

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
5 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,
10 269/271, 273/275, 277/279, 281/283, and 285/287.

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
15 in Table 5.

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
20 Table 5.

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
25 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.

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,
35 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.

20 14. 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.

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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 comprises a CDR1 and a CDR2, wherein the CDR1 comprises any one of the alpha chain variable
35 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.

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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.

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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.

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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, 893/805, 897/899, 901/903, 905/907, 909/911, 913/915, 917/919, 921/923, and 925/927.

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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.

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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.

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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
 5 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
 10 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,
 15 362, 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,
 20 363, 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,
 25 371, 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,
 30 372, 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
 35 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.

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 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.

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 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.

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 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.

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 36. A method of treating a subject having a PRAME-associated disease or disorder, comprising administering to the subject a therapeutically effective amount 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, thereby treating the subject.

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 37. The method of claim 36, wherein the PRAME-associated disease or disorder is PRAME-associated cancer.

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 38. The method 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 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
5 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,
10 pancreatic adenocarcinoma, liver cancer, hepatocellular carcinoma, mesothelioma, or a recurrent non-small cell lung cancer.

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

40. The method of any one of claims 36-39, wherein the TCR, the pharmaceutical composition, or the plurality of cells is administered subcutaneously, intravenously, intradermally, intraperitoneally, orally, intramuscularly or intracranially to the subject.
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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,
25 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
30 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.

35 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.

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.

51. The polynucleotide molecule of claim 48, wherein the TCR comprises

25 (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;

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;

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(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 the amino acid sequence of SLLQHLIGL (SEQ ID NO:930) (PRAME 425-433), wherein the TCR
20 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.

56. A polynucleotide molecule encoding a T cell receptor (TCR) that binds specifically to
25 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.

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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.

58. A polynucleotide molecule encoding a T cell receptor (TCR) that binds specifically to
35 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;

5 (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
10 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
15 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
20 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,
25 797/799, 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.

30 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;

35 (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,
5 609, 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,
10 730, 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.

20 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, 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,
25 882/884, 886/888, 890/892, 894/896, 898/900, 902/904, 906/908, 910/912, 914/916, 918/920, 922/924, and 926/928.

67. A vector comprising the polynucleotide molecule of any one of claims 55-66.

30 68. An isolated cell comprising the vector of claim 67.

69. A method of treating a subject having a PRAME-associated disease or disorder, comprising administering to the subject a plurality of the cells of claim 54 or 68, thereby treating the subject.

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

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