

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 disclosure 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] In one aspect, the present disclosure refers to a T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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. Accordingly, in one example, the present disclosure 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 disclosure refers to a T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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. In another example, the present disclosure 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.

[0012a] In another aspect, the present disclosure provides a T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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 alpha chain CDR1, CDR2, and CDR3/beta chain CDR1, CDR2, and CDR3 amino acid sequences selected from the alpha chain/beta chain variable domain sequence pairs 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.

[0013] In some examples, 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.

[0014] In some examples, 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.

[0016] In some examples, 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.

[0017] In some examples, 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.

[0018] In some examples, 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.

[0019] In some examples, 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.

[0020] In some examples, 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 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 examples, 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.

[0022] In some examples, 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.

[0023] The present disclosure 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 disclosure.

[0024] In another aspect, the present disclosure refers to a T cell receptor (TCR) 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 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. In another aspect, the present disclosure refers to a T cell receptor (TCR) 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 comprises the amino acid sequence of any one of the beta chain variable domain CDR3 amino acid sequences set forth in Table 6. In one example, the present disclosure 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 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.

[0024a] In another aspect, the present disclosure refers to a T cell receptor (TCR) 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 alpha chain CDR1, CDR2, and CDR3/beta chain CDR1, CDR2, and CDR3 amino acid sequences selected from the alpha chain/beta chain variable domain sequence pairs 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, 893/895, 897/899, 901/903, 905/907, 909/911, 913/915, 917/919, 921/923, and 925/927.

[0025] In another example, the present disclosure 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 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 examples, 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 variable domain CDR2 amino acid sequences set forth in Table 6.

[0027] In some examples, 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 examples, 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 beta chain
10 variable domain CDR1, CDR2 and CDR3 contained within any one of the beta chain variable domain sequences listed in Table 8.

[0030] In some examples, 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 8.

15 **[0031]** In some examples, 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 examples, 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
20 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.

[0033] In some examples, the TCR comprises (a) an alpha chain variable domain CDR1 domain having an
25 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 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,
30 422, 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, 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
35 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.

[0034] In some examples, 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.

[0035] In some examples, 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.

[0036] The present disclosure 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 disclosure.

[0037] In some examples, the TCRs of the disclosure further comprise a detectable moiety.

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

[0038a] In one aspect, the present disclosure provides a TCR that competes for binding to the TCR as disclosed herein. In another aspect, the present disclosure provides a TCR that binds to the same epitope as the a TCR as disclosed herein. In another aspect, the present disclosure provides an isolated cell presenting the TCR as disclosed herein.

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

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

5 **[0041]** The present disclosure also provides vectors comprising the polynucleotide molecule of the disclosure; cells expressing the vectors of the disclosure.

[0041a] In one aspect, the present disclosure provides a vector comprising the polynucleotide molecule as disclosed herein. In another aspect, the present disclosure provides an isolated cell expressing the vector as disclosed herein. In another aspect, the present disclosure provides a
10 pharmaceutical composition comprising the isolated cell as disclosed herein and a pharmaceutically acceptable carrier or diluent. In another aspect, the present disclosure provides the use of the TCR as disclosed herein, the pharmaceutical composition as disclosed herein, or a plurality of the isolated cells as disclosed herein in the manufacture of a medicament for treating a subject having a PRAME-associated disease or disorder.

15 **[0042]** In one example, the present disclosure 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 disclosure, thereby treating the subject.

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

[0044] In some examples, 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 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.

[0045] In some examples of the disclosure, 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 disclosure is 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 disclosure refers to a polynucleotide molecule encoding a T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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. In one example, the present disclosure 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.

[0048] In another aspect, the present disclosure refers to a polynucleotide molecule encoding a T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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 5. In another example, the present disclosure 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 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.

[0048a] In another aspect, the present disclosure refers to a polynucleotide molecule encoding a T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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 alpha chain CDR1, CDR2, and CDR3/beta chain CDR1, CDR2, and CDR3 amino acid sequences selected from the alpha chain/beta chain variable domain sequence pairs 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.

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

[0050] In some examples, 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.

[0051] In some examples, 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.

[0052] In some examples, 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.

[0053] In some examples, 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.

[0054] In some examples, 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; (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 examples, 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.

[0056] In some examples, 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 examples, 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: 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, 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; 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 examples, 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, 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 disclosure also provides vectors comprising an isolated nucleic acid molecule of the disclosure and isolated cells comprising a vector of the disclosure.

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

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

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

[0063] In one example, the present disclosure 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 disclosure, thereby treating the subject.

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

[0065] In some examples, 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 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.

[0066] In some examples of the disclosure, 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 disclosure 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 intracranially to the subject.

[0068] In one aspect, the present disclosure refers to a polynucleotide molecule encoding a T cell receptor (TCR) 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 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 8. In one example, the present disclosure 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 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 disclosure refers to a polynucleotide molecule encoding a T cell receptor (TCR) 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 comprises the amino acid sequence of any one of the beta chain variable domain CDR3 amino acid sequences set forth in Table 8. In another example, the present disclosure 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 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.

[0069a] In another aspect, the present disclosure refers to a polynucleotide molecule encoding a T cell receptor (TCR) 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 alpha chain CDR1, CDR2, and CDR3/beta chain CDR1, CDR2, and CDR3 amino acid sequences selected from the alpha chain/beta chain variable domain sequence pairs 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, 893/895, 897/899, 901/903, 905/907, 909/911, 913/915, 917/919, 921/923, and 925/927.

[0069b] In another aspect, the present disclosure refers to the use of a plurality of the cells as disclosed herein in the manufacture of a medicament for treating a subject having a PRAME-associated disease or disorder.

[0070] In some examples, 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 examples, 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.

[0072] In some examples, 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.

[0073] In some examples, 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.

[0074] In some examples, 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 examples, 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: 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, 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 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
5 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 examples, 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,
10 857/859, 865/867, 873/875, 885/887, 893/805, 897/899, 901/903, 913/915, and 925/927.

[0077] In some examples, 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,
15 869/871, 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 examples, 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,
20 655, 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,
25 552, 558,
30
35

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 examples, 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, 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 disclosure also provides vectors comprising an isolated nucleic acid molecule of the disclosure and isolated cells comprising a vector of the disclosure.

[0081] In one example, the present disclosure 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 disclosure, thereby treating the subject.

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

[0083] In some examples, 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 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 examples, a plurality of cells is administered to the subject in combination with a second therapeutic agent.

[0085] The present disclosure 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 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.

CLAIMS

We claim:

- 5 1. A T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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
10 sequences set forth in Table 3.
2. A T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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
15 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.
3. The TCR of any one of claims 1-2, wherein the TCR comprises at least one TCR
20 alpha chain variable domain and/or at least one beta chain variable domain.
4. The TCR of claim 3, wherein the TCR comprises a TCR alpha chain variable domain and a TCR beta chain variable domain.
- 25 5. The TCR of any one of claims 1-4, wherein 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.
- 30 6. The TCR of claim 5, wherein 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.
- 35 7. The TCR of any one of claims 4-6, comprising 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.

8. A T cell receptor (TCR) that binds specifically to an HLA-A2 presented preferentially expressed antigen in melanoma (PRAME) peptide comprising the amino acid sequence of

5 RLDQLLRHV (SEQ ID NO:929) (PRAME 312-320), wherein the TCR comprises alpha chain CDR1, CDR2, and CDR3/beta chain CDR1, CDR2, and CDR3 amino acid sequences selected from the alpha chain/beta chain variable domain sequence pairs 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.

10 9. The TCR of any one of claims 1-8, comprising 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.

15 10. The TCR of any one of claims 1-9, comprising 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.

20 11. The TCR of any one of claims 1-10, comprising: (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
25 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.

12. The TCR of any one of claims 4-11, comprising:

30 (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;
- 5 (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 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
- 10 (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.

13. The TCR of claim 12, comprising an alpha chain variable domain/beta chain variable
15 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.

14. A T cell receptor (TCR) that binds specifically to an HLA-A2 presented preferentially
20 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.

25 15. A T cell receptor (TCR) 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.

16. The TCR of claim 14 or 15, wherein the alpha chain variable domain further
35 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 variable domain CDR2 amino acid sequences set forth in Table 6.

17. The TCR of claim 16, wherein 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
18. The TCR of any one of claims 14-17, wherein the TCR comprises at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.
19. The TCR of claim 18, wherein the TCR comprises a TCR alpha chain variable domain and a TCR beta chain variable domain.
- 10
20. The TCR of any one of claims 17-19, comprising alpha chain variable domain CDR1, 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.
- 15
21. A T cell receptor (TCR) 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 alpha chain CDR1, CDR2, and CDR3/beta chain CDR1, CDR2, and CDR3 amino acid sequences selected from the alpha chain/beta chain variable domain sequence pairs 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, 893/895, 897/899, 901/903, 905/907, 909/911, 913/915, 917/919, 921/923, and 925/927.
- 20
22. The TCR of any one of claims 14-21, comprising 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.
- 25
23. The TCR of any one of claims 14-22, comprising 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.
- 30
- 35

24. The TCR of any one of claims 14-23, comprising: (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.

25. The TCR of any one of claims 17-24, comprising:

(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 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, 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.

26. The TCR of claim 25, comprising 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.

- 5 27. A TCR that competes for binding to the TCR of any one of claims 1-26.
28. A TCR that binds to the same epitope as the a TCR of any one of claims 1-26.
29. The TCR of any one of claims 1-28, further comprising a detectable moiety.
- 10 30. An isolated cell presenting the TCR of any one of claims 1-29.
31. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes an alpha chain variable domain of the TCR as set forth in any one of claims 1-29.
- 15 32. An isolated polynucleotide molecule comprising a polynucleotide sequence that encodes a beta chain variable domain of the TCR as set forth in any one of claims 1-29.
33. A vector comprising the polynucleotide molecule of claim 31 or 32.
- 20 34. An isolated cell expressing the vector of claim 33.
35. A pharmaceutical composition comprising the isolated cell of claim 34 and a pharmaceutically acceptable carrier or diluent.
- 25 36. Use of the TCR as set forth in any one of claims 1-29, the pharmaceutical composition of claim 35, or a plurality of the isolated cells of claim 30 in the manufacture of a medicament for treating a subject having a PRAME-associated disease or disorder.
- 30 37. The use of claim 36, wherein the PRAME-associated disease or disorder is PRAME-associated cancer.
38. The use of claim 37, wherein 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
- 35

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.

39. The use of any one of claims 36-38, wherein the TCR, the pharmaceutical composition, or the plurality of cells is to be administered to the subject in combination with a second therapeutic agent.

40. The use of any one of claims 36-39, wherein the TCR, the pharmaceutical composition, or the plurality of cells is to be administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially to the subject.

41. A polynucleotide molecule encoding a T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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.

42. A polynucleotide molecule encoding a T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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 5.

43. The polynucleotide molecule of claim 41 or 42, encoding at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.

44. The polynucleotide molecule of claim 43, wherein 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.
45. A polynucleotide molecule encoding a T cell receptor (TCR) that binds specifically to an HLA-A2 presented 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 alpha chain CDR1, CDR2, and CDR3/beta chain CDR1, CDR2, and CDR3 amino acid sequences selected from the alpha chain/beta chain variable domain sequence pairs 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.
46. The polynucleotide molecule of any one of claims 41-45, wherein the TCR 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.
47. The polynucleotide molecule of any one of claims 41-46, wherein 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.
48. The polynucleotide molecule of any one of claims 41-47, wherein 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.
49. The polynucleotide molecule of any one of claims 41-48, wherein 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;
- 5 (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;
- 10 (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.
- 15

50. The polynucleotide molecule of claim 48, wherein 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.

20

51. The polynucleotide molecule of claim 48, wherein the TCR comprises
- (a) an alpha chain variable domain CDR1 encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 109, 115, 121, 127, 133, 139, 145, 151, 157, 163, 169, 175, 181, 187, 193, 199, 205, and 211;
- 25 (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;
- 30 (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, 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;
- 35

(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; and

5 (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.

52. The polynucleotide molecule of claim 51, wherein the TCR comprises an alpha chain variable domain/beta chain variable domain nucleic acid sequence pair selected from the group
10 consisting of SEQ ID NOs: 218/220, 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.

53. A vector comprising the polynucleotide molecule of any one of claims 41-52.
15

54. An isolated cell comprising the vector of claim 53.

55. A polynucleotide molecule encoding a T cell receptor (TCR) that binds specifically to an HLA-A2 presented preferentially expressed antigen in melanoma (PRAME) peptide comprising
20 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 8.

25 56. A polynucleotide molecule encoding a T cell receptor (TCR) 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 comprises the amino acid sequence of any one of the beta chain variable domain
30 CDR3 amino acid sequences set forth in Table 8.

57. The polynucleotide molecule of claim 55 or 56, encoding at least one TCR alpha chain variable domain and/or at least one beta chain variable domain.

35 58. A polynucleotide molecule encoding a T cell receptor (TCR) 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 alpha chain CDR1, CDR2, and CDR3/beta chain CDR1, CDR2, and CDR3 amino acid sequences selected from the alpha chain/beta chain variable domain sequence pairs 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, 893/895, 897/899, 901/903, 905/907, 909/911, 913/915, 917/919, 921/923, and 925/927.

59. The polynucleotide molecule of claim 58, wherein 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.

60. The polynucleotide molecule of any one of claims 55-59, wherein the TCR 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.

61. The polynucleotide molecule of any one of claims 55-60, wherein 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.

62. The polynucleotide molecule of any one of claims 55-61, wherein 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.

63. The polynucleotide molecule of any one of claims 55-62, wherein 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 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, 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.

64. The polynucleotide molecule of claim 63, wherein 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, 893/895, 897/899, 901/903, 905/907, 909/911, 913/915, 917/919, 921/923, and 925/927.

65. The polynucleotide molecule of claim 62, wherein the TCR 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;
- 5 (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
10 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
15 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
20 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.
66. The polynucleotide molecule of claim 65, wherein 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, 774/776, 778/780, 782/784, 786/788, 790/792, 794/796,
25 798/800, 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.
- 30 67. A vector comprising the polynucleotide molecule of any one of claims 55-66.
68. An isolated cell comprising the vector of claim 67.
69. Use of a plurality of the cells of claim 54 or 68 in the manufacture of a medicament
35 for treating a subject having a PRAME-associated disease or disorder.

70. The use of claim 69, wherein the PRAME-associated disease or disorder is PRAME-associated cancer.

71. The use of claim 70, wherein 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 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.

72. The use of any one of claims 69-71, wherein the plurality of cells is to be administered to the subject in combination with a second therapeutic agent.