleic acid sequences for VelociT TCRs specific for PRAME (425-433) / HLA-A2

Domain name	Domain Sequences Amino Acid Sequence (SEQ ID NO); CDR1, CDR2, and CDR3 sequences are <u>underlined</u> Nucleic Acid Sequence (SEQ ID NO) ; CDR1, CDR2, and CDR3 sequences are <u>underlined</u>
PN42365 V α	TQLLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLCAANGGSQGNLIFGKGTKLSV KP (SEQ ID NO: 769) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGTGTTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACGGGTG <u>GAGAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA</u> <u>AGGACAGTTCTCTCCACATCACTGCGGCCAGCCTGGTGATACAGGCCTCTA</u> <u>CCTCTGTGCCGCTAATGGAGGAAGCCAAGGAAATCTCATCTTTGGAAAAGGC</u> <u>ACTAACTCTCTGTAAACCA</u> (SEQ ID NO: 770)
PN42365 V β	DAGVTQSPTHLIKTRGQQVTLRCSPKSGHDTVSWYQQALGQGPQFIFQYYEEEE RQRGNFPDRFSGHQFPNYSSELNVNALLLGDSALYLCASSLQDYGYTFGSGTRL TVV (SEQ ID NO: 771) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTCTGGTA CCAACAGGCCCTGGGTCAGGGGCCCCAGTTTATCTTTTCAGTATTATGAGGAG <u>GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAAGTTCC</u> <u>CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTGCTGGGGGACTCGGC</u> <u>CCTCTATCTCTGTGCCAGCAGCTTACAGGACTATGGCTACACCTTCGGTTCGG</u> <u>GGACCAGGTTAACCGTTGTA</u> (SEQ ID NO: 772)
PN42378 V α	DAKTTQPNSMESNEEPPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSTLILHRSTLRDAVYYCILRPDSWGKFQFGAGTQVVVT P (SEQ ID NO: 773) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCCAGGGTCCAGAGTACGTGATTATGGTCTTACAA <u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u> <u>CAGTACCTTGATCCTGCACCGTTCTACCTTGAGAGATGCTGCTGTGTACTACT</u> <u>GCATCCTGCGGCCTGACAGCTGGGGGAAATTCCAGTTTGGAGCAGGGACCCA</u> <u>GGTTGTGGTCACCCCA</u> (SEQ ID NO: 774)
PN42378 V β	DAGVTQSPTHLIKTRGQQVTLRCSPKSGHDTVSWYQQALGQGPQFIFQYYEEEE RQRGNFPDRFSGHQFPNYSSELNVNALLLGDSALYLCASSLQDYGYTFGSGTRL TVV (SEQ ID NO: 775) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTCTGGTA CCAACAGGCCCTGGGTCAGGGGCCCCAGTTTATCTTTTCAGTATTATGAGGAG <u>GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAAGTTCC</u> <u>CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTGCTGGGGGACTCGGC</u>

	CCTCTATCTCTGTGCCAGCAGCTTACAGGACTATGGCTACACCTTCGGTTCGG GGACCAGGTAAACCGTTGTA (SEQ ID NO: 776)
PN42386 V α	TQLEEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLCA ~~TNNGGSQGNLIFGKGTKLSV~~ KP (SEQ ID NO: 777) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAGAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGT ~~TTTTTCCAGCTTACAATGGTAC~~ AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACGGGTG <u>GAGAAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA</u> <u>AGGACAGTTCTCTCCACATCACTGCGGCCCAGCCTGGTGATACAGGCCTCTA</u> <u>CCTCTGTGCCACTAATGGAGGAAGCCAAGGAAATCTCATCTTTGAAAAGGC</u> <u>ACTAAACTCTCTGTAAACCA</u> (SEQ ID NO: 778)
PN42386 V β	DAGVTQSPTHLIKTRGQQVTLRCSPKSGHDTVSWYQQALGQGPQFIFQYEEEE RQRGNFPDRFSGHQFPNYSSSELNVNALLGDSALYLC ~~ASSLQDYGTYFGSGTRL~~ TVV (SEQ ID NO: 779) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTGGTA CCAACAGGCCCTGGGTCAGGGGCCCCAGTTTATCTTTCAGTATTATGAGGAG <u>GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAGTTCC</u> <u>CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTTGCTGGGGGACTCGGC</u> <u>CCTCTATCTCTGTGCCAGCAGCTTACAGGACTATGGCTACACCTTCGGTTCGG</u> <u>GGACCAGGTAAACCGTTGTA</u> (SEQ ID NO: 780)
PN42441 V α	DAKTTQPNMESNEEEPVHLPCHNSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSTLILHRATLRDAAVYYC ~~IRRPGNQFYFGTGTSLTVIP~~ (SEQ ID NO: 781) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTATGTTCTTACAA <u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u> <u>CAGTACCTTGATCCTGCACCGTGCTACCTTGAGAGATGCTGCTGTGTACTACT</u> <u>GCATCAGGCGGCCCGGTAACCAAGTTCTATTTTGGGACAGGGACAAGTTTGAC</u> <u>GGTCATTCCA</u> (SEQ ID NO: 782)
PN42441 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE <u>YTDKGDVPEGYKVSREKERNFPLILESPSPNQTSLYFCASSLWTGSEAFFGQGTR</u> LTVV (SEQ ID NO: 783) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGTACAAAGTCTCTCGAAAA</u> <u>GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACAGACCT</u> <u>CTCTGTACTTCTGTGCCAGCAGTTTATGGACAGGGTCTGAAGCTTTCTTTGGA</u> <u>CAAGGCACCAGACTCACAGTTGTA</u> (SEQ ID NO: 784)
PN42442 V α	TQLEEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLCA ~~AGGTSPTYKYIFGTGTRLKV~~

	LA (SEQ ID NO: 785) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGTTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACTGGTG <u>GAGAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA</u> AGGACAGTTCTCTCCACATCACTGCGGCCCAGCCTGGTGATACAGGCCTCTA CCTCTGTGCAGGAGGGACCTCAGGAACCTACAAATACATCTTTGGAACAGGC ACCAGGCTGAAGGTTTTAGCA (SEQ ID NO: 786)
PN42442 Vβ	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE VTDKGDVPEGYKVSREKERNFPLILESPSPNQTSLYFCASSPGTANYGYTFGSGT RLTVV (SEQ ID NO: 787) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA</u> GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTCCAGGGACAGCTAACTATGGCTACACCTTC GGTTCGGGGACCAGGTAAACCGTTGTA (SEQ ID NO: 788)
PN42450 Vα	AQRVTQPEKLLSVFKGAPVELKCNYSYSGSPELFWYVQYSRQRLQLLLRHISRES IKGFTADLNKGETSFHLKKPFAQEEDSAMYYCALGNTDKLIFGTGTRLQVFP (SEQ ID NO: 789) GCCCAGAGAGTGACTCAGCCCGAGAAGCTCCTCTCTGTCTTTAAAGGGGGCC CAGTGGAGCTGAAGTGCAACTATTCCTATTCTGGGAGTCCTGAACTCTTCTGG TATGTCCAGTACTCCAGACAACGCCTCCAGTTACTCTTGAGACACATCTCTAG <u>AGAGCATCAAAGGCTTCACTGCTGACCTTAACAAAGGCGAGACATCTTTC</u> CACCTGAAGAAACCATTGCTCAAGAGGAAGACTCAGCCATGTATTACTGTG <u>CTCTAGGGAAACCCGACAAGCTCATCTTTGGGACTGGGACCAGATTACAAGT</u> CTTTCCA (SEQ ID NO: 790)
PN42450 Vβ	DVKVTQSSRYLVKRTGEKVFLCVQDMDHENMFWYRQDPGLGLRLIYFSYDVK MKEKGDIEGYSVSREKKERFSLILEASTNQTSMYLCASSSPRTGWYGYTFGSG TRLTVV (SEQ ID NO: 791) GATGTGAAAGTAACCCAGAGCTCGAGATATCTAGTCAAAAGGACGGGAGAG AAAGTTTTTCTGGAATGTGTCCAGGATATGGACCATGAAAATATGTTCTGGTA TCGACAAGACCCAGGTCTGGGGCTACGGCTGATCTATTTCTCATATGATGTTA <u>AAATGAAAGAAAAAGGAGATATTCCTGAGGGGTACAGTGTCTCTAGAGAGA</u> AGAAGGAGCGCTTCTCCCTGATTCTGGAGTCCGCCAGCACCAACCAGACATC TATGTACCTCTGTGCCAGCAGTTCGCCAGGACAGGGTGGTATGGCTACACC TTCGGTTCGGGGACCAGGTAAACCGTTGTA (SEQ ID NO: 792)
PN42455 Vα	DAKTTQPNSMESNEEPPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSTLILHRSTLRDAVVYYCILRPDSWGKFQFGAGTQVVVT P (SEQ ID NO: 793) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTGATGGTCTTACAA

	<u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u> <u>CAGTACCTTGATCCTGCACCGTTCTACCTTGAGAGATGCTGCTGTGTACTACT</u> <u>GCATCCTGCGGCCTGACAGCTGGGGGAAATTCCAGTTTGGAGCAGGGACCCA</u> <u>GTTGTGGTCACCCCA</u> (SEQ ID NO: 794)
PN42455 Vβ	DAGVTQSPTHLIKTRGQQVTLRCSPKSGHDTVSWYQQALGQGPQFIFQYEEEE RQRGNFPDRFSGHQFPNYSSELNVNALLGDSALYLC <u>CASSLV</u> DYGYTFGSGTRL TVV (SEQ ID NO: 795) GACGCTGGAGTCACCCAAAGCCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTCTGGTA CCAACAGGCCCTGGGTCAGGGGCCCCAGTTTATCTTTTCACTATTATGAGGAG <u>GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCACTTCC</u> <u>CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTGCTGGGGGACTCGGC</u> <u>CCTCTATCTCTGTGCCAGCAGCTTGGTGGATTATGGCTACACCTTCGGTTCGG</u> <u>GGACCAGGTTAACCGTTGTA</u> (SEQ ID NO: 796)
PN42476 Vα	DAKTTQPNMESNEEPPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSSTLILHRSTLRDAVYYCILRPDSWGKFQFGAGTQVVVT P (SEQ ID NO: 797) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCC <u>ACAATCAGTGGA</u> ACTGATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTATGTTCTTACAA <u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u> <u>CAGTACCTTGATCCTGCACCGTTCTACCTTGAGAGATGCTGCTGTGTACTACT</u> <u>GCATCCTGCGGCCTGACAGCTGGGGGAAATTCCAGTTTGGAGCAGGGACCCA</u> <u>GTTGTGGTCACCCCA</u> (SEQ ID NO: 798)
PN42476 Vβ	EAQVTQSPRYLITVTGKKLTVTCSQNMDHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVPKEKRSFPLILESPCCSQTPPLYLC <u>CASSLGGV</u> DERLSFGSGT QLSVL (SEQ ID NO: 799) GAAGCCCAAGTGACCCAGAGCCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGGACCATGAGTATATGTCTGGTA TCGACAGGACCCGGGGCTGGGCCTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACAGATAAGGGAGATGTTCTGAAGGGTACAAAGTCCCTCGAAAA</u> <u>GAGAAGAGGAGTTTCCCCCTGATCCTGGAGTCGCCCTGCTGCAGCCAGACCC</u> <u>CTCTGTACCTCTGTGCCAGCAGTTT</u> AGGGGGCGTGGATGAAAGACTGTCTTTT GGCAGTGGAACCCAGCTCTCCGTCTTG (SEQ ID NO: 800)
PN42483 Vα	TQLLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVTTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLC <u>AGDGG</u> SQGNLIFGKGTKLSV KP (SEQ ID NO: 801) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGTTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACGGGTG <u>GAGAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA</u> <u>AGGACAGTTCTCTCCACATCACTGCGGCCAGCCTGGTGATACAGGCCTCTA</u> <u>CCTCTGTGCAGGGGATGGAGGAAGCCAAGGAAATCTCATCTTTGGA</u> AAAGGC ACTAACTCTCTGTAAACCA (SEQ ID NO: 802)

PN42483 V β	EAQVTQSPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVSREKRNFLILESPSPNQTSLYFC<u>ASSLGGGADEKLFFGSGT</u> QLSVL (SEQ ID NO: 803) GAAGCCCAAGTGACCCAGAGCCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA</u> GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCAGCCCCAACCCAGACCT CTCTGTACTTCTGTGCCAGCAGTTTAGGGGGCGCGGATGAAAACTGTTTTT GGCAGTGGAACCCAGCTCTCTGTCTTG (SEQ ID NO: 804)
PN42496 V α	DAKTTQPNMESNEEEPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSTLILHRATLRDAAVYYC<u>ILGQGAQKL</u>VFGQGRITINP (SEQ ID NO: 805) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTCATGGTCTTACAA <u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u> CAGTACCTTGATCCTGCACCGTGCTACCTTGAGAGATGCTGCTGTGTACTACT <u>GCATCCTGGGTCAGGGAGCCCAAGCTGGTATTTGGCCAAGGAACCCAGGCT</u> GACTATCAACCCA (SEQ ID NO: 806)
PN42496 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVSREKRNFLILESPSPNQTSLYFC<u>ASSLWTGGGYTFGSGTR</u> LTVV (SEQ ID NO: 807) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA</u> GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCAGCCCCAACCCAGACCT CTCTGTACTTCTGTGCCAGCAGTTTATGGACAGGGGGCGGCTACACCTTCGGT TCGGGGACCAGGTAAACCGTTGTA (SEQ ID NO: 808)
PN42498 V α	TQLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLC<u>AGDGGSQGNLIFGKGTKLSV</u> KP (SEQ ID NO: 809) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGTTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACGGGTG <u>GAGAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA</u> AGGACAGTTCTCTCCACATCACTGCGGCCAGCCTGGTGATACAGGCCTCTA CCTCTGTGCAGGGGATGGAGGAAGCCAAGGAAATCTCATCTTTGAAAAAGGC ACTAACTCTCTGTAAACCA (SEQ ID NO: 810)
PN42498 V β	DAGVTQSPTHLIKTRGQQTLCRSPKSGHDTVSWYQQALGQGPQFIFQYEEEE RQRGNFPDRFSGHQFPNYSSSELNVNALLLGDSALYLC<u>ASSLVDYGYTFGSGTRL</u> TVV (SEQ ID NO: 811) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG

	CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTGGTA CCAACAGGCCCTGGGTGAGGGGCCCCAGTTTATCTTTTCAGTATTATGAGGAG <u>GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAAGTTCC</u> CTAAGTATAGCTCTGAGCTGAATGTGAACGCCTTGTGCTGGGGGACTCGGC CCTCTATCTCTGTGCCAGCAGCTTGGTGGATTATGGCTACACCTTCGGTTCGG GGACCAGGTTAACCGTTGTA (SEQ ID NO: 812)
PN42558 V α	GIQVEQSPDLILQEGANSTLRNFS<u>DSVNNLQWFHQNPWGQLINLFYIPSGTKQ</u> NGRLSATTVATERYSLLYISSSQTTDSGVYFC<u>VLGGGSQGNLIFGKGTKLSVKP</u> (SEQ ID NO: 813) GGAATACAAGTGGAGCAGAGTCCTCCAGACCTGATTCTCCAGGAGGGAGCC AATTCACGCTGCGGTGCAATTTTTCTGACTCTGTGAACAATTTGCAGTGGTT TCATCAAAACCCCTGGGGACAGCTCATCAACCTGTTTTACATTCCTCAGGGA <u>CAAAACAGAATGGAAGATTAAGCGCCACGACTGTCGCTACGGAACGCTACA</u> GCTTATTGTACATTTCTCTTCCCAGACCACAGACTCAGGCGTTTATTTCTGT <u>GTCTAGGGGGAGGAAGCCAAGGAAATCTCATCTTTGAAAAGGCACTAAA</u> CTCTCTGTAAACCA (SEQ ID NO: 814)
PN42558 V β	DAGVTQSPTHLIKTRGQQVTLRCSKSGHDTVSWYQQALGQGPQFIFQYEEEE RQRGNFPDRFSGHQFPNYSSSELNVNALLGDSALYLC<u>CASFTDYGYTFGSGTRLT</u> VV (SEQ ID NO: 815) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTGGTA CCAACAGGCCCTGGGTGAGGGGCCCCAGTTTATCTTTTCAGTATTATGAGGAG <u>GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAAGTTCC</u> CTAAGTATAGCTCTGAGCTGAATGTGAACGCCTTGTGCTGGGGGACTCGGC CCTCTATCTCTGTGCCAGCAGCTTACAGACTATGGCTACACCTTCGGTTCGG GGACCAGGTTAACCGTTGTA (SEQ ID NO: 816)
PN42561 V α	DAKTTQPNMESNEEPPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSSTLILHRATLRDAAVYYCILRDGTGNQFYFGTGTSLTVIP (SEQ ID NO: 817) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTATGGTCTTACAA <u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u> CAGTACCTTGATCCTGCACCGTGCTACCTTGAGAGATGCTGCTGTGTACTACT <u>GCATCCTGAGAGACGGGACCGGTAACCAAGTTCTATTTGGGACAGGGACAAG</u> TTTGACGGTCATTCCA (SEQ ID NO: 818)
PN42561 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE <u>YTDKGDVPEGYKVS</u>RKEKNRFLILESPSPNQTSLYFC<u>ASSLWTGGGYTFGSGTR</u> LTVV (SEQ ID NO: 819) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTTGAAGGTACAAAGTCTCTCGAAA</u> GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCAGCCCCAACCAAGACCT CTCTGTACTTCTGTGCCAGCAGTTTATGGACAGGGGGTGGCTACACCTTCGGT

	TCGGGGACCAGGTTAACCGTTGTA (SEQ ID NO: 820)
PN42562 V α	TQLLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLCAGGPPSGTYKYIFGTGTRLKV LA (SEQ ID NO: 821) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGTTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACGGGTG GAGAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA AGGACAGTTCTCTCCACATCACTGCGGCCCAGCCTGGTGATACAGGCCTCTA CCTCTGTGCAGGAGGACCTCAGGAACCTACAAATACATCTTTGGAACAGGC ACCAGGCTGAAGGTTTTAGCA (SEQ ID NO: 822)
PN42562 V β	EAQVTQNPRYLITVTGKKLTVTCNQNMNHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVSREKERNFLILESPSPNQTSLYFCASSPGTPNYGYTFGSGT RLTVV (SEQ ID NO: 823) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTCTCAGAATATGAACCATGAGTATATGTCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACCCAGACCT CTCTGTACTTCTGTGCCAGCAGTCCCGGGACACCTAACTATGGCTACACCTTC GGTTCGGGGACCAGGTTAACCGTTGTA (SEQ ID NO: 824)
PN42610 V α	QKEVEQNSGPLSVPEGAIASLNCTYSDRGSSQFFWYRQYSGKSPELIMSIYSNGD KEDGRFTAQLNKASQYVSLLRDSQPSDSATYLCAGNYGQNFVFGPGRTRLSVP (SEQ ID NO: 825) CAGAAGGAGGTGGAGCAGAATTCTGGACCCCTCAGTGTTCCAGAGGGAGCC ATTGCCTCTCTCAACTGCACCTACAGTGACCGAGGTCCCGAGTCCCTTCTCTG GTACAGACAATATTCTGGGAAAAGCCCTGAGTTGATAATGTCCATATACTCC AATGGTGACAAAGAAGATGGAAGGTTTACAGCACAGCTCAATAAAGCCAGC CAGTATGTTTCTCTGCTCATCAGAGACTCCCAGCCCAGTGATTCAGCCACCTA CCTCTGTGCCGGGAACCTATGGTCAGAATTTTGTCTTTGGTCCCGGAACCAGAT TGTCCGTGCTGCCC (SEQ ID NO: 826)
PN42610 V β	AAGVIQSPRHLIKEKRETATLKCYPPIRHDTVYWYQQGPGQDPQFLISFYEKMQS DKGSIPDRFSAQQFSDYHSELNMSSELGDSALYFCASSIGLNQPHFGDGTLSI L (SEQ ID NO: 827) GCTGCTGGAGTCATCCAGTCCCCAAGACATCTGATCAAAGAAAAAGAGGGAA ACAGCCACTCTGAAATGCTATCCTATCCCTAGACACGACACTGTCTACTGGTA CCAGCAGGTCCAGGTCAGGACCCCCAGTTCCTCATTTCGTTTTATGAAAAG ATGCAGAGCGATAAAGGAAGCATCCCTGATCGATTCTCAGCTCAACAGTTCA GTGACTATCATTCTGAACTGAACATGAGCTCCTTGGAGCTGGGGGACTCAGC CCTGTACTTCTGTGCCAGCAGCATCGGACTTAATCAGCCCCAGCATTTTGGTG ATGGGACTCGACTCTCCATCCTA (SEQ ID NO: 828)
PN42654 V α	DAKTTQPNSMESNEEEPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSTLILHRATLRDAAVYYCILRDGIGNQFYFGTGTSLTVIP (SEQ ID NO: 829)

	GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTATGGTCTTACAA <u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u> CAGTACCTTGATCCTGCACCGTGCTACCTTGAGAGATGCTGCTGTGTACTACT GCATCCTGAGAGACGGCATCGGTAACCAGTTCTATTTGGGACAGGGACAAG TTTGACGGTCATTCCA (SEQ ID NO: 830)
PN42654 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE VTDKGDVPEGYKVSREKRNFLILESPSPNQTSLYFCASSLWTGGGYTFGSGTR LTVV (SEQ ID NO: 831) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA</u> GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTTTATGGACAGGGGGAGGCTACACCTTCGGT TCGGGGACCAGGTTAACCGTTGTA (SEQ ID NO: 832)
PN42655 V α	DAKTTQPNSMESNEEEPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSSTLILHRSTLRDAAVYYCILRPDSWGKFQFGAGTQVVVT P (SEQ ID NO: 833) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTATGGTCTTACAA <u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u> CAGTACCTTGATCCTGCACCGTTCTACCTTGAGAGATGCTGCTGTGTACTACT GCATCCTGCGGCCTGACAGCTGGGGGAAATTCCAGTTTGAGACAGGGGACCCA GGTTGTGGTCACCCCA (SEQ ID NO: 834)
PN42655 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE VTDKGDVPEGYKVSREKRNFLILESPSPNQTSLYFCASSLWTGGGYTFGSGTR LTVV (SEQ ID NO: 835) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA</u> GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTTTATGGACAGGGGGAGGCTACACCTTCGGT TCGGGGACCAGGTTAACCGTTGTA (SEQ ID NO: 836)
PN42677 V α	DAKTTQPNSMESNEEEPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSSTLILHRATLRDAAVYYCILRDGTGNQFYFGTGTSLTVIP (SEQ ID NO: 837) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTATGGTCTTACAA <u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u>

	CAGTACCTTGATCCTGCACCGTGCTACCTTGAGAGATGCTGCTGTGTACTACT GCATCCTGAGAGACGGCACCGGTAACCAGTTCTATTTGGGACAGGGACAAG TTTGACGGTCATTCCA (SEQ ID NO: 838)
PN42677 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVSKEKRNFLILESPSPNQTSLYFCASSSTGYGYTFGSGTR LTVV (SEQ ID NO: 839) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTTTCGACAGGGTACTATGGCTACACCTTCGGT TCGGGGACCAGGTTAACCGTTGTA (SEQ ID NO: 840)
PN42683 V α	DAKTTQPNSMESNEEPPVHLPCHNSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSSTLILHRATLRDAAVYYCILRDREYGNKLVFGAGTILRVK S (SEQ ID NO: 841) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTGATGGTCTTACAA GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC CAGTACCTTGATCCTGCACCGTGCTACCTTGAGAGATGCTGCTGTGTACTACT GCATCCTGAGAGACCGGGAATATGGAAACAACTGGTCTTTGGCGCAGGAA CCATTCTGAGAGTCAAGTCC (SEQ ID NO: 842)
PN42683 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVSKEKRNFLILESPSPNQTSLYFCASSLWTGGGYTFGSGTR LTVV (SEQ ID NO: 843) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTTTATGGACAGGGGGCGGCTACACCTTCGGT TCGGGGACCAGGTTAACCGTTGTA (SEQ ID NO: 844)
PN42689 V α	TQLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLCAEDGGSQGNLIFGKGTKLSV KP (SEQ ID NO: 845) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGTTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACGGGTG GAGAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA AGGACAGTTCTCTCCACATCACTGCGGCCAGCCTGGTGATACAGGCCTCTA CCTCTGTGCAGAAGATGGAGGAAGCCAAGGAAATCTCATCTTTGGAAAAGGC ACTAACTCTCTGTAAACCA (SEQ ID NO: 846)
PN42689	DAGVTQSPTHLIKTRGQQVTLRCSPKSGHDTVSWYQQALGQGPQFIFQYEEEE

Vβ	RQRGNFPDRFSGHQFPNYSSELNVNALLLGDSALYLC<u>ASSLS</u>DYGYTFGSGTRLT VV (SEQ ID NO: 847) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTTGTA CCAACAGGCCCTGGGTCAGGGGCCCCAGTTTATCTTTAGTATTATGAGGAG <u>GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAGTTCC</u> CTAAGTATAGCTCTGAGCTGAATGTGAACGCCTTGTTGCTGGGGGACTCGGC CCTCTATCTCTGTGCCAGCAGCTTATCAGACTATGGCTACACCTTCGGTTCGG GGACCAGGTTAACCGTTGTA (SEQ ID NO: 848)
PN42706 Vα	GIQVEQSPDLILQEGANSTLRNFSDSVNNLQWFHQNPWGQLINLFYIPSGTKQ NGRLSATTVATERYSLLYISSQTTDSGVYFC<u>AVEAS</u>GTYYKIFGTGTRLKVL A (SEQ ID NO: 849) GGAATACAAGTGGAGCAGAGTCCTCCAGACCTGATTCTCCAGGAGGGAGCC AATTCCACGCTGCGGTGCAATTTTTCTGACTCTGTGAACAATTTGCAGTGTT TCATCAAAACCCCTGGGGACAGCTCATCAACCTGTTTTACATTCCTCAGGGA <u>CAAAACAGAATGGAAGATTAAGCGCCACGACTGTCGCTACGGAACGCTACA</u> GCTTATTGTACATTTCTCTTCCCAGACCACAGACTCAGGCGTTTATTTCTGT <u>GCTGTGGAGGCCTCAGGAACCTACAAATACATCTTTGGAACAGGCACCAGGC</u> TGAAGGTTTTAGCA (SEQ ID NO: 850)
PN42706 Vβ	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYY<u>SMNVE</u> <u>YTDKGDVPEGYKVS</u>RKEKRNFLILESPSPNQTSLYFC<u>ASSWG</u>TGGYGYTFGSGT RLTVV (SEQ ID NO: 851) GAAGCCCAAGTGACCCAGAACCCAAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTCTCAGAATATGAACCATGAGTATATGTCTTGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA</u> GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTTGGGGGACAGGGGGCTATGGCTACACCTT CGGTTTCGGGGACCAGGTTAACCGTTGTA (SEQ ID NO: 852)
PN42707 Vα	GESVGLHLPTLSVQEGDNSIINCAYSNSASDYFIWYKQESGKGPQFIID<u>IRSNMDK</u> RQGQRVTVLLNKTVKHLSLQIAATQPGDSAVYFC<u>AENKRDNYGQNFV</u>FGPGTR LSVLP (SEQ ID NO: 853) GGAGAGAGTGTGGGGCTGCATCTTCTACCCTGAGTGTCCAGGAGGGTGACA ACTCTATTATCAACTGTGCTTATTCAAACAGCGCCTCAGACTACTTCATTTGG TACAAGCAAGAATCTGGAAAAGGTCTCAATTCATTATAGACATTCGTTCAA <u>ATATGGACAAAAGGCAAGGCCAAAGAGTCACCGTTTTATTGAATAAGACAGT</u> GAAACATCTCTCTCTGCAAATTGCAGCTACTCAACCTGGAGACTCAGCTGTCT ACTTTGTGCAGAGAATAAGCGGGATAACTATGGTCAGAATTTGTCTTTGTT CCCGGAACCAGATTGTCCGTGCTGCCC (SEQ ID NO: 854)
PN42707 Vβ	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYY<u>SMNVE</u> <u>YTDKGDVPEGYKVS</u>RKEKRNFLILESPSPNQTSLYFC<u>ASSFW</u>VNTEAFGQGTR LTVV (SEQ ID NO: 855) GAAGCCCAAGTGACCCAGAACCCAAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTCTCAGAATATGAACCATGAGTATATGTCTTGTA

	TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA</u> GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTTTCTGGGTGAACACTGAAGCTTTCTTTGGA CAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 856)
PN42711 V α	GIQVEQSPPDLILQEGVNSTLRNFS <u>DSVNNLQWFHQNPWGQLINLFYIPSGTKQ</u> NGRLSATTVATERYSLLYISSRTTDSGVYFC <u>AVGSSNGYKLSFGAGTTVTVRA</u> (SEQ ID NO: 857) GGAATACAAGTGGAGCAGAGTCCTCCAGACCTGATTCTCCAGGAGGGAGTCA ATTCCACGCTGCGGTGCAATTTTTCTGACTCTGTGAACAATTTGCAGTGGTTT CATCAAAACCCCTTGGGGACAGCTCATCAACCTGTTTTACATTCCCTCAGGGAC <u>AAAACAGAATGGAAGATTAAGCGCCACGACTGTGGCTACGGAACGCTACAG</u> <u>CTTATTGTACATTTCTCTTCCCGGACCACAGACTCAGGCGTTTATTTCTGTGC</u> <u>TGTGGGGAGTTCTAACGGCTACAAGCTCAGCTTTGGAGCTGGAACACAGTA</u> ACTGTAAGAGCA (SEQ ID NO: 858)
PN42711 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE <u>YTDKGDVPEGYKVSREKRNFLILESPSPNQTSLYFCASSPGTGGFSPLHFGNGT</u> RLTVT (SEQ ID NO: 859) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGAAGTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA</u> GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTCCCGGGACAGGGGGATTTTACCCCTCCAC TTTGGGAACGGGACCAGGCTCACTGTGACA (SEQ ID NO: 860)
PN42712 V α	GIQVEQSPPDLILQEGANSTLRNFS <u>DSVNNLQWFHQNPWGQLINLFYIPSGTKQ</u> NGRLSATTVATERYSLLYISSQTDSGVYFC <u>AVGSSNDYKLSFGAGTTVTVRA</u> (SEQ ID NO: 861) GGAATACAAGTGGAGCAGAGTCCTCCAGACCTGATTCTCCAGGAGGGAGCC AATTCCACGCTGCGGTGCAATTTTTCTGACTCTGTGAACAATTTGCAGTGGTT TCATCAAAACCCCTTGGGGACAGCTCATCAACCTGTTTTACATTCCCTCAGGGA <u>CAAAACAGAATGGAAGATTAAGCGCCACGACTGTCGCTACGGAACGCTACA</u> <u>GCTTATTGTACATTTCTCTTCCAGACCACAGACTCAGGCGTTTATTTCTGT</u> <u>GCTGTGGGGAGTTCTAACGACTACAAGCTCAGCTTTGGAGCCGGAACACAG</u> TAACTGTAAGAGCA (SEQ ID NO: 862)
PN42712 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE <u>YTDKGDVPEGYKVSREKRNFLILESPSPNQTSLYFCASSPGTGGFSPLHFGNGT</u> RLTVT (SEQ ID NO: 863) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGAAGTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA</u> GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTCCCGGGACAGGGGGATTTTACCCCTCCAC TTTGGGAACGGGACCAGGCTCACTGTGACA (SEQ ID NO: 864)

PN42746 V α	GESVGLHLPTLSVQEGDNSIINCAYSNSASDYFIWYKQESGKGPQFIIDIRSNMDK RQGQRVTVLLNKTVKHLSLQIAATQPGDSAVYFCAENRQDNYGQNFVFGPGTR LSVLP (SEQ ID NO: 865) GGAGAGAGTGTGGGGCTGCATCTTCCTACCCTGAGTGTCCAGGAGGGTGACA ACTCTATTATCAACTGTGCTTATTCAAACAGCGCCTCAGACTACTTCATTTGG TACAAGCAAGAATCTGGAAAAGGTCCTCAATTCATTATAGACATTCGTTCAA ATATGGACAAAAGGCAAGGCCAAAGAGTCACCGTTTTATTGAATAAGACAGT GAAACATCTCTCTCTGCAAATTGCAGCTACTCAACCTGGAGACTCAGCTGTCT ACTTTTGTGCAGAGAATAGGCAGGATAACTATGGTCAGAATTTTGTCTTTGGT CCCGGAACCAGATTGTCCGTGCTGCCC (SEQ ID NO: 866)
PN42746 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVSREKERNFPLILESPSNQTSLYFCASSLWVNTEAFFGQGTR LTVV (SEQ ID NO: 867) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCAGCCCCAACCCAGACCT CTCTGTACTTCTGTGCCAGCAGTTTATGGGTAACTGAAGCTTCTTTGGA CAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 868)
PN42750 V α	DAKTTQPNMESNEEEPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSSTLILHRSTLRDAAVYYCILRPDSWGKFQFGAGTQVVVT P (SEQ ID NO: 869) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTCATGGTCTTACAA GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC CAGTACCTTGATCCTGCACCGTTCTACCTTGAGAGATGCTGCTGTGTACTACT GCATCCTGCGGCCTGACAGCTGGGGGAAGTTCCAGTTTGAGACAGGGACCCA GGTTGTGGTCACCCCA (SEQ ID NO: 870)
PN42750 V β	DVKVTQSSRYLVKRTGEKVFLFCVQDMDHENMFWYRQDPGLGLRLIYFSYDVK MKEKGDIPGYSVSREKKERFSLILESASTNQTSMYLCASSTVRQGNYGTYFGSG TRLTVV (SEQ ID NO: 871) GATGTGAAAGTAACCCAGAGCTCGAGATATCTAGTCAAAAGGACGGGAGAG AAAGTTTTCTGGAATGTGTCCAGGATATGGACCATGAAAATATGTTCTGGTA TCGACAAGACCCAGGTCTGGGGCTACGGCTGATCTATTTCTCATATGATGTTA AAATGAAAGAAAAAGGAGATATTCCTGAGGGGTACAGTGTCTCTAGAGAGA AGAAGGAGCGCTTCTCCCTGATTCTGGAGTCCGCCAGCACCAACCAGACATC TATGTACCTCTGTGCCAGCAGTACCGTGAGGCAGGGGAAGTATGGCTACACC TTCGGTTCGGGGACCAGGTTAACCGTTGTA (SEQ ID NO: 872)
PN42762 V α	DAKTTQPNMESNEEEPVHLPCNHSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSSTLILHRATLRDAAVYYCILTGTASKLTFGTGTRLQVTL (SEQ ID NO: 873)

	GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTATGGTCTTACAA <u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u> <u>CAGTACCTTGATCCTGCACCGTGCTACCTTGAGAGATGCTGCTGTGTACTACT</u> <u>GCATCCTGAATACCGGCACTGCCAGTAACTCACCTTTGGGACTGGAACAAG</u> ACTTCAGGTCACGCTC (SEQ ID NO: 874)
PN42762 V β	EAQVTQNPRLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVSREKRNFLILESPSPNQTSLYFC <u>ASSLSSNTEAFFGQGTRL</u> TVV (SEQ ID NO: 875) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA</u> <u>GAGAAGAGGAATTTCCCTGATCCTGGAGTCGCCAGCCCCAACAGACCT</u> <u>CTCTGTACTTCTGTGCCAGCAGTTTATCGTCGAACACTGAAGCTTTCTTTGGA</u> CAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 876)
PN42774 V α	QKEVEQNSGPLSVPEGAIASLNCTYSDRGSQSFFWYRQYSGKSPELIMSIYSNGD KEDGRFTAQLNKASQYVSLLRDSQPSDSATYLC <u>AVNRGTDKLI</u> FGTGTRLQVFP (SEQ ID NO: 877) CAGAAGGAGGTGGAGCAGAATTCTGGACCCCTCAGTGTTCCAGAGGGAGCC ATTGCCTCTCTCAACTGCACCTACAGTGACCGAGGTTCCTCCTTCTG GTACAGACAATATTCTGGGAAAAGCCCTGAGTTGATAATGTCCATATACTCC <u>AATGGTGACAAAGAAGATGGAAGGTTTACAGCACAGCTCAATAAAGCCAGC</u> <u>CAGTATGTTTCTCTGCTCATCAGAGACTCCCAGCCCAGTGATTACGCCACCTA</u> <u>CCTCTGTGCCGTGAACAGAGGCCACCGACAAGCTCATCTTTGGGACTGGGACC</u> AGATTACAAGTCTTTCCA (SEQ ID NO: 878)
PN42774 V β	DAGVTQSPTHLIKTRGQQVTLRCSKPSGHDTVSWYQQALGQGPQFIFQYEEEE RQRGNFPDRFSGHQFPNYSELNVNALLLGDSALYLC <u>CASSWTDYGYTF</u> SGSRTL TVV (SEQ ID NO: 879) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTTGTA CCAACAGGCCCTGGGTACAGGGGCCCCAGTTTATCTTTAGTATTATGAGGAG <u>GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAGTTCC</u> <u>CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTTGCTGGGGGACTCGGC</u> <u>CCTCTATCTCTGTGCCAGCAGCTGGACAGACTATGGCTACACCTTCGGTTCCG</u> GGACCAGGTTAACCGTTGTA (SEQ ID NO: 880)
PN42776 V α	DAKTTQPNSMESNEEPPVHLPNHNSTISGTDYIHWYRQLPSQGPEYVIHGLTSNV NNRMASLAIAEDRKSSTLILHRSTLRDAVYYC <u>LIRPDSWGKFQ</u> FGAGTQVVVT P (SEQ ID NO: 881) GATGCTAAGACCACACAGCCAAATTCAATGGAGAGTAACGAAGAAGAGCCT GTTCACTTGCCTTGTAACCACTCCACAATCAGTGGAAGTATTACATACATTG GTATCGACAGCTTCCCTCCAGGGTCCAGAGTACGTGATTATGGTCTTACAA <u>GCAATGTGAACAACAGAATGGCCTCTCTGGCAATCGCTGAAGACAGAAAGTC</u> <u>CAGTACCTTGATCCTGCACCGTTCTACCTTGAGAGATGCTGCTGTGTACTACT</u>

	GCATCCTGCGGCCTGACAGCTGGGGGAAATTCCAGTTTGGAGCAGGGACCCA GGTTGTGGTCACCCCA (SEQ ID NO: 882)
PN42776 V β	DAGVTQSPTHLIKTRGQQVTLRCSPKSGHDTVSWYQQALGQGPQFIFQYEEEE RQRGNFPDRFSGHQFPNYSSELNVNALLLGDSALYLCASSWTDYGYTFGSGTRL TVV (SEQ ID NO: 883) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTCTGGTA CCAACAGGCCCTGGGTCAGGGGCCCCAGTTTATCTTTTCAGTATTATGAGGAG GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAAGTTCC CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTTGCTGGGGGACTCGGC CCTCTATCTCTGTGCCAGCAGCTGGACAGACTATGGCTACACCTTCGGTTCCGG GGACCAGGTTAACCGTTGTA (SEQ ID NO: 884)
PN42780 V α	TQLLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLCAGGTSQTYKYIFGTGTRLKV LA (SEQ ID NO: 885) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGTCTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACGGGTG GAGAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA AGGACAGTTCTCTCCACATCACTGCGGCCAGCCTGGTGATACAGGCCCTCTA CCTCTGTGCAGGAGGAACCTCAGGAACCTACAAATACATCTTTGGAACAGGC ACCAGGCTGAAGGTTTTAGCA (SEQ ID NO: 886)
PN42780 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVSREKEKRNFLILESPSPNQTSLYFCASSPGTPNYGYTFGSGT RLTVV (SEQ ID NO: 887) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACCCAGACCT CTCTGTACTTCTGTGCCAGCAGTCCCGGGACACCCAACCTATGGCTACACCTTC GGTTCGGGGACCAGGTTAACCGTTGTA (SEQ ID NO: 888)
PN42795 V α	RKEVEQDPGPFNVPEGATVAFNCTYSNSASQSFFWYRQDCRKEPKLLMSVYSSG NEDGRFTAQLNRASQYISLLIRDSKLSDSATYLCVVNGGSQGNLIFGKGTKLSVK P (SEQ ID NO: 889) CGGAAGGAGGTGGAGCAGGATCCTGGACCCTTCAATGTTCCAGAGGGAGCC ACTGTGCTTTCAACTGTACTTACAGCAACAGTGCTTCTCAGTCTTTCTTCTG GTACAGACAGGATTGCAGGAAAGAACCTAAGTTGCTGATGTCCGTATACTCC AGTGGTAATGAAGATGGAAGGTTTACAGCACAGCTCAATAGAGCCAGCCAG TATATTTCCCTGCTCATCAGAGACTCCAAGCTCAGTGATTACGCCACCTACCT CTGTGTGGTGAATGGAGGAAGCCAAGGAAATCTCATCTTTGGAAAAGGCACT AACTCTCTGTAAACCA (SEQ ID NO: 890)
PN42795 V β	DAGVTQSPTHLIKTRGQQVTLRCSPKSGHDTVSWYQQALGQGPQFIFQYEEEE RQRGNFPDRFSGHQFPNYSSELNVNALLLGDSALYLCASSVGDYGYTFGSGTRL

	TVV (SEQ ID NO: 891) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTGGTA CCAACAGGCCCTGGGTGAGGGGCCCCAGTTTATCTTTCAGTATTATGAGGAG <u>GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAGTTCC</u> CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTGTGTTGGGGGACTCGGC CCTCTATCTCTGTGCCAGCAGCGTAGGGGACTATGGCTACACCTTCGGTTCGG GGACCAGGTTAACCGTTGTA (SEQ ID NO: 892)
PN42815 V α	GESVGLHPLTLSVQEGDNSIINCAYSNSASDYFIWYKQESGKGPPQFIIDIRSNMDK RQGQRVTVLLNKTVKHLSLQIAATQPGDSAVYFCAENNYGQNFVFGPGRLSVL P (SEQ ID NO: 893) GGAGAGAGTGTGGGGCTGCATCTTCTACCCTGAGTGTCCAGGAGGGTGACA ACTCTATTATCAACTGTGCTTATTCAAACAGCGCCTCAGACTACTTCATTTGG TACAAGCAAGAATCTGGAAAAGGTCCTCAATTCATTATAGACATTCGTTCAA <u>ATATGGACAAAAGGCAAGGCCAAAGAGTCACCGTTTTATTGAATAAGACAGT</u> <u>GAAACATCTCTCTGCAAATTGCAGCTACTCAACCTGGAGACTCAGCTGTCT</u> <u>ACTTTTGTGCAGAGAACAACCTATGGTCAGAATTTTGTCTTTGGTCCCGGAACC</u> AGATTGTCCGTGCTGCCC (SEQ ID NO: 894)
PN42815 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVSREKRNFLILESPSPNQTSLYFCASSLWDSSPLHFGNGTR LTVT (SEQ ID NO: 895) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTCTCAGAATATGAACCATGAGTATATGTCTCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTGACTGATAAGGGAGATGTTCTGAAGGTACAAAGTCTCTCGAAAA</u> <u>GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCAGCCCCAACACGACCT</u> <u>CTCTGTACTTCTGTGCCAGCAGTTTATGGGACAGTTCACCCCTCCACTTTGGG</u> AACGGGACCAGGCTCACTGTGACA (SEQ ID NO: 896)
PN42826 V α	DQQVKQNSPSLSVQEGRISILNCDYTNSMFDYFLWYKKYPAEGPTFLISISSIKDK NEDGRFTVFLNKS AKHLSLHIVPSQPGDSAVYFCAASAGSARQLTFGSGTQLTVL P (SEQ ID NO: 897) GACCAGCAAGTTAAGCAAAATTCACCATCCCTGAGCGTCCAGGAAGGAAGA ATTTCTATTCTGAACTGTGACTATACTAACAGCATGTTTGATTATTTCTATGG TACAAAAAATACCCTGCTGAAGGTCTACATTCTGATATCTATAAGTTCCAT <u>TAAGGATAAAAATGAAGATGGAAGATTCAGTGTCTTCTTAAACAAAAGTGCC</u> <u>AAGCACCTCTCTCTGCACATTGTGCCCTCCCAGCCTGGAGACTCTGCAGTGTA</u> <u>CTTCTGTGCAGCAAGCGCCGTTCTGCAAGGCAACTGACCTTTGGATCTGGG</u> ACACAATTGACTGTTTTACCT (SEQ ID NO: 898)
PN42826 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE YTDKGDVPEGYKVSREKRNFLILESPSPNQTSLYFCASSLYTHTEAFFGQGTR LTVV (SEQ ID NO: 899) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTCTCAGAATATGAACCATGAGTATATGTCTCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT

	<u>GAGGTG</u> ACTGATAAGGGAGATGTTCTCTGAAGGGTACAAAGTCTCTCGAAAA GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACCCAGACCT CTCTGTACTTCTGTGCCAGCAGTTTATACACCCACACTGAAGCTTTCTTTGGA CAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 900)
PN42833 V α	DAKTTQPPSMDCAEGRAANLPCNHSTISGNEYVYWYRQIHSQGPQYIIHGLKNN ETNEMASLIITEDRKSSSTLILPHATLRDТАVYYCIVRDТTSГTYKYIFGTGTRLKV LA (SEQ ID NO: 901) GATGCTAAGACCACCCAGCCCCCTCCATGGATTGCGCTGAAGGAAGAGCTG CAAACCTGCCTTGTAATCACTCTACCATCAGTGGAATGAGTATGTGTATTGG TATCGACAGATTCACTCCCAGGGGCCACAGTATATCATTCATGGTCTAAAAA <u>ACAATG</u> AAACCAATGAAATGGCCTCTCTGATCATCACAGAAGACAGAAAGTC CAGCACCTTGATCCTGCCCCACGCTACGCTGAGAGACACTGCTGTGTACTATT GCATCGTCAGAGACACTACCTCAGGAACCTACAAATACATCTTTGGAACAGG CACCAGGCTGAAGGTTTTAGCA (SEQ ID NO: 902)
PN42833 V β	EAQVTQNPRYLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE <u>YTDKGDV</u> PEGYKVSРKEKRNFLILESPSPNQTSLYFC <u>ASSLSSTGF</u> SPLHFGNGT RLTVT (SEQ ID NO: 903) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCTTGGA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT <u>GAGGTG</u> ACTGATAAGGGAGATGTTCTCTGAAGGGTACAAAGTCTCTCGAAAA GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCCAGCCCCAACCCAGACCT CTCTGTACTTCTGTGCCAGCAGTTTATCCTCGACAGGTTTTTACCCTCCACT TTGGGAACGGGACCAGGCTCACTGTGACA (SEQ ID NO: 904)
PN42840 V α	TQLLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLC <u>AEGGGSQGNL</u> IFGKGTKLSV KP (SEQ ID NO: 905) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGTTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACGGGTG <u>GAGAAGTGA</u> AGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA AGGACAGTTCTCTCCACATCACTGCGGCCAGCCTGGTGATACAGGCCTCTA CCTCTGTGCAGAGGGGGGAGGAAGCCAAGGAAATCTCATCTTTGGAAGAGG CACTAAACTCTCTGTТАAACCA (SEQ ID NO: 906)
PN42840 V β	DAGVTQSPTHLIKTRGQQVTLRCSPKSGHDTVSWYQQALGQGPQFIFQYEEEE RQRGNFPDRFSGHQFPNYSSSELNVNALLGDSALYLC <u>ASSWTDYGYT</u> FGSGTRL TVV (SEQ ID NO: 907) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTTGGA CCAACAGGCCCTGGGTCAGGGGCCCCAGTTTATCTTTCACTATTATGAGGAG <u>GAAGAG</u> AGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAGTTCC CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTTGCTGGGGGACTCGGC CCTCTATCTCTGTGCCAGCAGCTGGACAGACTATGGCTACACCTTCGGTTCGG GGACCAGGTTAACCGTTGTA (SEQ ID NO: 908)

PN42845 V α	TQLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLCAGIRSNDYKLSFGAGTTTVT RA (SEQ ID NO: 909) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAGAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGTTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACGGGTG GAGAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA AGGACAGTTCTCTCCACATCACTGCGGCCAGCCTGGTGATACAGGCCTCTA CCTCTGTGCAGGGATACGTTCTAACGACTACAAGCTCAGCTTTGGAGCCGGA ACCACAGTAACTGTAAGAGCA (SEQ ID NO: 910)
PN42845 V β	EAQVTQNPRYLITVTGKKLTVTCQNMMNHEYMSWYRQDPGLGLRQIYYSMNVE VTDKGDVPEGYKVSREKERNFPLILESPSNQTSLYFCASSWTAHTEAFFGQGT RLTVV (SEQ ID NO: 911) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCAGTGACTGGAAAG AAGTTAACAGTGACTTGTCTCAGAATATGAACCATGAGTATATGTCCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT GAGGTGACTGATAAGGGAGATGTTCTGAAGGGTACAAAGTCTCTCGAAAA GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTTCTGACAGCCACACTGAAGCTTTCTTT GGACAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 912)
PN42870 V α	TQLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLC AENSGGGADGLTFGKGTHLII QP (SEQ ID NO: 913) ACCCAGCTGCTGGAGCAGAGCCCTCAGTTTCTAAGCATCCAAGAGGGAGAGAAA ATCTCACTGTGTACTGCAACTCCTCAAGTGTTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCCTGTCCTCCTGGTGACAGTAGTTACGGGTG GAGAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA AGGACAGTTCTCTCCACATCACTGCGGCCAGCCTGGTGATACAGGCCTCTA CCTCTGTGCAGAAAATTCAGGAGGAGGTGCTGACGGACTCACCTTTGGCAA GGGACTCATCTAATCATCCAGCCC (SEQ ID NO: 914)
PN42870 V β	DAGVTQSPTHLIKTRGQQVTLRCSPKSGHDTVSWYQQALGQGPQFIFQYEEEE RQRGNFPDRFSGHQFPNYSELNVNALLLGDSALYLCASSFTDYGTYFGSGTRLT VV (SEQ ID NO: 915) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGACTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTGGTA CCAACAGGCCCTGGGTCAGGGGCCAGTTTATCTTTCAGTATTATGAGGAG GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAGTTCC CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTTGCTGGGGGACTCGGC CCTCTATCTCTGTGCCAGCAGCTTACAGACTATGGCTACACCTTCGGTTCGG GGACCAGGTTAACCGTTGTA (SEQ ID NO: 916)
PN42879 V α	TQLEQSPQFLSIQEGENLTVYCNSSSVFSSLQWYRQEPGEGPVLLVTVVTGGEV KKLKRLTFQFGDARKDSSLHITAAQPGDTGLYLCAGEDFGNEKLTFGTGTRLTII P (SEQ ID NO: 917) ACCCAGCTGCTGGAGCAGAGTCCTCAGTTTCTAAGCATCCAAGAGGGAGAGAAA

	ATCTCACTGTGTACTGCAACTCCTCAAGTGTTTTTCCAGCTTACAATGGTAC AGACAGGAGCCTGGGGAAGGTCTCTGTCCTCCTGGTGACAGTAGTTACGGGTG GAGAAGTGAAGAAGCTGAAGAGACTAACCTTTCAGTTTGGTGATGCAAGAA AGGACAGTTCTCTCCACATCACTGCGGCCAGCCTGGTGATACAGGCCTCTA CCTCTGTGCAGGAGAGGACTTTGGAAATGAGAAATTAACCTTTGGGACTGGA ACAAGACTCACCATCATACCC (SEQ ID NO: 918)
PN42879 Vβ	DAGVTQSPTHLIKTRGQQVTLRCSPKSGHDTVSWYQQALGQGPQFIFQYEEEE RQRGNFPDRFSGHQFPNYSELNVNALLLGDSALYLCASSWADYGYTFGSGTRL TVV (SEQ ID NO: 919) GACGCTGGAGTCACCCAAAGTCCCACACACCTGATCAAAACGAGAGGACAG CAAGTGA CTCTGAGATGCTCTCCTAAGTCTGGGCATGACACTGTGTCTCTGGTA CCAACAGGCCCTGGGTGAGGGGCCAGTTTATCTTTTCAGTATTATGAGGAG GAAGAGAGACAGAGAGGCAACTTCCCTGATCGATTCTCAGGTCACCAGTTCC CTAACTATAGCTCTGAGCTGAATGTGAACGCCTTGTGTCTGGGGGACTCGGC CCTCTATCTCTGTGCCAGCAGCTGGGCGGATTATGGCTACACCTTCGGTTCGG GGACCAGGTAAACCGTTGTA (SEQ ID NO: 920)
PN42888 Vα	ILNVEQSPQSLHVQEGDSTNFTCSFPSSNFYALHWYRWETAKSPEALFVMTLNG DEKKKGRISATLNTKEGYSYLYIKGSQPEDSATYLC AFLTGNQFYFGTGTSLTVIP (SEQ ID NO: 921) ATACTGAACGTGGAACAAAGTCCTCAGTCACTGCATGTTTCAGGAGGGAGACA GCACCAATTTACCTGCAGCTTCCCTTCCAGCAATTTTATGCCTTACACTGG TACAGATGGGAACTGCAAAAAGCCCCGAGGCCTTGTGTGTAATGACTTTAA ATGGGGATGAAAAGAAGAAAGGACGAATAAGTGCCACTCTTAATACCAAGG AGGGTTACAGCTATTTGTACATCAAAGGATCCCAGCCTGAAGACTCAGCCAC ATACCTCTGTGCCTTTCTCACC GGTAACCAGTTCTATTTTGGGACAGGGACAA GTTTGACGGTCATTCCA (SEQ ID NO: 922)
PN42888 Vβ	DVKVTQSSRYLVKRTGEKVLECVQDMDHENMFWYRQDPGLGLRLIYFSYDVK MKEKGDIPGYSVSREKKERFSLILESASTNQTSMYLCASSTVRQGNQGYTFGSG TRLTVV (SEQ ID NO: 923) GATGTGAAAGTAACCCAGAGCTCGAGATATCTAGTCAAAAGGACGGGAGAG AAAGTTTTCTGGAATGTGTCCAGGATATGGACCATGAAAATATGTTCTGGTA TCGACAAGACCCAGGTCTGGGGCTACGGCTGATCTATTTCTCATATGATGTTA AAATGAAAGAAAAAGGAGATATTCCTGAGGGGTACAGTGTCTCTAGAGAGA AGAAGGAGCGCTTCTCCCTGATTCTGGAGTCCGCCAGCACCAACCAGACATC TATGTACCTCTGTGCCAGCAGTACCGTGAGGCAGGGGA ACTATGGCTACACC TTCGGTTCGGGGACCAGGTTAACCGTTGTA (SEQ ID NO: 924)
PN42895 Vα	DQQVKQSSPSLSVQEGRISILNCDYTNSMFDYFLWYKKYPAEGPTFLISSIKDK NEDGRFTVFLNKS AKHLSLHIVPSQP GDSAVYFCAASAGSARQLTFGSGTQLTVL P (SEQ ID NO: 925) GACCAGCAAGTTAAGCAAAGTTCACCATCCCTGAGCGTCCAGGAAGGAAGA ATTTCTATTCTGAACTGTGACTATACTAACAGCATGTTTGATTATTTCTATGG TACAAAAAATACCCTGCTGAAGGTCTACATTCTGATATCTATAAGTTCCAT TAAGGATAAAAATGAAGATGGAAGATTCACTGTTTTCTTAAACAAAAGTGCC AAGCACCTCTCTCTGCACATTGTGCCCTCCAGCCTGGAGACTCTGCAGTGTA CTTCTGTGCAGCAAGCGCCGGTTCTGCAAGGCAACTGACCTTTGGATCTGGG

	ACACAATTGACTGTTTTACCT (SEQ ID NO: 926)
PN42895 V β	EAQVTQNPRLITVTGKKLTVTCSQNMNHEYMSWYRQDPGLGLRQIYYSMNVE VTDKGDVPEGYKVSKEKRNFLILESPSPNQTSLYFCASSLWSNTEAFFGQGTR LTVV (SEQ ID NO: 927) GAAGCCCAAGTGACCCAGAACCCAAGATACCTCATCACAGTGACTGGAAAG AAGTTAACAGTGACTTGTTCTCAGAATATGAACCATGAGTATATGTCTGGTA TCGACAAGACCCAGGGCTGGGCTTAAGGCAGATCTACTATTCAATGAATGTT GAGGTGACTGATAAGGGAGATGTTCTGAAGGTACAAAGTCTCTCGAAAA GAGAAGAGGAATTTCCCCCTGATCCTGGAGTCGCCAGCCCCAACAGACCT CTCTGTACTTCTGTGCCAGCAGTTTATGGTCGAACACTGAAGCTTTCTTTGGA CAAGGCACCAGACTCACAGTTGTA (SEQ ID NO: 928)

Table 9: Variable (V) and joining (J) region gene families for the α and β chains of VelociT TCRs specific for PRAME (312-320) / HLA-A2

TCR ID	V β	J β	V α	J α
PN46909	6-6	1-1	38-1	26
PN46889	6-2	1-1	12-2	11
PN46733	6-1	1-1	13-2	26
PN46723	5-5	1-4	20-1	42
PN46714	5-5	1-6	20-1	42
PN46735	5-5	1-2	26-2	45
PN46678	5-5	1-4	19-1	18
PN46884	28-1	1-3	19-1	34
PN46914	28-1	1-5	19-1	23
PN46883	18-1	1-1	19-1	34
PN46857	18-1	1-1	19-1	47
PN46880	18-1	1-1	16-1	6
PN46871	13-1	1-5	21-1	24
PN46853	13-1	1-5	24-1	37
PN46731	13-1	1-1	13-1	26
PN46777	10-2	1-2	38-1	47
PN46797	10-2	1-2	38-1	47
PN46738	10-2	1-2	38-1	45

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Table 10: Variable (V) and joining (J) region gene families for the α and β chains of VelociT TCRs specific for PRAME (425-433) / HLA-A2

TCR ID	Vb	Jb	Va	Ja
PN42365	5-6	1-2	27-1	42-1
PN42879	5-6	1-2	27-1	48-1
PN42774	5-6	1-2	12-2	34-1
PN42498	5-6	1-2	27-1	42-1

PN42558	5-6	1-2	22-1	42-1
PN42386	5-6	1-2	27-1	42-1
PN42378	5-6	1-2	26-2	24-1
PN42776	5-6	1-2	26-2	24-1
PN42455	5-6	1-2	26-2	24-1
PN42840	5-6	1-2	27-1	42-1
PN42795	5-6	1-2	12-1	42-1
PN42870	5-6	1-2	27-1	45-1
PN42689	5-6	1-2	27-1	42-1
PN42888	28-1	1-2	24-1	49-1
PN42450	28-1	1-2	16-1	34-1
PN42750	28-1	1-2	26-2	24-1
PN42562	27-1	1-2	27-1	40-1
PN42483	27-1	1-4	27-1	42-1
PN42712	27-1	1-6	22-1	20-1
PN42561	27-1	1-2	26-2	49-1
PN42442	27-1	1-2	27-1	40-1
PN42476	27-1	1-4	26-2	24-1
PN42496	27-1	1-2	26-2	54-1
PN42655	27-1	1-2	26-2	24-1
PN42677	27-1	1-2	26-2	49-1
PN42706	27-1	1-2	22-1	40-1
PN42654	27-1	1-2	26-2	49-1
PN42441	27-1	1-1	26-2	49-1
PN42683	27-1	1-2	26-2	47-1
PN42845	27-1	1-1	27-1	20-1
PN42826	27-1	1-1	29/DV5	22-1
PN42707	27-1	1-1	13-2	26-1
PN42833	27-1	1-6	26-1	40-1
PN42762	27-1	1-1	26-2	44-1
PN42780	27-1	1-2	27-1	40-1
PN42746	27-1	1-1	13-2	26-1
PN42815	27-1	1-6	13-2	26-1
PN42711	27-1	1-6	22-1	20-1
PN42895	27-1	1-1	29/DV5	22-1
PN42610	13-1	1-5	12-2	26-1

Table 11: Amino acid and polynucleic acid sequence identifiers for TCR alpha and beta variable chains and CDRs that were identified with PRAME (312-320).

TCR ID	Amino Acid Sequences										Polynucleic Acid Sequences									
	α CDRs					β CDRs					α CDRs					β CDRs				
	V α	CDR1	CDR2	CDR3	V β	CDR1	CDR2	CDR3	V α	CDR1	CDR2	CDR3	V β	CDR1	CDR2	CDR3	V β	CDR1	CDR2	CDR3
	SEQ ID NO:										SEQ ID NO:									
PN46678	217	1	2	3	219	4	5	6	218	109	110	111	220	112	113	114				
PN46714	221	7	8	9	223	10	11	12	222	115	116	117	224	118	119	120				
PN46723	225	13	14	15	227	16	17	18	226	121	122	123	228	124	125	126				
PN46731	229	19	20	21	231	22	23	24	230	127	128	129	232	130	131	132				
PN46733	233	25	26	27	235	28	29	30	234	133	134	135	236	136	137	138				
PN46735	237	31	32	33	239	34	35	36	238	139	140	141	240	142	143	144				
PN46738	241	37	38	39	243	40	41	42	242	145	146	147	244	148	149	150				
PN46777	245	43	44	45	247	46	47	48	246	151	152	153	248	154	155	156				
PN46797	249	49	50	51	251	52	53	54	250	157	158	159	252	160	161	162				
PN46853	253	55	56	57	255	58	59	60	254	163	164	165	256	166	167	168				
PN46857	257	61	62	63	259	64	65	66	258	169	170	171	260	172	173	174				
PN46871	261	67	68	69	263	70	71	72	262	175	176	177	264	178	179	180				
PN46880	265	73	74	75	267	76	77	78	266	181	182	183	268	184	185	186				
PN46883	269	79	80	81	271	82	83	84	270	187	188	189	272	190	191	192				
PN46884	273	85	86	87	275	88	89	90	274	193	194	195	276	196	197	198				
PN46889	277	91	92	93	279	94	95	96	278	199	200	201	280	202	203	204				
PN46909	281	97	98	99	283	100	101	102	282	205	206	207	284	208	209	210				
PN46914	285	103	104	105	287	106	107	108	286	211	212	213	288	214	215	216				

Table 12: Amino acid and polynucleic acid sequence identifiers for TCR alpha and beta variable chains and CDRs that were identified with PRAME (425-433).

	Amino Acid Sequences						Polynucleic Acid Sequences											
	α CDRs			β CDRs			α CDRs			β CDRs								
	Vα	CDR1	CDR2	CDR3	Vβ	CDR1	CDR2	CDR3	Vα	CDR1	CDR2	CDR3	Vβ	CDR1	CDR2	CDR3		
TCR ID	SEQ ID NO:						SEQ ID NO:						SEQ ID NO:					
PN42365	769	289	290	291	771	292	293	294	770	529	530	531	772	532	533	534		
PN42378	773	295	296	297	775	298	299	300	774	535	536	537	776	538	539	540		
PN42386	777	301	302	303	779	304	305	306	778	541	542	543	780	544	545	546		
PN42441	781	307	308	309	783	310	311	312	782	547	548	549	784	550	551	552		
PN42442	785	313	314	315	787	316	317	318	786	553	554	555	788	556	557	558		
PN42450	789	319	320	321	791	322	323	324	790	559	560	561	792	562	563	564		
PN42455	793	325	326	327	795	328	329	330	794	565	566	567	796	568	569	570		
PN42476	797	331	332	333	799	334	335	336	798	571	572	573	800	574	575	576		
PN42483	801	337	338	339	803	340	341	342	802	577	578	579	804	580	581	582		
PN42496	805	343	344	345	807	346	347	348	806	583	584	585	808	586	587	588		
PN42498	809	349	350	351	811	352	353	354	810	589	590	591	812	592	593	594		
PN42558	813	355	356	357	815	358	359	360	814	595	596	597	816	598	599	600		
PN42561	817	361	362	363	819	364	365	366	818	601	602	603	820	604	605	606		
PN42562	821	367	368	369	823	370	371	372	822	607	608	609	824	610	611	612		
PN42610	825	373	374	375	827	376	377	378	826	613	614	615	828	616	617	618		
PN42654	829	379	380	381	831	382	383	384	830	619	620	621	832	622	623	624		
PN42655	833	385	386	387	835	388	389	390	834	625	626	627	836	628	629	630		
PN42677	837	391	392	393	839	394	395	396	838	631	632	633	840	634	635	636		
PN42683	841	397	398	399	843	400	401	402	842	637	638	639	844	640	641	642		

	Amino Acid Sequences										Polynucleic Acid Sequences									
	α CDRs					β CDRs					α CDRs					β CDRs				
	V α	CDR1	CDR2	CDR3	V β	CDR1	CDR2	CDR3	V α	CDR1	CDR2	CDR3	V β	CDR1	CDR2	CDR3	V α	CDR1	CDR2	CDR3
TCR ID	SEQ ID NO:										SEQ ID NO:									
PN42689	845	403	404	405	847	406	407	408	846	643	644	645	848	646	647	648				
PN42706	849	409	410	411	851	412	413	414	850	649	650	651	852	652	653	654				
PN42707	853	415	416	417	855	418	419	420	854	655	656	657	856	658	659	660				
PN42711	857	421	422	423	859	424	425	426	858	661	662	663	860	664	665	666				
PN42712	861	427	428	429	863	430	431	432	862	667	668	669	864	670	671	672				
PN42746	865	433	434	435	867	436	437	438	866	673	674	675	868	676	677	678				
PN42750	869	439	440	441	871	442	443	444	870	679	680	681	872	682	683	684				
PN42762	873	445	446	447	875	448	449	450	874	685	686	687	876	688	689	690				
PN42774	877	451	452	453	879	454	455	456	878	691	692	693	880	694	695	696				
PN42776	881	457	458	459	883	460	461	462	882	697	698	699	884	700	701	702				
PN42780	885	463	464	465	887	466	467	468	886	703	704	705	888	706	707	708				
PN42795	889	469	470	471	891	472	473	474	890	709	710	711	892	712	713	714				
PN42815	893	475	476	477	895	478	479	480	894	715	716	717	896	718	719	720				
PN42826	897	481	482	483	899	484	485	486	898	721	722	723	900	724	725	726				
PN42833	901	487	488	489	903	490	491	492	902	727	728	729	904	730	731	732				
PN42840	905	493	494	495	907	496	497	498	906	733	734	735	908	736	737	738				
PN42845	909	499	500	501	911	502	503	504	910	739	740	741	912	742	743	744				
PN42870	913	505	506	507	915	508	509	510	914	745	746	747	916	748	749	750				
PN42879	917	511	512	513	919	514	515	516	918	751	752	753	920	754	755	756				
PN42888	921	517	518	519	923	520	521	522	922	757	758	759	924	760	761	762				
PN42895	925	523	524	525	927	526	527	528	926	763	764	765	928	766	767	768				

Example 2. Dose-dependent T cell receptor activation

[00197] A Jurkat cell line lacking endogenous TCR α and TCR β expression was generated by gene disruption. These cells were then engineered with a genomic landing pad site that allowed single copy Cre recombinase-mediated insertion of transgenic TCR constructs. An Activator Protein 1 (AP1) response element-driven luciferase reporter was subsequently incorporated into this parental bioassay cell line. Specific TCR bioassay lines were generated by Cre-mediated insertion of constructs expressing the VelociT®-derived TCR α and TCR β sequences.

[00198] Jurkat bioassay lines expressing TCR constructs were sorted to homogeneity using Fluorescence-Activated Cell Sorting (FACS), then tested in peptide-MHC stimulation assays.

HEK293T cells (HLA-A2*01) were plated in assay wells with varying dilutions of antigenic PRAME peptide (PRAME 425-433; SEQ ID NO: 930) or an irrelevant HLA-A2 restricted peptide (SLLMWITQC; SEQ ID NO: 953). These dilutions were made as indicated in Table 13.

Table 13: Peptide dilutions for testing dose response of anti-PRAME TCRs

Dilution	Concentration (μ M)	Irrelevant peptide (μ g/ml)	PRAME (425-433) peptide (μ g/ml)
1	100	109	98.9
2	20	21.8	19.8
3	4	4.4	4.0
4	0.8	0.87	0.79
5	0.16	0.17	0.16
6	0.032	0.035	0.032
7	0.0064	0.0070	0.0063
8	0.00128	0.0014	0.0013
9	0.000256	0.00028	0.00025
10	0.0000512	5.6E-5	5.1E-5
11	0.00001024	1.1E-5	1.0E-5
12	0 (no peptide)	0	0

[00199] After a 2 hour incubation, engineered Jurkat cells were added to wells at a 3:1 Jurkat:293T cell ratio and incubated a further 5 hours. Luciferase reporter activity was determined by measuring endpoint luminescence output in assay wells. PRAME-specific TCRs mediated dose-dependent AP1 reporter activation in response to HLA-A2*01 HEK293T cells pulsed with cognate peptide, but not those cells pulsed with the irrelevant peptide. EC50 data is shown in Table 14, below.

Table 14: Antigen-specific response of HLA-A2/PRAME (425-433)-specific TCRs in a Jurkat cell bioassay, normalized to negative control

TCR ID	EC50 (μ M)
PN42365	0.01594
PN42386	0.02711
PN42441	0.8205
PN42442	0.2324
PN42450	0.03355
PN42483	*
PN42496	0.02937
PN42498	0.002418
PN42558	0.2614
PN42561	0.0137
PN42562	0.02807
PN42610	*
PN42654	*
PN42655	
PN42677	*
PN42683	*
PN42689	0.0095
PN42706	0.7274
PN42707	0.01182
PN42711	0.05688
PN42712	0.01329
PN42746	0.04598
PN42762	114.8
PN42774	0.8757
PN42780	1.255
PN42795	0.2454
PN42815	0.1261
PN42826	4.915
PN42833	0.04786
PN42840	0.03092
PN42845	0.911
PN42870	0.1302
PN42879	*
PN42888	0.0119
PN42895	0.94

* Not above negative control/did not respond in assay

Equivalents

[00200] Those skilled in the art will recognize or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. such equivalents are intended to be encompassed by the following claims. The contents of all
5 references, patents and published patent applications cited throughout this application are incorporated herein by reference.